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SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN DIEGO

Teagan Hamilton and **Cardwell Hamilton**, minors, by and through their Guardian Ad Litem, **Chris Hamilton,**

Plaintiffs,

v.

Novartis Pharmaceuticals Corporation, et al.,

Defendants.

Case No.: 37-2013-00070440-CU-MM-CTL

PLAINTIFFS' MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO DEFENDANT NOVARTIS PHARMACEUTICALS CORPORATION'S MOTION FOR SUMMARY JUDGMENT

Date:	July 24, 2020
Time:	8:30 a.m.
Dept.:	C-65
Judge:	Hon. Ronald F. Frazier
Complaint Filed:	October 8, 2013
Trial Date:	September 4, 2020

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INTRODUCTION

This is a personal-injury action involving the prescription drug "Brethine" ("terbutaline"), a "beta-agonist" drug that was FDA-approved in the 1970s to treat asthma.

Plaintiffs are fraternal twins who experienced prolonged prenatal exposure to terbutaline after an OB/GYN prescribed it to Plaintiffs' mother "off-label" to prevent preterm labor in a practice known as "maintenance tocolysis." Plaintiffs brought this action against Novartis, the former manufacturer of Brethine, for its failure to issue two important warnings required by federal law that would have prevented their injuries:

- First, Novartis failed to warn physicians that published, peer-reviewed studies had shown terbutaline administered to pregnant rats resulted in abnormal brain development in the exposed offspring.
- Second, Novartis failed to place a black-box warning on the Brethine label that terbutaline should not be used for a "maintenance tocolysis" based on those risks.

According to Dr. David Kessler, former Commissioner of the FDA, Novartis's duty to add these warnings was triggered by, among other things, six peer-reviewed studies published between 1985 and 2001 that showed that terbutaline administered to pregnant rats resulted in abnormal brain development in the exposed offspring.

Novartis's failure to add the required warnings was made worse by the fact that it had known since 1983 that Brethine was commonly used off-label to treat preterm labor for maintenance tocolysis. Indeed, Novartis was aware that, in the United States, over **260,000** women a year were being treated with Brethine for preterm labor, and that preterm labor accounted for **65%** of all Brethine prescriptions.

But rather than provide necessary warnings that would obviously threaten Brethine's popularity for preterm labor—and, thus, the market value of its drug, which was earning Novartis over $20 million a year—Novartis instead sold Brethine to another manufacturer for $26.6 million in December 2001. Predictably, the successor manufacturer *also* neglected to update Brethine's label, allowing it to persist in a deficient state for another decade.

The FDA finally intervened in 2011 in response to a letter from a concerned citizen urging the FDA to add badly needed warnings to the Brethine label. In light of the animal studies showing

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that terbutaline administered to pregnant rats resulted in abnormal brain development in the exposed offspring, the FDA raised the pregnancy-risk rating on the Brethine label, directed manufacturers to warn that animal studies had shown abnormal brain development in offspring exposed to prenatal terbutaline, and added a black-box warning against use of terbutaline for maintenance tocolysis.

While the FDA's action undoubtedly prevented future harm, it came too late for Plaintiffs, who were exposed to terbutaline in 2007, six years after Novartis sold Brethine to aaiPharma.

Had Novartis added either of the warnings it was required to, Plaintiffs would have avoided injury. Indeed, the doctor who prescribed Brethine to Plaintiff's mother testified that he has stopped using Brethine for tocolysis ever since the boxed warning was added, and would not have prescribed it to Plaintiffs' mother if it had the boxed warning back in 2007. He further testified that, at a minimum, he would have taken evidence of neurotoxic risk to the fetus into account, and would have related that concern to Plaintiffs' mother. Plaintiffs' mother has indicated she would not have agreed to take terbutaline had that concern been related to her at the time.

Plaintiffs' lawsuit was initially dismissed at the demurrer stage on the belief that Novartis could not be held liable for any deficiencies in the Brethine warning label after it sold the drug in 2001. But the Supreme Court disagreed, holding "that a brand-name manufacturer's sale of the rights to a drug does not, as a matter of law, terminate its liability for injuries foreseeably and proximately caused by deficiencies present in the warning label prior to the sale." (*T.H. v. Novartis Pharms. Corp.* (2017) 4 Cal.5th 145, 192.)

Novartis now urges this Court to summarily dismiss Plaintiffs' case *yet again* on the audacious claim that no reasonable jury could find Novartis negligent, or that its negligence played a role in Plaintiffs' injuries. But as set forth below, material factual disputes regarding Novartis's negligence, and its causal role in Plaintiffs' injuries, preclude summary judgment.

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BACKGROUND

A. Terbutaline's popularity as an off-label treatment for preterm labor

Although Brethine was only FDA-approved to treat asthma, it quickly became popular among OB/GYNs as an "off-label" treatment for preterm labor.

