EXHIBIT 44

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	**MDL DOCKET NO.**
This document relates to:	**6:06-MDL-1769-ACC-DAB**
ALL CASES	

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

1. My name is Laura M. Plunkett. I am competent to make this declaration, and the facts stated herein are within my personal knowledge and are true and correct.

2. I am a pharmacologist, toxicologist, United States Food and Drug Administration ("FDA") Regulatory Specialist and principal of a consulting company known as Integrative Biostrategies, L.L.C. Based in Houston, Texas, Integrative Biostrategies 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.

3. I am board certified as a Diplomat of the American Board of Toxicology. I am a member of several professional organizations and have authored or coauthored numerous scientific publications. I have over 20 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.

4. 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.

5. 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 at 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.

6. 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 graduates students in pharmacology and toxicology as well as the neurosciences. During this time I studied drugs of all classes that affect brain function, including antipsychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions.

7. From December of 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 with 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 current labeling regulations and generally acted as a regulatory affairs staff for small companies in early stages of product development. A tool common to all my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. I have attached hereto a copy of my curriculum vitae and the expert report I prepared for the Plaintiffs in this litigation, which are attached hereto as Exhibits A and B respectively, and incorporated by reference herein.

8. In my regulatory affairs experience and work with prescription drugs, as well as through my knowledge, skill, training, and experience as a pharmacologist, I am knowledgeable about the "warning" standard established in 21 C.F.R. § 201.57(e). That section requires that drug warnings "shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should have been taken if they occur." Importantly, "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." I am also knowledgeable of the fact that, by law, a prescription

drug "label" includes promotional and marketing materials associated with the drug as well as the "package insert" accompanying the drug's packaging.

9. Based on my knowledge, skill, training, and experience as a pharmacologist and toxicologist and in working with prescription drugs, I am further able to assess the risks associated with a particular drug and, in particular, identify whether the standard "reasonable association of a serious hazard with a drug" is consistent with information related to drug risks and hazards that was known or should have been known by the drug manufacturer. After my review and analysis of AstraZeneca company documents, as well as based on my review of peer-reviewed medical literature pertinent to Seroquel and other antipsychotics, I have formed the following opinions with respect to the adequacy—specifically the accuracy, clarity, and unambiguousness—of Seroquel's labeling from 1999 to present, premised on whether AstraZeneca provided a warning "as soon as there [was] reasonable evidence of an association of a serious hazard" with Seroquel.

10. Regarding the label/package insert accompanying Seroquel from 1999 to the present, studies that I have reviewed reveal that weight gain has long been identified as a serious side effect of anti-psychotic drugs. However, it has also been recognized more recently, according to the pertinent medical literature, that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain. When considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel can cause serious health effects that pose a risk to a person's health, such as weight gain. Further, my review of AstraZeneca's own documents revealed that the company was aware of the propensity for Seroquel to cause rapid, clinically

significant weight gain. For example, 1997 internal correspondence that I have reviewed show that the company's "Study 15" indicated that weight gain was "rapid," "consistent," "clinically significant," "dose related," and "doesn't stop" during Seroquel treatment. Additionally, by 1999, Dr. Joyce Small, who conducted the company's "Trial 8" for Seroquel, wrote that because the second generation antipsychotics clozapine, olanzapine, and quetiapine "cause the most weight, these drugs may be most likely to induce diabetes." By 2000, AstraZeneca's Global Drug Safety Physician had stated in a company "Safety Position Paper" that there was "reasonable evidence" to suggest that Seroquel "can cause" diabetes, as Dr. Small predicted would result by Seroquel causing clinically significant weight gain. The above constitutes reasonable evidence of an association of a serious hazard with Seroquel.

