Products Liability Law Daily Wrap Up, TOP STORY—DRUGS—E.D. Pa.: Causation testimony by three plaintiffs' experts in Zoloft MDL rejected as speculative, (Aug. 13, 2014)

By John W. Scanlan, J.D.

Three plaintiffs' experts would not be permitted to testify in multi-district litigation that Zoloft causes birth defects when taken by pregnant women because their opinions would be speculative, the U.S. District Court for the Eastern District of Pennsylvania held. However, the court allowed them to offer their opinions that there was a plausible biological mechanism by which Zoloft could cause the injures at issue (*In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, August 12, 2014, Rufe, C.).

Background. Zoloft is a prescription antidepressant, a member of the class of drugs known as selective serotonin reuptake inhibitors (SSRIs). Plaintiffs in multi-district litigation involving Zoloft alleged that Zoloft causes birth defects in the unborn children of mothers who take it while pregnant. The plaintiffs' steering committee (PSC) proffered the testimony of various witnesses on general causation, including Dr. Sadler, an embryologist and teratologist with a Ph.D. in anatomy and embryology; Dr. Cabrera, a teratologist with a Ph.D. in Medical Sciences; and Dr. Levin, a molecular developmental biologist with a Ph.D. in genetics. Pfizer, the manufacturer of Zoloft, moved to exclude their testimony, challenging the reliability of their opinions but not their qualifications.

Biological mechanism. Each of the experts could testify that there was a plausible biological mechanism by which Zoloft could impact embryonic development. Dr. Cabrera opined that serotonin was an important signaling molecule for organ development in a developing embryo and that SSRI exposure alters normal serotonin signaling pathways, resulting in various congenital malformations. He reviewed some of the relevant scientific literature on Zoloft, including Pfizer's pre-clinical animal trials, along with in vitro studies testing the importance of serotonin pathways in embryonic development. Although Pfizer argued that Dr. Cabrera had never tested his Zoloft hypothesis, the court stated that it was acceptable to rely upon the testing of others as long as one addresses both supportive and contrary evidence, which it found that Dr. Cabrera had done in forming his opinion.

Dr. Sadler opined that serotonin has a known critical role in cell signaling, with his report listing why SSRI exposure was a plausible biological mechanism of injury for a number of birth defects. His opinion was based on his use of an in vitro whole embryo culture system he developed. Pfizer argued that there were limitations to in vitro methodology because it differed from administration of a drug to a pregnant animal or human, but the court found that these limitations were not flaws in his methodology and could be addressed on cross-examination.

Finally, Dr. Levin opined that serotonin was a "profoundly important medium for cell-to-cell communication during embryogenesis," with at least three obvious routes by which an SSRI could affect embryonic development and cause various malformations. His opinion was based mainly on studies using non-mammals. Pfizer argued that his arguments on plausible biological mechanisms were unreliable because he had not demonstrated that blocking serotonin receptions caused laterality defects (affecting normal left-right patterning in embryos), but the court found that he had sufficiently supported his opinion that serotonin played an essential role in embryonic patterning in some species; limitations in his research could be addressed during cross-examination.

However, the court would not allow Dr. Levin to testify as to his hypothesis that SSRIs alter ion or calcium signaling in developing embryos. The studies he relied upon to support his calcium signaling opinion were conducted by exposing human cancer cells and canine kidney cells, not embryos, to Zoloft concentrations far higher than therapeutic levels, and his ion channel opinion was supported by a study measuring cultured adult human brain cells exposed to Zoloft. The court said that it would not allow an expert to testify as to an untested hypothesis.

Human causation. The court would not let the three experts testify about human causation because their opinions that Zoloft can cause birth defects when taken by a pregnant woman during the first trimester were premature under the current state of the science, considering the Bradford-Hill criteria and Wilson's principles of teratology. The court first determined that there had been a significant amount of epidemiological research

conducted during the 20 or so years Zoloft has been on the market, but that the three experts had given it little attention and had not reconciled inconsistent epidemiological evidence with their opinions.

Further, there were problems with their opinions on human causation largely being based upon extrapolation from in vitro or in vivo animal studies. The experts did not reconcile dose-response evidence that adverse effects of SSRIs were largely found in doses higher than those that would normally be given to pregnant humans and they did not identify studies that showed an increased risk of birth defects at normal doses. Drugs are not metabolized by the mother in an in vitro system, and there was no supportive data from live mammals that would show an association between birth defects and Zoloft use at typically-used levels, the court said. There was a lack of evidence that the proposed pathways identified from in vitro studies were conserved in humans, as well as a lack of evidence on optimal serotonin levels in humans.

Because the experts had not adequately considered the Bradford-Hill criteria, the court determined that their conclusions on causation were not formed using a reliable scientific methodology. In vitro and in vivo animal research were useful for generating hypotheses about human causation, but the court warned that these hypotheses must be tested and scientifically verified, which had not been demonstrated by these experts. The evidence they relied upon was insufficient to support a non-speculative opinion that Zoloft can cause birth defects in humans when used at conventionally prescribed doses.

The case number is 12-md-2342.

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Companies: Greenstone, LLC; Pfizer, Inc.; Walgreens Co.; GlaxoSmithKline LLC; Forest Laboratories Inc.

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