This fact was well known to Novartis as early as 1983. (PUMF #2.) In light of Brethine's popularity for preterm labor, a Novartis executive recommended in 1983 that Novartis "[redacted]." (PUMF #3.)

But Novartis did no such thing. Instead, in May 1984, Novartis hired a prominent OB/GYN to fly to various OB/GYN conferences across the United States where he would then hand out brochures regarding the "cost-effectiveness of arresting preterm labor with beta-adrenergic drugs," and terbutaline in particular. (PUMF #4.) Dr. Kessler opined that, in his view as the former FDA Commissioner, these and other activities by Novartis constituted illegal off-label promotion which likely helped inspire the use of Brethine for preterm labor. (PUMF #5.)

By 1998, it was reported that, in the United States, over **260,000** women a year received terbutaline for preterm labor (PUMF #22.)[1]

Perhaps the most common use of Brethine for preterm labor was a practice known as "maintenance tocolysis." In contrast to "acute tocolysis"—in which the mother is given a single dose of a tocolytic to stop contractions in order to transfer the mother to a facility better equipped to handle a premature baby (PUMF #30)—maintenance tocolysis involved repeatedly dosing terbutaline over a prolonged period, often as long as weeks on end. In 1998, it was reported that "thousands of practicing physicians" in the United States were using "terbutaline maintenance therapy" to treat preterm labor. (PUMF #27.) Maintenance tocolysis was accomplished through frequent oral terbutaline tablets or by repeatedly dosing terbutaline subcutaneously. (PUMF #20.)

The FDA viewed maintenance tocolysis with disfavor and undertook efforts to curb the practice.

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[1] Citations to Plaintiffs' Undisputed Material Facts are abbreviated as **(PUMF #X).** Citations directly to the consecutively paginated exhibits in Plaintiffs' Notice of Lodgment are abbreviated as **(PNOL XXXX).** Citations to Novartis's brief are abbreviated as **(Def. Br. at X.)**

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In 1993, the FDA began formally "investigating off label promotion/use of Brethine … in prevention of premature labor." (PUMF #6.) As part of that effort, the FDA visited Novartis's distribution centers to obtain documents regarding Novartis's shipments of Brethine to various entities whom the FDA suspected of using injectable terbutaline for maintenance tocolysis via infusion pumps. (PUMF #6.)

Then, in 1997, the FDA issued a "Dear Colleague" letter to healthcare providers, health insurers, and others to express "concern" about the "increasingly widespread" practice of using injectable terbutaline for maintenance tocolysis. (PUMF #17.) In its letter, the FDA stressed that there was no evidence maintenance tocolysis was effective. (PUMF #18.) The FDA further noted that there had been at least one maternal death associated with the use of terbutaline for preterm labor. (PUMF #19.)

In 1998, the FDA again contacted Novartis to express the FDA's "concern[] about the sale, distribution, and promotion of terbutaline" for "the treatment and prevention of preterm labor." (PUMF #23.) To that end, the FDA asked Novartis to provide any materials it may have sent to doctors or home health agencies promoting or discussing the tocolytic use of terbutaline. (*Ibid.*)

In 1999, the FDA responded to a petition filed by a coalition of OB/GYNs urging the FDA to retract the assertions in its 1997 letter that were critical of using terbutaline for maintenance tocolysis. (PUMF #29.) In its response, the FDA once again emphasized that there was no evidence maintenance tocolysis with terbutaline was effective. (PUMF #30.) Moreover, the FDA advised that whether maintenance tocolysis was accomplished with either subcutaneous administration or oral tablets, "the available systemic drug levels are quite similar." (PUMF #31.) Finally, the FDA noted that 13 maternal deaths had been reported to the FDA "in patients using terbutaline sulfate for tocolysis." (PUMF #32.)

But despite the FDA's efforts, the pernicious use of terbutaline for maintenance tocolysis persisted. Indeed, of the $20 million in annual sales that Novartis enjoyed from Brethine in 1998, 1999, and 2000 (PUMF #11), **65%** were attributable to Brethine's use for preterm labor. (PUMF #10.)

