UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation

MDL DOCKET NO. 1769

This document relates to:

Linda Guinn	6:07-cv-10291
Janice Burns	6:07-cv-15959
Richard Unger	6:07-cv-1581 2
Connie Curley	6:07-cv-15701
Linda Whittington	6:07-cv-10475
Eileen McAlexander	6:07-cv-10360
~~Sandra Carter~~	~~6:07-cv-13234~~
~~Clemmie Middleton~~	~~6:07-cv-10949~~
~~Hope Lorditch~~	~~6:07-cv-12657~~
David Haller	6:07-cv-15733
~~Charles Ray~~	~~6:07-cv-11102~~
~~William Sarmiento~~	~~6:07-cv-10425~~

DECLARATION OF LAURA M. PLUNKETT, PH.D., DABT

My name is Laura M. Plunkett. I am over twenty-one years of age, am of sound mind, have never been convicted of a felony, and am otherwise competent to make this Declaration. I have personal knowledge of all factual statements contained herein and all such factual statements are true and correct as outlined herein in this declaration-report.

A. Qualifications and Expertise

I am board-certified as a Diplomate of the American Board of Toxicology, a pharmacologist and United States Food and Drug Administration (FDA) regulatory specialist. I have over twenty years of experience in the areas of pharmacology[1] and

[1] Pharmacology is the study of how substances interact with living organisms to produce a change in function. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 6th edition.

toxicology[2] and have worked in both government and academic research and taught pharmacology and toxicology at the undergraduate and postgraduate levels.

I received a B.S. degree in 1980 from the University of Georgia, and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides. From June of 1984 through August of 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health and my research there focused on neurochemical systems that control body functions, including dopaminergic and serotonergic systems. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. From December of 1989 to August of 1997 I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. At ENVIRON I was a consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy with a focus on products regulated by the U.S. Food and Drug Administration (FDA). Since forming my own company in 1997, I have consulted for a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy with a focus on products regulated by the U.S. Food and Drug Administration.

B. Responses to Particular Astra-Zeneca Statements

I have reviewed the brief of Astra Zeneca that criticizes my opinions and methodology and I believe it is important to respond.

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[2] Toxicology is the study of the adverse effects of xenobiotics, or chemicals, on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people. *Casarett & Doull's Toxicology: The Basic Science of Poisons*, 7th edition.

1. Use of a Non-Scientific Method

Astra-Zeneca (AZ) has suggested that I have employed a method for assessing causation that is "non-scientific". Contrary to AZ's suggestion, I have employed a method that is routinely used by scientists when examining the possible cause-and-effect relationship between exposure and a disease or condition, namely weight-of-the-evidence. This method is based on use of a series of considerations or guidelines first articulated by Sir Austin Bradford Hill in 1965 in a speech before the Royal Society of Medicine and will be referred to hereafter as the "Bradford Hill" considerations[3]. These considerations or guidelines, there are nine of them outlined[4], have been used for decades by scientists as a tool for organizing and classifying evidence to support a weight-of-the-evidence assessment for causation. As discussed in the speech and paper, all nine are not necessary for causation to be established. In order to understand how the author himself meant for these nine considerations to be used it is best to examine his own statements:

> "Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (from page 299, left column, second full paragraph of Hill, A.B. 1965. The environment and disease: association or causation? *Proc. Royal Soc. Med.* 58:295-300).

Clearly, in order to be consistent with the Bradford Hill methodology, the nine points are used as guidelines to assess the body of literature and evidence that is available for any one situation being investigated. However, no one of the nine considerations should be

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[3] The "Bradford Hill" guidelines or considerations are described in the 1965 publication (Hill, A.B. 1965. The environment and disease: association or causation? *Proc. Royal Soc. Med.* 58:295-300).

[4] The nine viewpoints or considerations described by Sir Austin Bradford Hill were: 1) strength; 2) consistency; 3) specificity; 4) temporality; 5) biological gradient (dose-response); 6) plausibility; 7) coherence; 8) experiment; and 9) analogy.

viewed as an absolute requirement, consistent with the Bradford Hill method as described by Sir Austin Bradford Hill himself.

Therefore, in my current weight-of-the-evidence assessment for Seroquel and diabetes, I employed the Bradford Hill method as a guide in my assessment (see my expert report which is attached to this Declaration and which I affirm contains my scientific opinions in this matter). My use of the Bradford Hill method and weight-of-the-evidence assessment in the Seroquel litigation are consistent with my use of these same tools in my practice as a pharmacologist throughout the years, and has also been accepted by courts in other litigations including phenylpropanolamine (PPA) products, diet drugs known as "Fen-phen", and Zyprexa. It should also be pointed out that a number of the defense experts have also employed a similar method for causation analysis.

AZ has asserted that my use of the Bradford Hill method and weight-of-the-evidence assessment are "non-scientific" because I have limited my discussion only to studies and evidence that support my position, ignoring studies that do not support my position. This is totally false. As in any weight-of-the-evidence assessment, there may be studies that both support a causation opinion and studies that do not. What is important to show is that both types of studies have been considered. In my reference list provided to defense counsel and during my deposition I discussed the fact that indeed studies do exist that I have not cited and that may not support my position. However, also, as discussed in my report and my deposition, it is the totality of the evidence that is important to my eventual finding that Seroquel can cause hyperglycemia and diabetes as well as weight gain. Although I have not given detailed rebuttals of each paper in my expert report, I was prepared to discuss those papers at my deposition and in some cases they were discussed while in other cases defense counsel chose not to discuss certain published studies. Therefore, contrary to the defense's assertions I have not "cherry-picked" studies but have considered all of the studies available and concluded that the totality of the evidence supports a weight-of-the-evidence assessment that Seroquel can cause hyperglycemia and diabetes as well as weight gain.

I have used a method that is based on sound science and considers more than just observational study data. It includes a consideration of the totality of available evidence,

which is consistent with the Bradford Hill method and would include experimental data in cells, animals, and humans (experimentation and biologic plausibility under Bradford Hill), data collected in chemically similar compounds (analogy under Bradford Hill), epidemiological data, case reports, AZ clinical study data, and any other data or information that I felt was relevant to the question of Seroquel and metabolic effects. Although defense counsel attempt to discount the value of *in vitro* and animal studies, I believe that all types of data (animal, *in vitro*, and human) are relevant to a cause and effect assessment of diabetes risk and Seroquel use. Indeed, much of the data submitted by AZ to the FDA as part of the drug approval process was animal experiments AZ performed to assess safety and efficacy of Seroquel. It is curious that the company in this litigation context now chastises the very type of data it values in the drug approval context.

I have also included case reports within my weight-of-the-evidence assessment because, as described by Bradford Hill, such data are a type of experiment where there is a component of challenge/dechallenge, where challenge refers to administration of a drug, in this case Seroquel, and dechallenge refers to the situation where the drug is removed. It should be noted that in the case of Seroquel, there are several case reports that show that with dechallenge of a patient that developed hyperglycemia or diabetes while taking Seroquel, the hyperglycemia or diabetes improved (*e.g.*, Sobel *et al.* 1999[5]; Domon and Cargile 2002[6]; Sneed and Gonzalez 2003[7]; Takahashi *et al.* 2005[8]; Marlowe *et al.* 2007[9]). These type of case reports are consistent with the type of experimentation described by Bradford Hill and are validly used in a weight-of-the-evidence causation assessment.