11. It is my opinion, therefore, that the 1999-present label/package insert with respect to weight gain is inaccurate, unclear, and ambiguous because the so-called "warning" of weight gain is not contained under the "Warnings" section of the label, but appears much further into the body of the label/package insert in the "Adverse Reactions" section—literally dozens of paragraphs after the "Warnings" section, which is near the top of the label. The weight gain information also fails to describe any of the serious, potentially life threatening side effects associated with weight gain—namely diabetes mellitus and hyperglycemia—of which AstraZeneca was aware. Because there existed reasonable evidence of an association with Seroquel and weight gain, and the company did not revise the label to clearly, accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

12. Moreover, the promotional and marketing materials utilized by the company with regard to weight gain also constituted "label" information that were unclear, inaccurate, and ambiguous in part because they directly contradicted the information contained, for example, in the adverse reactions section of the package insert. For example, the materials that I have reviewed, including Dr. Brecher's 2000 article and Dr. Nasrallah's 2002 article, informed doctors that Seroquel did not cause weight gain or that Seroquel had a favorable weight profile. A handout discussing Dr. Reinstein's experiences with Seroquel in his patients, which I have reviewed, suggested that weight loss along with improvement of diabetes was a beneficial side effect of Seroquel. AstraZeneca has also repeatedly stated in sponsored literature and marketing material that I reviewed (such as the Nasrallah and Brecher articles) that there is not a dose-dependent relationship between Seroquel and weight gain. I have also reviewed other sales and marketing "messages" or "themes" that were used by AstraZeneca salespersons in direct contact with physicians during this same time period. Those "messages" or "themes" included claims that Seroquel is "weight neutral," or causes "minimal weight gain" or has a "favorable weight profile." The sales messages contradicted what AstraZeneca knew to be true about Seroquel and weight gain, but also ran counter to Seroquel's own Adverse Reactions section of the label/package insert, which showed (and still shows) that 23% of Seroquel users will experience clinically significant weight gain. For those additional reasons, Seroquel's "label" information regarding "weight gain"—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous with respect to warning about weight gain.

13. Regarding the label/package insert accompanying Seroquel from 1999 to 2004 concerning hyperglycemia and diabetes mellitus, studies that I have reviewed reveal that, when considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel can cause serious metabolic effects that adversely impact health including diabetes and hyperglycemia, effects that can even become life-threatening if not treated. Further, my review of AstraZeneca's own documents reveals that the company was aware of an association with Seroquel and hyperglycemia/diabetes since at least 1999, when Dr. Small recognized after Trial 8 that Seroquel and two other antipsychotic drugs caused the most weight gain and also were likely to cause diabetes. In 2000, as noted above, the company's Global Drug Safety Physician concluded that Seroquel can cause impaired glucose dysregulation including diabetes. In addition, by November 2002, the Japanese government had evidently reached a similar conclusion, requiring that AstraZeneca send a "Dear Doctor" letter to Seroquel prescribers informing them of the increased risk of diabetes and related complications and mandating that (a) Seroquel not be administered to patients with a history of diabetes; (b) patients treated with Seroquel be monitored carefully including measurement of blood glucose levels; and (c) information regarding the severe adverse reactions that may occur, including diabetic ketoacidosis and diabetic coma, must be fully explained to the patient and family. The above constitutes reasonable evidence of an association of a serious hazard with Seroquel.

14. It is my opinion, therefore, that the 1999-2004 label/package insert with respect to hyperglycemia/diabetes is inaccurate, unclear, and ambiguous because the so-called "warning" of diabetes and hyperglycemia is not contained under the "Warnings"

section of the label, but appears (again) in the "Adverse Reactions" section of the label/package insert. That section mentions the words "diabetes" and "hyperglycemia" once, and classifies those reactions as "infrequent." The diabetes and hyperglycemia risk is also distorted by the fact that "hypoglycemia" and "weight loss" are also listed as infrequently occurring adverse reactions. As the manufacturer of Seroquel, AstraZeneca was under a duty to revise the label as soon as there was reasonable evidence of an association with the serious health hazards of hyperglycemia and diabetes. Because there existed reasonable evidence of an association with Seroquel and hyperglycemia and diabetes, and the company did not revise the label to clearly, accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

15. Moreover, the promotional and marketing materials utilized by the company with regard to Seroquel and hyperglycemia and diabetes risks during this period also constitute "label" information that was unclear, inaccurate, and ambiguous because it too downplayed the severity of the risk of hyperglycemia and diabetes associated with Seroquel treatment. For example, a study by Dr. Reinstein that was shown to, distributed to, and/or discussed with Seroquel prescribers, the integrity of which has since been discredited, implies that Seroquel patients lost weight and their diabetes was cured after taking Seroquel for ten weeks. For those additional reasons, Seroquel's "label" information regarding hyperglycemia and diabetes—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous.