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B. Increasing evidence Brethine is neurotoxic to the developing brain

As the practice of using Brethine for maintenance tocolysis continued unabated, evidence also began to mount that terbutaline may disrupt brain development in exposed offspring. Indeed, between 1985 and December 2001, six peer-reviewed studies showed that terbutaline caused abnormal brain development in rats whose mothers were administered terbutaline while they were pregnant:

- A 1985 study showed that prenatal exposure to terbutaline "may interfere with basic biochemical events which influence neuronal maturation."
- A 1989 study showed that "terbutaline may be a neurobehavioral teratogen" based on evidence it reduces the number of brain cells in exposed offspring.
- A 1990 study showed that exposing pregnant rats to terbutaline "may be accompanied by alterations of neural development and function in the offspring."
- A 1992 study showed that terbutaline affects "nervous system development" in the offspring of pregnant rats exposed to it.
- A 1998 study showed that terbutaline "suppress[es] the proliferation of microglia,"—i.e., nerve cells critical to brain development—in the developing rat brain.
- An October 2001 study showed "that administering terbutaline in pregnant rats 'may lead to disruption of neural cell development' in the exposed offspring."

(PUMF #48.)

In addition, three studies between 1986 and 2001 demonstrated that children "of women treated with terbutaline during pregnancy showed impaired school performance, cognitive dysfunction, and an increased risk of psychiatric disorders." (PUMF #115.)

Given the tension between Brethine's popularity for maintenance tocolysis and the increasing evidence that it may pose a risk to fetal brain development when used as such, one might wonder what Novartis did in response. After all, as the manufacturer, Novartis had "a duty under federal law to draft, update, and maintain the warning label so that it provide[d] adequate warning of the drug's potentially dangerous effects." (*T.H. v. Novartis Pharm. Corp.* (2017) 4 Cal.5th 145, 166, citing 21 U.S.C. § 352(f)(2).) And this duty extends even to off-label uses of which the manufacturer is aware. (See 21 C.F.R. § 201.128, available at PNOL Ex. 2.)

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As discussed in more detail below, federal regulations required Novartis to update the Brethine label to address the significant evidence of potential adverse risks to fetal brain health *and* to strongly discourage, once and for all, the use of Brethine for maintenance tocolysis with a black-box warning.

But of course, doing so would have killed Novartis's "golden goose." Thus, Novartis chose instead "to remain reactive instead of proactive" by leaving it to the "FDA [to] warn the medical community of using terbutaline off-label in preterm labor." (PNOL 0095; PUMF #8.)

Ultimately, rather than update the Brethine label, Novartis instead looked to sell the drug to another manufacturer, touting its popularity as a treatment for preterm labor as a selling point. (PUMF #13; PNOL 0097 ["He wants to have in the memo the fact that 2/3 of sales derive from off label use[.]"].)

In December 2001, Novartis sold Brethine to aaiPharma for $26.6 million (PUMF #15), with the badly deficient warning label intact. Predictably, like Novartis itself, aaiPharma failed to make the necessary changes to the Brethine label and continued to use the same label as Novartis, which persisted until 2011.

C. The FDA intervenes, adding the warnings Novartis neglected to provide

In 2008, James P. Reichmann, a lay citizen, submitted a petition to the FDA urging it update the Brethine label to adequately address the risks to mother and the fetus. (PUMF #35.) Reichmann supported his petition with a detailed bibliography that included 15 animal studies between 1989 and 2007 showing that terbutaline administered to pregnant rats resulted in abnormal brain development in the offspring, of which five were published in or before 2001. (PUMF #36.)

The FDA formally responded to the Reichmann petition in 2011. (PUMF #37.) In its response, the FDA did the very things that Novartis had a duty to do back in 2001:

First, in view of the "[p]ublished animal studies show[ing] that rat offspring" exposed to terbutaline in utero "exhibit alterations in behavior and brain development"—including five of the six studies available before December 2001—the FDA raised the pregnancy-risk designation on the Brethine label and directed manufacturers to add language to the Brethine label that animal studies had shown abnormal brain development in offspring exposed to Brethine in utero. (PUMF #35, #45.)

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Second, the FDA added a boxed warning to the Brethine label specifically contraindicating its use for maintenance tocolysis, based significantly on "the animal data regarding neurotoxic risks." (PUMF #43.)

Moreover, the FDA took efforts to "notify obstetricians of the labeling changes" by posting the information on its website, and by "issuing a drug safety communication and a press release." (PUMF #44, #46–47.)

The FDA's efforts to curb the use of Brethine as a maintenance tocolytic had their intended effect: For example, Dr. David Dowling—the OB/GYN who treated Plaintiffs' mother for preterm labor while she was pregnant with Plaintiffs—testified that "when that black box warning came out I basically stopped using terbutaline in my practice." (PUMF #86.) His partner, Dr. Larry Cousins, also stopped using terbutaline after the boxed warning came out. (PUMF #81.)

D. Plaintiffs suffer neurodevelopmental damage from prenatal terbutaline exposure

But, of course, there was no boxed warning on the Brethine label in 2007, nor was there any reference to the animal studies showing that administering terbutaline to pregnant rates resulted in abnormal brain development in the exposed offspring. (PNOL 0283–0285.)