I testified throughout my deposition, and explained in my expert report, that I have relied on a variety of different types of data (*in vitro* data, animal data, clinical data,

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[5] Sobel, M. et al. 1999. New-onset of diabetes mellitus associated with the initiation of quetiapine treatment. *J. Clin. Psychiatry* 60:556-557.

[6] Domon, S.E. and C.S. Cargile. 2002. Quetiapine-associated hyperglycemia and hypertriglyceridemic. *J. Am. Acad. Child Adolesc. Psychiatry* 41: 495-496.

[7] Sneed, K.B. and E.C. Gonzalez. 2003. Type 2 diabetes mellitus induced by an atypical antipsychotic medication. *J. Am. Board Fam. Pract.* 16:251-254.

[8] Takahashi, M. et al. 2005. Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient. *Pharmacopsychiatry* 38:183-184.

[9] Marlowe, K.F. et al. 2007. New onset diabetes with ketoacidosis attributed to quetiapine. *South. Med. J.* 100:829-831.

epidemiological data, and statements in authoritative texts or by authoritative bodies) to support my opinions regarding the adverse metabolic effects and human health risks associated with Seroquel. Therefore, the method I have used is consistent with methodology routinely used by scientists to assess causation and I have considered all of the evidence before forming my opinion. The fact that after I formed my causation opinions some studies were identified or published that when considered individually may not support my findings is not sufficient evidence to suggest that my method was non-scientific. In fact since then, there have also been new positive studies reflecting the diabetogenic potential of Seroquel (*e.g.*, Savoy et al. 2008[10]; DuMouchel et al. 2008[11]; Meyer et al. 2008[12]). I have not put more weight on papers that support my opinions; I have simply listed those papers in my expert report in order to fully define the evidence that I have relied on.

2. AZ Counsel Suggest It Is Inappropriate to Consider Data on Drugs Chemically Similar to Seroquel In a Weight-of-the-Evidence Assessment

In performing the weight-of-the-evidence causation assessment relating to Seroquel, I used the Bradford Hill method, a standard, well recognized methodology (discussed above) to guide my evaluation of the body of published literature. As already discussed, these nine areas listed by Bradford Hill are not meant to be strictly applied but instead used to guide the health professional. Several of the nine considerations, however, have become an integral part of causation analysis. One such criterion is "analogy" (see Hill 1965). As I discussed in my expert report and my deposition, analogy is the process of examining a potential cause and effect relationship by looking for chemically similar compounds, or other compounds with similar physical or chemical properties, that may or may not have produced similar adverse effects. This is the same

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[10] Savoy, Y.E. et al. 2008. Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: evidence for the involvement of sympathetic regulation. *Schizophr. Bull.* Aug 14 [Epub ahead of print].

[11] DuMouchel, W. et al. 2008. Antipsychotics, glycemic disorders, and life-threatening diabetic events: a Bayesian data-mining analysis of the FDA adverse event reporting system (1968-2004). *Ann. Clin. Psychiatry.* 20:21-31.

[12] Meyer, J.M. et al. 2008. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE schizophrenia trial: prospective data from phase 1. *Schizophr. Res.* 101:273-286.

way that textbooks of pharmacology and toxicology are organized. Classes of compounds or drugs are discussed together in terms of the similarities in both their toxicological and pharmacological profiles. Although any two chemically similar substances may differ quantitatively in terms of the doses required to produce certain effects in animals and humans, the qualitative aspects of a pharmacological and toxicological profile of chemically similar compounds are usually very similar. In any event, as a pharmacologist I carefully reviewed the pharmacological similarities and differences of the agents. In fact, to ignore chemical classes would be contrary to fundamental teachings of pharmacology.

To evaluate Seroquel, I thought it was important to look for chemically similar compounds to predict the likely toxicological and pharmacological profile of Seroquel, since it has been known for decades that anti-psychotic drugs, including the atypical anti-psychotics, have effects to alter metabolism that can lead to weight gain and effects on glucose metabolism (see any standard textbook of pharmacology such as Baldessarini, R.J. 1980. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 6th edition,* A.G. Gilman et al. (eds.), chapter 19, McMillan Publishing Co.: New York). In these standard textbooks of pharmacology, it is taught that clozapine and olanzapine (Zyprexa) are the two most chemically similar compounds to Seroquel. This is seen by inspecting the ring structures of the compounds and the types of chemical groups attached. Therefore, in these textbooks, the effects of clozapine are used as a standard for comparison of the other chemically similar atypical anti-psychotics, including Zyprexa and Seroquel. As a result, using the Bradford Hill methods of causation analysis, I have used data on clozapine and Zyprexa as part of my weight-of-the-evidence assessment for causation. Never have I only used data on chemically similar compounds. The clozapine and Zyprexa data are only used as supporting information that demonstrate that there was some predictability surrounding the effects of Seroquel on metabolic parameters and its likely propensity to induce diabetes. It is a standard practice for a pharmacologist and toxicologist to perform a causation assessment and to use chemical analogy.

In my deposition and my expert report, I discussed my reasons for concluding that clozapine and Zyprexa data were relevant to the Seroquel assessment. I noted that the drugs were "chemically similar" and they had similar potencies on dopamine and

serotonergic receptors which, for efficacy and likely safety, is an important part of the pharmacological profile of the drugs. Therefore, I believe I have provided valid scientific reasons and used valid scientific methodology for utilizing clozapine and Zyprexa data as part of the body of evidence supporting my conclusions about Seroquel. Therefore, although other scientists may challenge my interpretation of the data, the use of chemically similar compounds in my causation analysis is based on well-accepted principles of pharmacology and toxicology.

3. AZ Counsel Suggest Three Things Are Needed to Establish Causation and These Three Things Are Not Provided for Seroquel

Defense counsel has suggested that three things are needed in order to establish causation: 1) biologic mechanism; 2) dose-response effect; and 3) general acceptance. Defense counsel then suggests that I have failed to provide all three of these necessary supports for causation in my opinions. I strongly disagree with both of defense counsel's suggestions.

First, as discussed in detail above in section 1 of my declaration, there are NOT three absolute requirements for establishing causation. Instead, consistent with the method of Sir Austin Bradford Hill, there are nine considerations that should be applied to the available data for any given situation and two of those nine do include plausibility and biologic gradient. Plausibility is usually interpreted to mean biologic plausibility. As the 1965 paper states: "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand." (see page 298 of Hill, A.B. 1965. The environment and disease: association or causation? *Proc. Royal Soc. Med.* 58:295-300). This does not mean that it is necessary to completely understand any mechanism of injury only that the cause-and-effect between the injury in question and the agent being examined is based on some type of plausible mechanism. As discussed below, I have addressed this issue in my opinions. More importantly, however, general acceptance is NOT one of the nine considerations for establishing causation. Therefore, defense counsel is simply wrong in its suggestions.

Regardless, my expert report clearly outlines evidence that would support each of these three areas, or provides reasons why certain aspects of all three areas cannot be

provided based on currently available data. I will briefly point out the evidence I have identified for each of these three areas.