16. Regarding the label/package insert accompanying Seroquel from 2004 to 2007 concerning hyperglycemia and diabetes mellitus (the so-called "class warning"), studies that

I have reviewed reveal that, when considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel's effect on weight gain and blood glucose levels differed from some other members of the class of second generation anti-psychotics. Further, the class warning does not describe accurately or clearly the rate and severity of hyperglycemia and diabetes risk associated with Seroquel uniquely, as opposed to other second generation anti-psychotics generally. For example, studies and medical literature that I have reviewed indicate that Abilify and Geodon, two of Seroquel's competitors, are not associated with statistically significant weight gain or hyperglycemia/diabetes to the critical degree that Seroquel has such an association.

17. The warning contained on the 2004-2007 label simply states that hyperglycemia and diabetes "has been reported." The warning is also qualified by statements that elevations in the rates of occurrence of hyperglycemia/diabetes in the schizophrenic or general populations may be confounding factors. In addition, AstraZeneca documents that I have reviewed show the company was aware of this risk long before and during this time period. For example, before and during that time, other international regulatory bodies were requiring specific changes to Seroquel's product labeling related to risks of hyperglycemia and diabetes, but not to anti-psychotics generally—*e.g.,* the Japanese "Dear Doctor" letter. Additionally, in 2005, permission to market Seroquel in France was denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Because there existed reasonable evidence of an association with Seroquel and hyperglycemia/diabetes, and the company did not revise the label to clearly,

accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

18. Additionally, the marketing and promotional materials utilized by the company with regard to Seroquel and hyperglycemia and diabetes risks during this time also constitute "label" information that was unclear, inaccurate, and ambiguous because it minimized the severity and frequency of the risk of hyperglycemia and diabetes associated with Seroquel treatment. For example, I have reviewed AstraZeneca documents evidencing that the Reinstein study and the Brecher article were still being disseminated during this time period. In 2006, the FDA Division of Drug Marketing, Advertising, and Communications (FDA DDMAC) admonished the company because it had not satisfactorily disclosed information concerning hyperglycemia and diabetes risks—in accord with the then, current "class warning"—causing the FDA DDMAC to determine that the promotional materials were "misleading" and "undermined the warning." For those additional reasons, Seroquel's "label" information regarding hyperglycemia and diabetes—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous.

19. Regarding the label that now accompanies Seroquel, that label (which was revised in or about October 2007) still fails to accurately, clearly, and unambiguously warn of Seroquel's dangers relative to diabetes. Following the cross-reference contained in the "Warnings" section to the "Adverse Reactions" reactions section, one sees that "diabetes" is never mentioned in the Adverse Reactions section. However, the data contained in that section shows that, in two long-term clinical trials, Seroquel users exhibited diabetes-level

hyperglycemia more than two times as often as subjects taking placebo. The fact that the Warnings section itself does not mention the disturbing rate with which Seroquel is associated with diabetes renders the warning patently unclear, inaccurate, and ambiguous.

20. The shortcomings of the Warnings section are exacerbated by the Adverse Reaction section's characterization of diabetes-level hyperglycemia as merely "hyperglycemia" and "increased blood sugar." (Fasting blood glucose $\geq$ 126/mg/dl or non-fasting blood glucose $\geq$ 200/mg/dl, as identified in the Adverse Reactions section, is diabetes, not merely "hyperglycemia," according to my knowledge, training, and review of the medical literature identified in my report.). Furthermore, I have reviewed an AstraZeneca internal document in which Seroquel's risk of diabetes-level blood glucose dysregulation is characterized as "common." Because there exists reasonable evidence of an association with Seroquel and diabetes, yet the company failed to revise the label to state the risk of "diabetes" rather than simply "hyperglycemia," the company did not revise the label as required, and it is therefore inaccurate, unclear, and ambiguous.

