June 16, 2009

[redacted]
Belmont MA 02478

Dear Mr. [redacted]:

Re: Re: [redacted], Administratrix of the Estate of [redacted] vs. [redacted], MD; [redacted] P.C.; [redacted] Inc., and [redacted] Commonwealth of Massachusetts, Plymouth County Superior Court, C.A. No: [redacted]
Our File: L08-694

At your request, I have evaluated the medical records, medication records and events surrounding the death [redacted] on February 19, 2007, in an effort to determine the cause of her death. For the Court's information, my qualifications follow.

I, Richard A. Parent, PhD, DABT, FATS, RAC, ERT, am a board certified toxicologist with over 12 years' experience in the field of industrial toxicology and an additional 25 years' experience in litigation support for both the plaintiff and defense. I have testified in local and federal courts as an expert in toxicology and have given expert testimony in the disciplines of toxicology and chemistry. During my career, I have spent 10 years in research on organic chemicals at American Cyanamid Company. In the field of toxicology, I have initiated and carried out an active program in product safety relating to toxicology for the Xerox Corporation. I have directed two contract toxicology laboratories: Food and Drug Research Laboratories, Inc. and Gulf South Research Institute, Life Sciences Division. In 1984, I established Consultox, Limited, a toxicology consulting firm, and have since consulted in product safety for various industries and have designed toxicology studies to assess the safety of materials being considered for use in a variety of products. For litigants, I have provided toxicological support and have addressed causation issues for the plaintiff as well as the defense. I am board certified by the American Board of Toxicology, the Academy of Toxicological Sciences, and the Regulatory Affairs Professional Society. I am a recognized expert in toxicology in France and the European Community. I present myself to the Court as an expert in the fields of toxicology and chemistry. For the Court's information, I offer my curriculum vitae in Attachment A and references in Attachment B.

It is my understanding that Ms. [redacted] was suffering from rheumatoid arthritis for which she was prescribed the anti-cancer drug, methotrexate, in 2.5 mg tablets. Because of an error in the way that the prescription was written, Ms. [redacted] took four 2.5 mg pills per day for four days (total of 10 mgs/day) beginning on January 9 to January 12, 2007, instead of four pills per week. I believe that this represents a toxicologically significant dose of methotrexate that would have serious health effects in an elderly woman. Four days after completing the erroneous dosing protocol, she was admitted to Jordan Hospital with methotrexate poisoning. She was suffering from muscle weakness, rectal bleeding, nausea, low platelet count, low leukocyte count, and elevated liver enzymes, all of which are adverse effects that are typical of methotrexate[1,3]. It is difficult to understand why Dr. [redacted] does not acknowledge these obvious toxic manifestations of methotrexate overdose in his expert report and difficult to understand why Dr. [redacted] does not acknowledge the potential for prolonged effects of this toxicity on a 71 year-old woman.

Ms. [redacted] was treated for the poisoning, including urine alkalization, folic acid, and leucovorin. She appeared to recover, but on February 1, 2007, she was hospitalized at the South Shore Hospital for a change in mental status that started about the time of her methotrexate overdose. At this time she again demonstrated elevated liver enzymes, blood in stool, fever, slightly decreased hematologic parameters, and a metabolic encephalopathy. The following day, the patient continued with fever, elevated liver enzymes, decrements in blood counts, and continued decline of mental status. A working differential diagnosis at that time included meningitis, sepsis, toxic metabolic encephalopathy, and pneumonia, among others. Over the next few days, her condition worsened, as did her fever, anemia, and abnormal liver function tests. She then developed pancreatitis, anemia, a retroperitoneal hematoma, and acute tubular necrosis. Her condition deteriorated, and she died on February 19, 2007. The Death Certificate reads that her death was caused by "complications of methotrexate toxicity", but methotrexate was not found in her body fluids. This is not surprising since methotrexate has a very short half-life in the body.[1-3] Note that the wording in the Death Certificate is specific; she did not die of methotrexate poisoning but of "complications" resulting from methotrexate toxicity. I believe that this cause of death is consistent with a cascade of events that were initiated by exposure to methotrexate.

Consider the following well known information on methotrexate toxicity. The drug is known to cause bone marrow suppression,[1,4-10] including thrombocytopenia[1,8,11-14] and leukopenia,[1,3,8,11,12,14] resulting in an increased risk of infection,[1,2,5,9] including sepsis.[1] Methotrexate is known to result in elevated liver enzyme activity and hepatotoxicity [1-3,5,10,13] and gastrointestinal problems, including rectal bleeding.[1,2,10,13] Aphasia with mood alterations and cognitive dysfunction are also characteristic of methotrexate overdose.[1,3] Finally, an overdose of methotrexate is known to be life threatening, increasing the risk of death.[1,2,6,9,11,13,15-19] One case reported a patient dying 22 days after overdose.[13]

It is clear that Ms. [redacted] was given an overdose of methotrexate and was subsequently treated appropriately; however, as a result of the overdose, she suffered symptoms typical of methotrexate

toxicity. In his expert report, Dr. [redacted] erroneously does not recognize the pattern of methotrexate toxicity, nor does he acknowledge the prolonged effects that such an overdose could have on a 71 year-old woman. As a result of this poisoning incident involving methotrexate, a sequella of medical events followed, including toxic encephalopathy, pancreatitis, pneumonia, and coma, among others, that later led to her death. I opine with a reasonable degree of scientific certainty that Ms. [redacted] overdose of methotrexate resulted in toxicity typical of this drug; and, even though she was subsequently treated appropriately, these and other medical events precipitated by this toxic incident eventually led to her demise. I reserve the right to alter this report should additional information become available.

Sincerely,

Richard A. Parent, PhD, DABT, FATS, RAC, ERT
President

RAP/ecp

Enclosures

[redacted]