With respect to biologic mechanism, I have stated in my expert report and my deposition that no one knows the exact molecular mechanism in any one individual that is responsible for the metabolic effects of Seroquel, including its effects to induce hyperglycemia, weight gain, and diabetes. In fact, AZ's package insert for Seroquel states in the Clinical Pharmacology Section 12.1 that "the mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, is unknown." Instead, the insert goes on to discuss proposed mechanisms that may explain its actions. Thus, not knowing with certainty the precise mechanism of action of a therapeutic or an adverse effect does not mean that there is not evidence for a likely biologic mechanism. Nor does it mean that you must need to know the precise mechanism. If that was the case, Seroquel and many drugs, which are recognized to have certain intended therapeutic effects, yet the precise mechanism is not precisely understood, would not be approved for human use, if one applied the same standards is AZ is suggesting should be applied here. Moreover, often in medicine and pharmacology, there can be more than one mechanism underlying therapeutic and adverse drug effects.

In paragraphs 35-40 of my report, I discuss the likely mechanisms underlying the adverse metabolic effects of Seroquel. Then, in my deposition I discussed these mechanisms in even more detail.

I would first like to respond to defense counsel's statements regarding two specific studies, Henderson *et al.* 2006[13] and Melkersson *et al.* 2005[14]. Melkersson *et al.* (2005) is a study of insulin release *in vitro* from rat pancreatic cells and the authors reported that at the doses of Seroquel tested (10^{-6} M), there was no statistically significant increase in insulin release, indicating that the drug did not directly stimulate insulin release in rat pancreas under the conditions of the assay. Interestingly, in a similar study

[13] Henderson, D.C. et al. 2006. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J. Clin. Psychiatry* 67:789-797.

[14] Melkersson, K.I. et al. 2005. The atypical antipsychotics quetiapine, risperidone, and ziprasidone do not increase insulin release in vitro. Neuroendocrinol. Lett. 26:205-208.

reported in 2001 (Melkersson *et al.* 2001[15]), clozapine but not olanzapine exhibited the ability to directly stimulate insulin release in this experimental system. Given the well-accepted relationship between olanzapine (Zyprexa) and diabetes (see labeling from Physicians' Desk Reference, 2008; ADA Consensus statement 2004[16]), it is clear that this experimental model is not a sensitive indicator of the diabetogenic potential of anti-psychotic drugs in humans. Now considering the paper cited by the defense counsel known as Henderson *et al.* (2006), this study reports results of testing in non-obese schizophrenic patients where measures of insulin resistance in 7 patients taking Seroquel was compared to 8 patients taking Zyprexa or 9 normal controls (not schizophrenic). Although only Zyprexa was associated with statistically significant decreases in insulin sensitivity index as compared to controls (where decreased insulin sensitivity is thought to be associated with Type II diabetes), the insulin sensitivity index in Zyprexa-treated patients was not statistically significant from the index value reported for Seroquel-treated patients. In most endpoints measured in the study, Seroquel treatment affected insulin and glucose homeostasis in the same direction as did Zyprexa, although Zyprexa showed greater diabetogenic potential. This result is actually consistent with my opinions as I have identified Zyprexa as having a greater diabetogenic potential than Seroquel, although the weight-of-the-evidence shows both drugs are capable of causing hyperglycemia and diabetes.

I would also like to respond to defense counsel's concerns that some available studies have shown that Seroquel lacks certain specific activity under the conditions of the assay being tested (*e.g.,* Henderson *et al.* 2006; Melkersson *et al.* 2005) by pointing out that there are peer-reviewed published studies that do provide basic mechanistic or biologic mechanism data specific to Seroquel (*e.g.,* Dwyer and Donohoe 2003[17]; Savoy *et al.* 2008[18]; Vestri *et al.* 2006[19]; Cope *et al.* 2005[20]). The following is a brief discussion of

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[15] Melkersson, K.I. et al. 2001. Different effects of antipsychotic drugs on insulin release in vitro. *Eur. Neuropsychopharmacology* 11:327-332.

[16] American Diabetes Association et al. 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 27:596-601.

[17] Dwyer, D.S. and D. Donohoe. 2003. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. *Pharm. Biochem. Behav* 75:255-260.

[18] Savoy, Y.E. et al. 2008. Differential effects of various typical and atypical antipsychotics on plasma glucose and insulin levels in the mouse: evidence for the involvement of sympathetic regulation. *Schizophr. Bull.* Aug 14 [Epub ahead of print].

these papers and how they contribute to the potential or likely biologic mechanism of Seroquel to produce metabolic effects including weight gain, hyperglycemia, and diabetes.

Cope *et al.* (2005) provides a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report development of a mouse model to evaluate the effects of anti-psychotic drugs on food consumption, body weight, and body composition. This model development was undertaken in order to assist in understanding the known effects of some anti-psychotic drugs to induce significant weight gain in patients undergoing pharmacological treatment. The authors report that 4 weeks treatment with olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone, or risperidone caused significant weight increases in mice but only olanzapine and quetiapine were associated with significantly increased food intake. The authors also conclude that their mouse model of anti-psychotic-induced weight gain resembled the human experience with these medications. It should be noted that animals treated with quetiapine showed a dose-response effect on food consumption (see page 611 of Cope *et al.* 2005). Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced weight gain that is related to increased caloric intake.

Dwyer and Donohoe (2003) also provide a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report use of the same mouse strain used by Cope *et al.* (2005), C57BL/6J mice, of the same age range but a different sex (Cope *et al.* used only female animals while Dwyer and Donohoe employed only male animals). Interestingly, using only a single dose of 10 mg/kg/day of Seroquel (a dose that would be equivalent to giving 700 mg to a 70 kg human; a dose within the therapeutic range for humans), the authors reported statistically significant increases in blood glucose levels at both 30 minutes and 3 hours after dosing. The authors also reported that inhibition of glucose transport was correlated with the hyperglycemic responses seen in the animals. It is the inhibition of glucose transport that

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[19] Vestri, H.S. et al. 2007. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. *Neuropsychopharmacology* 32:765-772.

[20] Cope, M.B. et al. 2005. Antipsychotic drug-induced weight gain: development of an animal model. *Int. J. Obesity.* 29:607-614.

is proposed as an underlying biologic mechanism for Seroquel as well as the other drugs shown to have similar activity (*e.g.,* risperidone, clozapine)[21]. Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced hyperglycemia.

Vestri *et al.* (2006) is another paper that provides a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report results of *in vitro* testing to examine the effects of anti-psychotics, including Seroquel, to exert direct cellular effects on insulin action and substrate metabolism in adipocytes (fat cells). The cell lines used are ones routinely used to examine adipocyte functions. The authors reported that quetiapine treatment significantly reduced the lipolytic response to insulin in these cells; normally insulin stimulates lipolysis, or fat breakdown. The effect of quetiapine was similar to the effect seen with olanzapine and clozapine, in terms of potency. Quetiapine also reduced the basal rate of lipolysis in the cells, again similar in potency in producing this effect as compared to olanzapine and clozapine. The authors conclude that they have shown that drugs like quetiapine directly modulate insulin action and metabolic processes, *"and the results are relevant to the high risk of obesity and diabetes conferred by these medications"* (see page 6, left column of Vestri *et al.* 2006). Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced weight gain and diabetes.