21. I have reviewed June 2008 FDA correspondence to AstraZeneca regarding the 2007 label indicating that the FDA also deems the current label inadequate. The FDA has requested that AstraZeneca modify the information in the Adverse Reactions section to explain potential design limitations in the studies from which the data mentioned in the above paragraph was drawn. The FDA states that the more than two-fold increase in Seroquel patients contracting diabetes over placebo patients in the studies should be clarified by linking the same to "[t]he mean change in glucose from baseline," which "was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo," a more than five-times greater increase. The

FDA also requested that AstraZeneca state that the blood glucose data may be "underestimated" because of the fact that the studies pre-screened participants who could not tolerate Seroquel (including, for example, because of high blood glucose readings) in the open-label phase prior to randomization, effectively dropping those intolerant participants from the studies, and skewing the results in AstraZeneca's favor. After reviewing the current package insert on the Seroquel.com website at the time of executing this Declaration, AstraZeneca has still not adhered to the FDA's request to change the current label as described. For those additional reasons, Seroquel's current label is inadequate because it inaccurately, unclearly, and ambiguously states the risk of diabetes with Seroquel.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 21st day of November, 2008.

Laura M. Plunkett, Ph.D., DABT

CURRICULUM VITAE

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

OFFICE ADDRESS 1223 Melford Drive
Houston, TX 77077-1544

EDUCATION

1984	Ph.D.	Pharmacology	University of Georgia
1980	B.S.	Zoology	University of Georgia

PROFESSIONAL EXPERIENCE

President. Integrative Biostrategies (IB) LLC, 2001- present
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Owner. Plunkett & Associates, Houston, Texas, 1997 – 2001
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Houston, Texas, 1992 – 1997
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Arlington, Virginia, 1989 – 1992
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration.

Assistant Professor. University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, 1986 – 1989

Taught medical and graduate student courses in pharmacology (lecture and laboratory), neurosciences, cardiovascular pharmacology, and neuropharmacology. Performed basic research in area of autonomic control of cardiovascular function and neurochemical systems involved in autonomic function. Recipient of extramural funding from the Arkansas Heart Association (principal investigator).

Postdoctoral fellow. National Institute of General Medical Sciences, Pharmacology Research Associate Training Program, 1984 – 1986

Performed basic research in area of neurochemical control of cardiovascular function and neurochemical systems involved in autonomic function.

Research Assistant. University of Georgia, College of Pharmacy, Department of Pharmacology and Toxicology 1980 – 1984

Taught laboratory courses in pharmacology to pharmacy students as part of graduate student assistantship responsibilities.

HONORS AND AWARDS

Chosen for PRAT program at National Institutes of Health. Pharmacology Research Associate Training Program, 1984-1986.

Rho Chi. The University of Georgia, College of Pharmacy, Initiated, 1984.

Recipient of Excellence in Graduate Research Award. The University of Georgia, College of Pharmacy, 1983.

Alpha Lambda Delta. The University of Georgia Chapter, 1978.

PROFESSIONAL CERTIFICATION

Diplomate, American Board of Toxicology, 1993 to present.

Registered patent agent, 1999.

PROFESSIONAL MEMBERSHIPS

Member, Society for Toxicology 1992 - present

Member, American College of Toxicology, 1997 - present

Member, Society for Risk Analysis, 2007- present

President, Lone Star Chapter of the Society for Risk Analysis, 1998

Counselor, Lone Star Chapter of the Society for Risk Analysis, 1999-2000

Member, Society for Neuroscience 1985 - present

Member, American Association for Pharmaceutical Sciences 1992 - present

Member, Society for Environmental Geochemistry and Health 1992 - present

Member, ASTM Committee E06, 1990 - present

PUBLICATIONS

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ABSTRACTS

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1. **Plunkett LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Florida A&M University, Tallahassee, FL, October 26, 2006.