Finally, Savoy *et al.* (2008) is another paper that provides a basis for a plausible and scientifically-based mechanism that underlies the metabolic effects of Seroquel. The authors report on the effects of anti-psychotic drugs, including Seroquel, on plasma glucose and insulin levels *in vivo* in mice. Again, it is important to note that the dose of Seroquel administered to the mice was 10 mg/kg, which if given to a 70 mg human would be approximately 700 mg (in the therapeutic range). The authors report that quetiapine produced statistically significant increases in plasma glucose (produced hyperglycemia) but did not significantly increase plasma insulin levels in the mice; a similar effect was reported for olanzapine and clozapine. It is also reported that the strain of mice had an intact glucose-insulin homeostatic mechanism as evidenced by their

[21] It should be noted that there is published literature available which supports the link of these two drugs to hyperglycemia and diabetes as well.

responses seen following glucose administration. The authors reported that the lack of change in insulin levels in the mice with quetiapine treatment indicates that this drug is blocking the acute insulin secretory compensation mechanism that is usually apparent with hyperglycemic responses, an effect that is in agreement with other studies showing inadequate insulin secretion in dogs treated with olanzapine. The authors further suggest that the glucose response seen following treatment with quetiapine, as well as drugs such as olanzapine and clozapine, is driven by activation of the sympathetic nervous system via a central mechanism. Therefore, the results of this paper provide evidence for a biologic mechanism of Seroquel-induced hyperglycemia and diabetes.

Clearly, contrary to the defense counsel's assertions, I have provided a biologic mechanism that is plausible and scientifically-based for the metabolic effects of Seroquel, including a likely mechanism that could be acting independent of the additional weight gain mechanism.

Now, with respect to dose-response assessment and review of the studies I have cited as support for the weight-of-the-evidence, there are a variety of studies in cells, animals and humans, studies that often examine different endpoints. As a result, there is often a lack of dose-response information in any one study. However, as mentioned above with respect to the study by Cope *et al.* (2005), some studies do specifically provide dose-response data. The study by Cope *et al.* (2005), for example, provides dose-response information for weight gain and food consumption in mice, a model for the effects of Seroquel in humans. The AZ clinical trials for Seroquel also provide data on dose-response for weight gain in patients. However, due to the design of most epidemiological studies, such dose-response information is generally not available, a fact that is not an indicator of the lack of an effect for Seroquel but due to the fact that design of such a study would require enormous resources in order to recruit patients at both low and high doses of the drug, across diseases. For example, since higher doses of Seroquel are generally needed in order to treat schizophrenia, much lower doses of Seroquel may be used for less difficult to treat psychiatric conditions. Comparing doses across disease states is thus almost impossible with the epidemiological data currently available due to the way the drug is used by physicians.

There are, however, data from several AZ clinical trials that can be used to examine the dose-response of metabolic effects with Seroquel treatment. For example, data from AZ clinical trial 125 provides evidence that Seroquel treatment produces statistically significant adverse effects on glucose metabolism. Study 125, the AZ study that was supposedly designed to examine the adverse metabolic effects of Seroquel, was a 24 week, open label study comparing effects of glucose metabolism and insulin sensitivity in patients taking Seroquel (mean dose of 607 mg/day), and its closest market competitors, Zyprexa and Risperdal. It was not a blinded study, nor was it placebo-controlled, two important features of well-designed trials. The design of the study did attempt to control for factors which might confound indicators of glucose dysregulation: it was conducted in primarily white Eastern Europeans, with average baseline BMI of 24, and was intended to exclude patients with history of diabetes or recent atypical antipsychotic use. In other words, the study population was, in general, metabolically healthy; this population is not representative of the general population that is exposed to Seroquel. The study report shows that there were statistically significant increases in both mean fasting blood glucose (3.19 mg/dl) and the marker HbA1c (0.122%), indicating that Seroquel may have disrupted the body's ability to regulate glucose in a fasting state. Fasting C-peptide (a measure of endogenous insulin production) also increased, indicating that the patients were now producing more insulin in a fasting state: a marker for insulin resistance. Further, patients taking Seroquel experienced a mean weight gain of 3.65 kg (8 pounds) in just 24 weeks, a large amount of weight increase in a short period of time. The results of Study 125 provide evidence that Seroquel at doses in the range of 600 mg/day causes adverse metabolic effects, and that it may do so by increasing body weight and/or by inducing insulin resistance.

Other AZ clinical studies also provide dose-response information relating to adverse metabolic effects. Data from AZ Clinical Trial Report 50771L0015 reveals that the company observed a dose-response effect of Seroquel on weight gain across the dose range of 75 mg, 300 mg, and 600 mg Seroquel (see Table 45 of report). These effects are supported by data from a recent June 2008 FDA submission by AZ in response to a specific request by FDA to provide detailed analysis of clinical trials with metabolic data. In this recent submission, which I received after my report and deposition transpired, AZ

reported that in placebo-controlled trials with Seroquel, there was a significant increase in fasting blood glucose levels in patients taking Seroquel for a median time of only 55 days, with a significant number of the patients having fasting levels in the range of diabetes (greater than 126 mg/dL; see Table 339 of the report; attached to the Plaintiffs' exhibit submission). Inspection of data in Table 400 of this same report, also attached to the Plaintiffs' exhibition submission accompanying the opposition to the Daubert motion, reveals that in all trials, a list that did not include trials 41 and 49, despite the fact that they did not appear to meet the exclusion criteria, there was still a significant shift to diabetic levels of fasting blood glucose (*i.e.*, greater than 126 mg/dL) with Seroquel treatment after a median treatment time of only 71 days. While AZ does not explicitly articulate in the submission that the findings are statistically significant, it is clear from the reading of the tables and considering the confidence interval that they are, in fact, statistically significant. This is seen when one performs the relative risk (RR) calculation which AZ neglected to include. I calculate that this data resulted in a RR of 1.73 (95% confidence intervals 1.05-2.85) when quetiapine-treated patients from placebo-controlled trials are compared with placebo-treated patients. In addition to the striking consistency among the data in terms of seeing these effects (hyperglycemia that reaches levels indicative of diabetes) across trials, the median time to appearance of the effects are short, in days, characteristic of drug-induced effects, which can occur in days and weeks. I believe the analysis of this totality of clinical trial data itself supports the dose-response nature of the adverse metabolic effects of Seroquel.