2. **Plunkett LM.** The guidance as currently implemented: experience with Minnesota's draft risk levels. Presented at the ISRTP workshop entitled: EPA's New (Proposed) Guidance for Assessing Cancer Risks from Early Life Exposures. Genotoxic Mode of Action and Implications for Human Health-Based Standards. Baltimore, MD February 10, 2005.

3. **Plunkett LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 17, 2004.

4. **Plunkett LM.** Moderator of the symposium entitled "Regulation of genetically modified cells, foods, organisms and animals for consumer and therapeutic use. Meeting of the American Association of Pharmaceutical Sciences (AAPS), Baltimore, MD, November 11, 2004.

5. **Plunkett LM.** A Road map to the US Food And Drug Administration Regulations. Invited Speaker and Session Co-chair, Federation of European Biochemical Societies (FEBS), Istanbul, Turkey, October 20-24, 2002.

6. **Plunkett LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 2001.

7. **Plunkett LM .** Differences and Similarities Between Children and Adults in their Exposure and Response to Environmental Chemicals: An Update Since 1992. Invited Speaker at ToxForum, Aspen CO, July 2001.

8. **Plunkett LM.** Do current FIFRA guideline tests protect infants and children? Lead as a case study. Invited speaker at the Sixteenth International Neurotoxicology Conference, Pesticides and Susceptible Populations: Who is at Risk and When? Little Rock, Arkansas, September 13-16 1998

9. **Plunkett LM.** An overview of biotechnology regulations: the USFDA and the USEPA. Lecturer at University of Houston at Clearlake, October 16 1998.

10. Rodricks JV, Santamaria AB, **Plunkett LM.** Risk Assessment as a Tool in Litigation: A Discussion of the Uses and Their Limits [Presented by **Plunkett LM**]. Society for Risk Analysis, , New Orleans, LA. December 10 1996.

11. **Plunkett LM.** Current Issues in Lead Exposure and Risk Assessment. Symposia at the annual meeting of The American College of Toxicology, Valley Forge, PA. November 9 1996.

12. **Plunkett LM .** An Overview of Biotechnology Regulations: Environmental Regulations. Lecturer at the South Texas School of Law, October 1995.

13. **Plunkett LM.** An Overview of Biotechnology Regulations: FDA Regulations. Lecturer at the South Texas School of Law, October 1995.

14. **Plunkett LM .** A Discussion of Toxicokinetics. Featured speaker at a symposium at the Int. Congress of Toxicol., July 5 1995.

15. **Plunkett LM.** Chutes and Ladders: The Hazardous Journey for R&D to Market. Featured speaker at the Futurist's Conference, Irvine, CA, June 28, 1995.

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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

List of Testimony for Dr. Laura M. Plunkett, Ph.D, DABT for previous 4 years

Year	Case Name	Law Firm Represented
2004	*Freeman v. Bayer* *Caldwell v. Bayer* *January 6, 2004*	Beckenstein & Oxford (Beaumont, TX)
2004	*Nichols v. Bayer* *January 7, 2004*	Hare, Wynn, Newell, & Newton (Birmingham, AL)
2004	*Sheets v. Perrigo* *February, 2004*	Miller & Associates (Richmond, VA)
2004	*Crowson v. Davol, Inc.* *April 6, 2004*	Hicks Thomas & Lilienstern, LLP (Houston, TX)
2004	*McAllister v. Metabolife* *Deposition - April 15, 2004*	Fibich, Hampton, Garth & Leebron (Houston, TX)
2004	*Valverde v. Bayer* *May 26, 2004*	Waters & Kraus (Dallas, TX)
2004	*McAllister v. Metabolife* *Trial - June 15, 2004*	Fibich, Hampton, Garth & Leebron (Houston, TX)
2004	*Havey v. Wyeth* *Deposition – July 16, 2004*	Waters & Kraus (Dallas, TX)
2004	*Jensen v. Wyeth* *Deposition – August 12, 2004*	Neilsen & Senior (Salt Lake City, UT)
2004	*Thompson v. Wyeth* *Deposition – August 24, 2004*	Williams, Dailey, O'Leary, Craine & Love (Portland, Oregon)
2004	*Havey v. Wyeth* *Trial – September 14, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Valverde v. Bayer Corp* *Trial – September 29, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Berg v. Bayer* *Deposition – October 13, 2004*	Williams Love O'Leary Craine & Powers, P.C. (Portland, OR)