It is also important to point out that the dose-response information available for Seroquel and adverse metabolic effects such as weight gain, hyperglycemia and diabetes indicates that these effects of Seroquel can be seen even at low doses. For example, inspection of the tables from the AZ June 2008 FDA submission reveals that data from Table 450 provide evidence for effects of Seroquel to produce hyperglycemia and diabetic level fasting blood glucose at low doses. In Table 450 it is seen that with Seroquel treatment there was a statistically significant increase in the number of patients exhibiting fasting blood glucose levels indicative of diabetes (> 126 mg/dL) as compared to patients receiving placebo, with the average dose of Seroquel administered being only 180 mg for about 56 days of exposure (median exposure duration). The RR can be

calculated to be 2.15 (95% confidence intervals 1.02-4.56) for Seroquel treatment. Further support for the adverse effects of Seroquel even at low doses is found in the paper by Buse et al. (2003)[22]. In this retrospective analysis of a patient claims database, the authors reported that at a mean dose of only 80 mg quetiapine (Seroquel) was associated with a statistically significant increase in the hazard ratio (HR) for development of diabetes with Seroquel treatment to 1.7. Both of these studies provide evidence that the effects of Seroquel to produce adverse metabolic effects are not limited to high doses of the drug.

Finally, defense counsel has suggested that the weight-of-the-evidence opinions I have expressed, that Seroquel can cause adverse metabolic effects that include weight gain, hyperglycemia and diabetes, are not generally accepted. I strongly disagree. In my deposition I discussed with counsel the fact that there are review articles available on diabetes risk and anti-psychotic drugs that state that Seroquel is associated with an increased risk of weight gain as well as diabetes. I would point to the 2004 consensus statement by the American Diabetes Association (ADA 2004) where they conclude by stating that *"These three adverse conditions [obesity, diabetes, and dyslipidemia] are closely linked, and their prevalence appears to differ depending on the SGA [second generation anti-psychotic] used. Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain, diabetes, or dyslipidemia, although they have not been used as extensively as the other agents."* (see page 600, far right column of ADA 2004). Therefore, this panel of experts has singled out certain anti-psychotics as being of greater risk than others in terms of weight gain and diabetes, with quetiapine being one listed has having a greater risk than some of the others. This is again consistent with my opinions where olanzapine would pose a greater risk than Seroquel.

Similarly, I would point the Court to the most authoritative and widely relied upon treatise in the field of pharmacology, *Goodman & Gilman's: The Pharmacological*

[22] Buse, J.B. et al. 2003. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J. Clin. Epidemiol.* 56:164-170.

Basis of Therapeutics, a resource that is available at every hospital formulary and the resource that I used when teaching pharmacology to medical students. This text notes:

> *"**Weight Gain and Metabolic Effects**. Weight gain and its associated long-term complications can occur with extended treatment with most antipsychotic and antimanic drugs. Weight gain is especially prominent with clozapine and olanzapine; somewhat less with quetiapine; even less with fluphenazine, haloperidol, and risperidone; and is very low with aripiprazole, molindone, and ziprasidone (Allison et al., 1999). Adverse effects of weight gain likely include increased risk of new-onset or worsening of type 2 diabetes mellitus, hypertension, and hyperlipidemia. Only some of these consequences are explained by risk factors associated with major psychiatric disorders themselves."*[23]

In addition to this authoritative pharmacology text, there are other textbooks that describe the adverse metabolic effects of anti-psychotic drugs, including Seroquel. The fact that this discussion is found in textbooks is proof of the general acceptance of the fact that Seroquel can cause adverse metabolic effects including weight gain, hyperglycemia, and diabetes. For example, in a textbook entitled "Applied Therapeutics: The Clinical Use of Drugs" it is stated that *"Among the atypical agents, weight gain is most common with clozapine and olanzapine, lowest with ziprasidone and aripirazole, and intermediate with risperidone and quetiapine."*; further that *"The issue of weight gain has important clinical implications in light of the link with impaired glucose tolerance and type II diabetes, hyperlipidemia, and increased mortality."*; further that *"Patients who had no weight gain due to atypical antipsychotics can still develop diabetes mellitus."*[24] In another textbook entitled "Pharmacotherapy Principles & Practice" it is stated that in the case of quetiapine, *"Mild weight gain and minor elevations in triglycerides can occur."*; under the section for antipsychotics that *"As a group, however, they are more likely [than conventional agents] to cause metabolic side effects such as weight gain, glucose dysregulation, and dyslipidemia."*; and further that

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[23] See page 480 of Baldessarini, R.J. and F.I. Tarazi. 2006. Pharmacotherapy of psychosis and mania. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edition.* L.L.

[24] Koda-Kimble, M.A. et al. 2009. *Applied Therapeutics: The Clinical Use of Drugs*, 9th edition. Lippincott Williams & Wilkins: Philadelphia, PA.

"Among the atypical antipsychotic drugs approved for treatment of bipolar disorder, olanzapine is more likely to cause metabolic side effects. Quetiapine and risperidone cause fewer metabolic effects than olanzapine. Aripiprazole and ziprasidone are neutral in effects on weight, glucose, and lipids."[25] These statements provide further support for the fact that the adverse metabolic effect profile of Seroquel is generally accepted by the medical community.

Moreover, the above statements from these medical texts reflect to me, clear general acceptance.

I hold additional relevant opinions as set forth in my expert report in this matter, which is attached and incorporated by reference.

I declare under penalty of perjury that the foregoing is true and correct. Executed this 22 day of November 2008.

Laura M. Plunkett, Ph.D, DABT

[25] Chisholm-Burns, M.A. et al. 2008. Pharmacotherapy Principles & Practice. McGraw-Hill: New York.

IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

IN AND FOR NEW CASTLE COUNTY

IN RE: SEROQUEL LITIGATION C.A. No.: 07C-SER-1

THIS DOCUMENT RELATES TO:

ALL CASES IN FIRST HALF OF
INITIAL TRIAL GROUP

EXPERT REPORT AND DECLARATION OF LAURA M. PLUNKETT, PH.D., DABT

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Producst Liability Litigation
MDL DOCKET NO. 1769
This Document Relates to ALL CASES

EXPERT REPORT OF
Laura M. Plunkett, Ph.D., DABT
September 6, 2008

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies, based in Houston, Texas, is a consulting firm that works at the interface of biological science, regulatory affairs and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral

research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. During this time, I studied drugs of all classes that affect brain function, including anti-psychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions. Much of my focus was on drugs that affect brain function, which includes anti-psychotics.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA, including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on the current labelling regulations and generally acted as a regulatory affairs staff for small companies

in their early stages of product development. A tool common to all work my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. Attached here in Appendix A is a copy of my curriculum vitae.

II. Information Reviewed

7. During the course of work on this case, I have reviewed the following materials:

a) scientific literature relating to the pharmacology and toxicology of anti-psychotic drugs in general and quetiapine (Seroquel) in particular;

b) labelling for Seroquel as provided by the Physician's Desk Reference; and

c) regulations of the U.S. Food and Drug Administration (FDA) relating to the development, approval, labelling and marketing of prescription drug products.

III. Summary of Bipolar Disorder and Schizophrenia

8. Schizophrenia is a major mental illness described by the Diagnostic and Statistical Manual of Mental Disorders ("DSM IV") as a psychotic disorder that is a chronic, severe and disabling brain disease. The hallmark of schizophrenia is disordered thought and perception. Typical symptoms include delusions and hallucinations. While most people diagnosed with schizophrenia are not gainfully employed, a substantial minority do have gainful employment.

9. Bipolar disorder is described by the DSM IV as a mood disorder. Bipolar disorder is a major mental illness, the hallmark of which is manic episodes marked by a euphoric, irritable or expansive mood. Patients with bipolar disorder usually also experience major depressive episodes.