Year	Case Name	Law Firm Represented
2004	*Turney v. Novartis Consumer* *Deposition – October 19, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Spencer v. Duramed* *Deposition – November 9, 2004*	Ashcraft & Gerel (Washington, DC)
2005	*Hawkins v. Metabolife* *Deposition – February 1, 2005*	Simmons-Cooper, L.L.C. (East Alton, IL)
2005	*Spears v. Swift* *Deposition – February 8, 2005*	Johanson & Fairless, LLP (Sugar Land, TX)
2005	*Sandejo-Villa v. Rexall Sundown, Inc., et al* *Deposition – March 1, 2005*	Snapka, Turman & Waterhouse (Corpus Christi, TX)
2005	*Turney v. Novartis* *Trial – March 7, 2005*	Waters & Kraus (Dallas, Texas)
2005	*Kelly Longoria, Douglas Woody v. Metabolife Intl.* *Deposition – March 14, 2005*	Blizzard Law Firm (Houston, TX)
2005	*Sandejo-Villa v. Rexall Sundown, Inc., et al* *Deposition – April 19, 2005*	Snapka, Turman & Waterhouse (Corpus Christi, TX)
2005	*Vogt v. Wyeth* *Deposition – May 18, 2005*	Ashcraft & Gerel (Washington, DC)
2005	*Crowe v. Perrigo* *Deposition – May 18, 2005*	Ashcraft & Gerel (Washington, DC)
2005	*Moore v. Wyeth* *Deposition – August 17, 2005*	Abraham Watkins Sorrel & Friend (Houston, TX)
2005	*Sheets v. Perrigo* *Deposition – September 12, 2005*	Miller & Associates (Richmond, VA)
2005	*Blanton* *Deposition – November 11, 2005*	Owens & Fazio (Dallas, TX)
2006	*Geers v. Wyeth* *Trial Testimony – January 23, 2006*	Fleming & Associates (Houston, TX)

Year	Case Name	Law Firm Represented
2006	*Smoot v. AST Sports Science, Inc. et. al.* *Deposition– April 26, 2006*	Ashcraft & Gerel (Alexandria, VA)
2006	*Arrigale/Grossberg v. Merck* *Deposition - June 1, 2006*	Robinson, Calcagnie, & Robinson (California)
2006	*Anderson v. Merck* *Deposition – June 5, 2006*	Abraham Watkins (Houston, TX)
2006	*McNeill v. Ford* *Trial Testimony – June 15, 2006*	Fleming & Associates (Houston, TX)
2006	*Miller v. Merck* *Deposition – June 20, 2006*	Abraham Watkins (Houston, TX)
2006	*Rhone-Poulenc* *Deposition – October 4, 2006*	White and Williams, LLP (Philadelphia, PA)
2007	*Allen* *Deposition – January 25, 2007*	Blizzard Law Firm (Houston, TX)
2007	*Arts Street Fire* *Deposition – February 6, 2007*	The Caluda Law Firm (Metairie, LA)
2007	*Zyprexa MDL 1596* *Deposition – April 25, 2007*	Fibich, Hampton & Leebron (Houston, TX)
2007	*Armendariz* *Deposition – June 13, 2007*	Waters & Kraus (Dallas, TX)
2007	*NJ Education Day* *Testimony – July 24, 2007*	Weitz & Luxembourg (New York, NY)
2008	*Arts Street Fire* *Deposition – February 27, 2008*	The Caluda Law Firm (Metairie, LA)
2008	*Steele v. GSK* *Deposition – July 10, 2008*	Tracey Law Firm (Houston, TX)