IV. Atypical Anti-psychotics

10. The primary class of drugs used to treat symptoms of schizophrenia and bipolar disorder is known as anti-psychotics. Additionally, mood stabilizers or anti-depressants may also be used to treat bipolar disorder.

11. Anti-psychotics fall into two general categories: the newly developed atypical anti-psychotics and the older, conventional or typical anti-psychotics. The term "atypical" is

applied to the newer drugs mainly because of the lower risks of adverse neurological effects known as extrapyramidal effects. As a general rule, because many atypical anti-psychotics (including Seroquel) still have patent protection, generic versions are not available and as such they are more expensive to purchase and, as a result, more profitable to the manufacturer.

12. Conventional, or typical, anti-psychotics as a group include drugs of a number of different chemical classes. These drugs have efficacy to treat both bipolar disorder and schizophrenia but also often exhibit significant side effects, including risk of acute and long-term neurological side effects, including extrapyramidal effects.

13. Atypical anti-psychotic drugs are considered as having less of a risk of producing extrapyramidal side effects, the unwanted neurological effects that are characterized by changes in movement. In fact, the goal of introducing atypical anti-psychotics to the marketplace was to provide an effective treatment that also improved the quality of life of the patient. While the exact mechanisms responsible for the pharmacological differences between typical and atypical anti-psychotics have not yet been clearly defined, differences have been identified in the pattern of brain neurotransmitter receptor systems affected by the various drugs, effects that can be seen in responses elicited in animal models and/or effects that relate to the pharmacological and toxicological responses in humans.

14. Anti-psychotics will only treat the symptoms of schizophrenia and bipolar disorder; there is no "cure" for such disorders. The etiology of schizophrenia and bipolar disorder also remains to be elucidated, although genetics appears to play some role in these disorders.

15. Quetiapine, marketed in the U.S. under the trade name of Seroquel, is a widely prescribed prescription drug product that was approved by the FDA in 1997 for the treatment of schizophrenia. Seroquel was subsequently approved for management of acute manic episodes associated with bipolar disorder in 2004. I believe that Seroquel is also widely prescribed for off-label uses, including the treatment of sleep disorders, control of agitation, anxiety, aggression and behavioural disturbances.

16. The psychotic symptoms treated with atypical anti-psychotic drugs such as Seroquel include disordered thought processes, disorganized and/or irrational behaviour, and degrees of altered mood, from severe agitation to severe withdrawal. Other drugs that have been or are used in the treatment of psychotic disorders include phenothiazines (*e.g.*, chlorpromazine, also known as Thorazine; thioridazine, also known as Mellaril), thioxanthines (*e.g.*, chloprothixene, also known as Taractan; thiothixene, also known as Navane), haloperidol (Haldol), clozapine (Clorazil), aripiprazole (Abilify), loxapine (Loxitane), molindrone (Moban), pimozide (Orap), olanzapine (Zyprexa), riperidone (Risperdal), and ziprasidone (Geodon). The optimum therapy for treating schizophrenia and bipolar disorder is chosen for each patient based on the patient's medical history, including any risks of known side effects of the drug, and the patient's response to the drug in relation to the drug's efficacy and adverse events.

17. The pharmacology of Seroquel and other similar anti-psychotic drugs is described in many textbooks and review articles (*e.g., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edition.* 2006. Brunton, L.L. et al. (eds.), McGraw-Hill: New York, chapter 18). Seroquel produces its therapeutic and adverse effects through its activity on various receptor systems in the brain and throughout the body. Seroquel is known to be an antagonist of D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, H_1, α_1, and α_2 receptors. The efficacy of Seroquel and other atypical anti-psychotic drugs has been linked to dopaminergic and serotonergic system antagonist activity. However, the exact mechanism by which atypical anti-psychotic drugs produce their effects in schizophrenia and bipolar disorders is not known.

V. Seroquel and Associated Health Risks

18. Seroquel is well absorbed following oral administration, with peak concentrations achieved in the blood within 1.5 hours, and an elimination half-life in the range of 6 hours. It is widely distributed in the body and steady state blood levels are achieved within a few days. Following oral administration, Seroquel is extensively metabolized although the major metabolites are not pharmacologically active.

19. Seroquel use has been associated with deaths that have been attributed to severe liver, kidney, and pancreatic damage. Its adverse effects include, but are not limited to,

ketoacidosis, pancreatitis, diabetes mellitus, weight gain, hyperglycemia, blindness, increased thirst, and hypoglycemia. Other serious injuries associated with Seroquel use include: a potentially fatal condition known as neuroleptic malignant syndrome (NMS); tardive dyskinesia, which can cause potentially irreversible, involuntary movements; and other serious health problems associated with the onset of diabetes including heart disease, blindness, coma, seizures and death. These adverse health effects have been reported following both short-term and longer-term use of Seroquel.

20. Some of the adverse health effects associated with Seroquel use have been attributed to activity of the drug on certain receptor systems in the body. For example, orthostatic hypotension seen in some patients administered Seroquel is thought to be attributed to α_1-adrenergic antagonist activity of the drug while somnolence has been attributed to antagonism of histamine type 1 (H_1) receptors by Seroquel.

21. While Seroquel is similar in basic pharmacological profile to other atypical anti-psychotic drugs, including olanzapine and risperidone, the potency of Seroquel as an antagonist at D_2 and 5-HT_{2A} receptors is less than either olanzapine or risperidone. Differences in potency as an antagonist at certain receptor types may explain some of the differences observed among the various atypical anti-psychotics in terms of both efficacy and toxicity.

22. It has been known for decades that many anti-psychotic drugs have effects to alter metabolism that can lead to weight gain and effects on glucose metabolism (*e.g.*, Baldessarini, R.J. 1980. Drugs and the treatment of psychiatric disorders. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 6th edition.* A.G. Gilman et al. (Eds.), chapter 19, MacMillan Publishing Co.: New York). However, it has been recognized more recently (since about 1999) that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain and changes in glucose metabolism, as well as the onset of diabetes (*e.g.*, Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723; American Diabetes Association et al. 2004. *Diabetes Care* 27:596-601; Allison, D.B. et al. 1999. *Am. J. Psychiatry* 156:1686-1896; Bobes, J. et al. 2003. *Schizophr. Res.* 62:77-88; Wetterling, T. 2001. *Drug Saf.* 24:59-73; Buse, J.B. et al. 2003. *J. Clin. Epidemiol.* 56:164-170). Moreover, it has

now been recognized that clinically significant hyperglycemia and diabetic complications can occur during anti-psychotic treatment both with and without changes in body weight (Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiatry* 59:337-345; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93). Because of the differences apparent among different anti-psychotic agents in terms of risks of diabetes and weight gain, the effects of Seroquel cannot be considered simply a "class" effect for atypical anti-psychotic drugs (Newcomer, J.W. 2005. *CNS Drugs* 19(Suppl. 1):1-93). Different anti-psychotic drugs, including the second generation atypical anti-psychotic agents, have different toxicological profiles.

23. Between January 1997 and July 2002, numerous adverse drug event reports were submitted to the FDA. These reports indicated that patients consuming Seroquel experienced significant adverse health effects, including hyperglycemia, diabetes, exacerbation of pre-existing diabetes, ketoacidosis, and death. These adverse event reports were discussed in an article by Koller *et al.* (2004. *J. Clin. Psychiatry* 65:857-863). The authors concluded that use of Seroiquel may unmask or precipitate hyperglycemia in patients.

24. Case reports linking Seroquel use with hyperglycemia and/or diabetes appeared in the published literature as early as 1999 (*e.g.*, Sobel *et al.* 1999. *J. Clin. Psychiatry* 60:556-557).

25. A large study involving the U.S. Veterans' Administration (Sernyak, M.J. *et al.* 2002. *Am. J. Psychiatry* 159:561-566) was performed in 1999 where records from all patients being treated nationally with anti-psychotics were examined. The authors reported that there was an increased risk of diabetes with exposure to certain anti-psychotic drugs. One of the drugs shown to be associated with an increased risk was Seroquel.

26. At a conference in Europe in 2002, Lambert and colleagues reported the results of a matched case-control study of California Medicaid claims data from 1997 through 2000. They found that there was an increased risk of developing type II diabetes in patients exposed to Seroquel (Lambert *et al.* 2002. *Eur. Neuropsychopharmacol.* 12:S307).

27. In or about August of 2003, a report in the *Wall Street Journal* showed that a study of 19,878 U.S. military veterans between October 1998 and October 2001 indicated that

Seroquel and other members of the new class of anti-psychotic drugs posed a higher risk of diabetes. The article stated that effects were most pronounced with Seroquel.

28. At a conference of the *International Society for Pharmacoepidemiology* held in Philadelphia on August 23 and 24, 2003, study data were reported that showed that patients on Seroquel had 3.34 times as many cases of diabetes as those on older antipsychotic drugs.

29. When considered as a whole in a weight-of-the evidence assessment, the available scientific data indicate that Seroquel can cause physiological effects known to be risk factors for diabetes, including increased body weight and other metabolic effects, and can cause diabetes itself. The scientific data include case reports published on an ongoing basis since 1999 (Sobel, M. et al. 1999. *J. Clin. Psychiatry* 60:556-557; Procshyn, R.M. et al. 2000. *Can. J. Psychiatry* 45:668-669; Wilson, D.R. et al. 2002. *Schizophr. Res.* 59:1-6; Domon, S.E. and C.S. Cargile. 2002. *J. Am. Acad. Child Adolesc. Psychiatry* 41: 495-496; Sneed, K.B. et al. 2003. *J. Am. Board Fam. Pract.* 16:251-254), clinical data (*e.g.*, Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Wirshing, D.A. et al. 2002. *J. Clin. Psychiatry* 63:856-865; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96; the product insert for Seroquel in 2005, *Physician's Desk Reference*, pp. 662-667), a survey of adverse drug reports (Koller, E.A. et al. 2004. *J. Clin. Psychiatry* 65:857-863), epidemiological data assembled since 1999 (Sobel et al. 1999. *J. Clin. Psychiatry* 60:556-557; Sernyak, M.J. et al. 2002. *Am. J. Psychiatry* 159:561-566; Ollendorf, D.A. et al. 2004. *MedGenMed* 6:5; Citrome, L. et al. 2004. *Psychiatr. Serv.* 55:1006-1013; Leslie, D.L. and R.A. Rosenheck. 2004. *Am. J. Psychiatry* 161:1709-1711; Feldman, P.D. et al. 2004. *J. Am. Med. Dir. Assoc.* 5:38-46; Sacchetti, E. et al. 2005. *Int. Clin. Psychopharm.* 20:33-37; Lambert, B.L. et al. 2006. *Am. J. Epidemiol.* 164:672-681; Guo, J.J. et al. 2006. *J. Clin. Psychiatry* 67:1055-1061; Guo, J.J. et al. 2007. *Pharmacotherapy* 27:27-35), and animal data (Cope, M.B. et al. 2005. *Int. J. Obesity* 29:607-614). Each source of information is important in the analysis of the risks associated with

use of Seroquel, and is consistent with accepted methods for establishing causation in a weight-of-the-evidence analysis (Hill, A.B. 1965. *Proc. Royal Soc. Med.* 58:295-300).

30. I believe that the available scientific data demonstrate that Seroquel consumption and use can cause adverse metabolic effects that include, but are not limited to an increased risk of clinically significant body weight gain, hyperglycemia, altered glucose metabolism, and an increased risk of diabetes and diabetes-related complications.

31. It is also important to remember that although clinical trials had been performed with Seroquel as part of the drug development process, such trials are limited in their ability to identify risks associated with drug use by the general population. This is because such drug development clinical trials are performed in either healthy volunteers or in patients that have often been pre-screened for the propensity to develop adverse effects such as hyperglycemia or diabetes, with such patients then usually excluded from studies. It is only after a drug has been placed on the market, and wider exposure is seen, that a true picture of the adverse effects associated with a drug can be observed. As a result, I believe that companies have the duty to carefully monitor their drugs after approval and during marketing for either the existence of new adverse events or a higher than expected incidence of known adverse effects.

32. Scientific studies have established that there are apparent differences among anti-psychotic drugs in terms of risks of diabetes, weight gain and other adverse health effects discussed above. As a result of these differences, and differences in toxicological profiles, I believe that side effects arising through the consumption of Seroquel cannot be described as a "class effect" for all atypical anti-psychotic drugs.

33. Finally, when considering the adverse health effects associated with use of Seroquel, it is important to realize that Seroquel is not unique in terms of its efficacy. Studies have shown that other anti-psychotic drugs have similar effectiveness to Seroquel but have less risk for hyperglycemia, weight gain, metabolic disturbances and diabetes. Therefore, there are safer alternative therapies that could be used that would also provide for effective treatment but with fewer side effects.

34. For example, in the CATIE Schizophrenia Trial, a trial sponsored by the National Institute of Mental Health which is the largest trial conducted to date comparing efficacy and safety of some of the most prescribed anti-psychotic drugs, it was shown that clozapine was more effective than other atypical anti-psychotics (*i.e.*, Seroquel, Zyprexa, Risperdal). Further, when all of the atypical agents studied were examined, including Seroquel, none of the agents was more effective or better tolerated than the typical anti-psychotic, perphenazine (Manschreck, T.C. and R.A. Boshes. 2007. *Harv. Rev. Psychiatry* 15:245-258; Nasrallah, H.A. 2007. *J. Clin. Psychiatry* 68:5-11).

VI. Mechanisms Underlying the Adverse Effects of Seroquel

35. Although the exact molecular mechanisms responsible for the metabolic effects of Seroquel have not been established, there are data that describe the basic mechanisms that lead to the effects of Seroquel on body weight gain and altered glucose metabolism, and eventually diabetes. However, weight gain is not a prerequisite for atypical anti-psychotic drug-induced effects on glucose metabolism and induction of type II diabetes (Newcomer, J.W. 2004. *Clin. Ther.* 26:1936-1946; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93; Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2002. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2001. *Am. J. Med.* 111:716-723; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

36. Clinically significant body weight gain is often seen with administration of Seroquel to patients (Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96). The effects of atypical anti-psychotics on weight gain have been shown to be attributable to both increased caloric intake (increased appetite) and decreased energy expenditure (Gothelf, D. et al. 2002. *Am.*

J. Psychiatry 159:1055-1057; Virkkunen, M. et al. 2002. *Pharmacopsychiatry* 35:124-126). These mechanisms for increased body weight gain are consistent with the fact that Seroquel has effects on neurotransmitter systems in the brain that affect appetite and mood. It is well-established in the medical literature that a clinically significant increase in body weight is a risk factor for diabetes (*e.g.*, Foster, D.W. 1994. Diabetes mellitus. In: *Harrison=s Principles of Internal Medicine, 13th edition.* K.J. Isselbacher et al. (Eds.), chapter 337, McGraw-Hill: New York). Therefore, any effect of Seroquel to increase body weight is a significant risk for the development of diabetes.

37. As discussed above, Seroquel administration to patients has been linked to an increased risk of type II diabetes (see the weight of the evidence discussion above). The mechanisms responsible for development of type II diabetes have been examined in both animals and humans. Type II diabetes is a disorder that is characterized by normal or high levels of insulin in blood at the same time that glucose levels in blood are elevated. The condition is sometimes referred to as insulin resistance. Insulin normally acts to promote transport of glucose across cell membranes (reducing blood glucose levels) and to inhibit lipolysis. Resistance to the activity of insulin leads to hyperlipidemia and eventually to hyperglycemia and even development of diabetes. Although increased weight gain has been discussed as a likely factor in the development of insulin resistance and drug-induced diabetes, there are data that demonstrate Seroquel-induced effects on glucose metabolism and insulin resistance that are independent of weight gain.

38. Observational data has shown that atypical anti-psychotics that are structurally similar to Seroquel (*i.e.*, clozapine and olanzapine) can exert direct effects on glucose-insulin homeostasis by induction of hyperinsulinemia (Melkersson, K.I. et al. 2003. *Psychopharmacology* 170:157-166; Melkersson, K.I. et al. 2000. *J. Clin. Psychiatry* 61:742-749). The increased levels of insulin lead to decreased insulin sensitivity in tissues and could lead to an insulin-resistant state (Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723). *In vitro* data have shown that olanzapine stimulates insulin release from pancreatic islet cells (Melkersson, K. 2004. *Eur. Neuropsychopharmacology* 14:115-119). Regardless of the exact molecular changes that may occur in any one patient treated with Seroquel, these data indicate

that atypical anti-psychotics that are pharmacologically and chemically similar to Seroquel have direct and indirect effects on glucose metabolism that are consistent with the development of insulin resistance, hyperglycemia and potentially type II diabetes. Considered together, the mechanistic data provide evidence for both direct and indirect effects that can lead to disturbances in glucose metabolism and development of type II diabetes. These findings are supported by findings with atypical anti-psychotic drugs, including data specific to Seroquel, that have linked the drugs to induction of diabetes, apart from the induction of weight gain (Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2003. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2004. *J. Clin. Psychiatry* 65:857-863; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

39. The data indicate that administration of Seroquel can cause diabetes and/or the effects on glucose metabolism that can lead to diabetes. The data also indicate that Seroquel poses a greater risk for hyperglycemia and diabetes, both with and without body weight gain, than some other anti-psychotic drugs.

40. Although available studies have focused on the association of type II diabetes with Seroquel treatment, as well as treatment with other atypical anti-psychotic drugs, the toxicity of these drugs, which includes altered glucose metabolism, obesity, and hyperglycemia, would also be significant risk factors for individuals with undiagnosed type I diabetes or a genetic predisposition for type I diabetes. Type I diabetes is characterized by a loss of insulin secretion capacity due to the loss of beta cells in the pancreas. The loss of insulin secretion capacity means that type I diabetics would need to rely on exogenous sources of insulin to control blood glucose levels. Therefore, it is only common sense that any effects of a drug such as Seroquel to affect glucose metabolism or blood glucose levels would be a greater risk for individuals who already are at risk of type I diabetes or who are not yet exhibiting clinical signs and symptoms of type I diabetes.

VII. Warning of Health Risks

41. Despite the findings of the studies discussed above, AstraZeneca failed to warn the FDA, physicians, other health practitioners, and patients of the adverse metabolic effects associated with the consumption of Seroquel at the time these risks were first identified.

42. A review of the most recent product labelling for Seroquel that is available to health professionals demonstrates that, in my opinion, the warnings related to risks of hyperglycemia and diabetes in particular are not adequate to convey the risks posed by Seroquel itself. The discussion of hyperglycemia and diabetes is put forth as an effect of anti-psychotics in general only.

43. At the time that the Seroquel labelling failed to adequately warn physicians of the risks associated with use of the drug, other international regulatory bodies were requiring specific changes to product labelling related to the risks of hyperglycemia and diabetes that were associated with Seroquel, not anti-psychotics in general. For example, in Japan, physicians were being specifically warned to not use Seroquel in patients with a history of diabetes and to monitor patients for development of glucose abnormalities during treatment with Seroquel, regardless of their medical history. Additionally, in 2005 permission to market Seroquel in France had been denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Accordingly, I believe that the physicians in the U.S., and as a result their patients, were not being supplied with adequate risk information related to hyperglycemia and diabetes even though actions had been taken in other countries to warn physicians and patients of these risks.

44. As a result, I believe that the product warnings were wholly inadequate to warn physicians and their patients of the significant adverse metabolic effects associated with the consumption of Seroquel. Nonetheless, Seroquel was marketed heavily as safe and effective for the treatment of bipolar disorder and schizophrenia, promising fewer side effects than other similar treatments including the other atypical anti-psychotics on the market. Further, Seroquel was being prescribed by physicians for treatment of conditions other than bipolar disorder and schizophrenia (off-label use), which use I believe was known by Astra-Zeneca.

VIII. Conclusion

45. In conclusion, based on my training and experience as a pharmacologist, toxicologist, and risk assessor, it is my opinion that Seroquel can cause hyperglycemia and diabetes. The adverse health effects, including these adverse metabolic effects, associated with the consumption and use of Seroquel were predictable based on the known pharmacological profile of the drug and would have been predicted prior to the approval of Seroquel based on the known effects of other structurally similar anti-psychotic drugs. Moreover, the adverse health effects associated with Seroquel consumption and use can be serious, life-threatening conditions and were recognized in the published medical literature soon after the drug was approved. All opinions expressed in this report are based on a reasonable degree of scientific certainty.

IX. Compensation

46. My compensation by plaintiff's attorney in this matter is at the rate of $300.00 per hour for review of documents and materials related to the case and $400.00 per hour for testimony.

X. Previous Testimony

47. A list of my previous testimony for the past four years is included in Appendix B.

I certify that the foregoing statements made by me are true and correct. Executed this 6th day of September 2008 at Houston, Texas.

LISA GONZALES
MY COMMISSION EXPIRES
February 15, 2009

Laura Plunkett, Ph.D., D.A.B.T.

STATE OF TEXAS)

) ss.

COUNTY OF HARRIS

Subscribed and sworn to me

Before this 6th day of Sept 2008.

Signature of Notary Public

My Commission Expires February 15, 2009