Thus, Dowling did not hesitate to put Plaintiffs' mother on maintenance tocolysis consisting of 2.5mg of oral terbutaline every four hours, each day, for nearly five weeks. (PNOL 0053–0059.) Plaintiffs were born in October 2007. Both parties agree they suffer from the neurodevelopmental disorder known more commonly as "autism."

Plaintiffs' believe their autism was caused by their prolonged prenatal exposure to terbutaline. That belief is supported by an impressive group of scientific and medical experts:

Indeed, Plaintiffs retained Theodore Slotkin, Ph.D., a neurotoxicologist at Duke University with 40 years' experience researching terbutaline. (PNOL 0714.) Of the 15 animal studies the FDA cited as justification for changing the Brethine label in 2011, 13 were Slotkin's. (PUMF #40.) Slotkin testified that there is "[a]bsolutely no question that terbutaline damages the developing brain" in mammals. (PUMF #112.)

Plaintiffs also retained William Brown, M.D., perhaps the world's foremost expert in the genetic origins of autism. On the basis of numerous state-of-the-art genetic tests, Dr. Brown has

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determined that Plaintiffs are free of the known genetic syndromes that might explain their autism.

Plaintiffs also retained Andrew Zimmerman, M.D., a pediatric neurologist who published one of the first human studies associating prenatal terbutaline exposure with increased autism risk; and Brad Pollock, Ph.D., a renowned epidemiologist at UC Davis. On the basis of human data—including human epidemiology—Zimmerman and Pollock have opined that, more likely than not, terbutaline is a substantial factor in the development of autism as a general matter, and in Plaintiffs in particular.

Notably, Novartis has challenged these very same experts before: All four experts—Slotkin, Brown, Zimmerman, and Pollock—testified on behalf of the plaintiffs in a virtually identical case in Maryland. (PUMF #62.) Like Plaintiffs here, the plaintiffs there were fraternal twin boys who alleged that the became autistic as a result of prolonged prenatal exposure to terbutaline that was prescribed as a maintenance tocolytic. (PUMF #62.) Novartis attempted to have these experts' causation opinions excluded, but the Maryland court denied that effort. (PUMF #63.)

The same result is warranted here: Although Novartis may have much to dispute about the science on which Slotkin, Brown, Zimmerman, and Pollock rely, disputes of that nature—particularly those involving esoteric, complex medical and scientific issues—cannot be resolved on summary judgment and must instead await trial.

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ARGUMENT

I. Plaintiffs' injuries were reasonably foreseeable to Novartis.

Because a drug manufacturer's liability for a failure to warn is limited to "foreseeable" risks (*T.H.*, *supra*, 4 Cal.5th at p. 192), Novartis first argues that Plaintiffs' claims fail because, in 2001, it could not foresee that prenatal terbutaline exposure causes autism. (Def. Br. at 16.)

But that argument unduly narrows the relevant foreseeability inquiry: "[I]t is settled that what is required to be foreseeable is the general character of the event or harm … *not its precise nature or manner of occurrence*." (*Bigbee v. Pac. Tel. & Tel. Co.* (1983) 34 Cal.3d 49, 57–58.)

And as Defendant's own autism expert confirmed, autism is, at bottom, a neurodevelopmental disorder. (PUMF #61.) Thus, the relevant foreseeability inquiry is not whether Novartis should have anticipated that prenatal terbutaline exposure causes autism *in particular*, but whether it was reasonably foreseeable that it might threaten human neurodevelopment *more generally*. Not coincidentally, this is exactly how the Supreme Court framed Plaintiffs' allegations in this case: "Plaintiffs allege that Novartis knew or should have known that Brethine carried a substantial risk of causing *developmental and neurological damage to the fetus*, yet failed to warn of that risk." (*T.H.*, *supra*, 4 Cal.5th at p. 156.)[2]

Accordingly, the mere fact that Novartis might not have been able to anticipate the link between prenatal terbutaline exposure and autism in particular does not absolve Novartis if it had a duty to warn about neurological damage to fetuses *more generally*. As discussed in the next section, Novartis unquestionably had that duty—among others—and breached those duties by failing to add necessary warnings to the Brethine label while it still owned the drug.

[2] The fact that the Supreme Court framed Plaintiffs' allegations as "developmental and neurological damage" and not "autism" specifically puts the lie to Novartis's claim that Plaintiffs have "abandoned" or "retrenched" from the claim that Novartis had a duty to warn about autism specifically. Notably, although Novartis repeats that assertion often, it is always devoid of a citation to Plaintiffs' complaint. This, of course, is because there is no such allegation to be found. Indeed, the Supreme Court's opinion pre-dated the operative complaint in this case.

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II. There are triable issues regarding whether Novartis breached a duty of care.

Novartis next argues that it did not breach its duty of care. Breach is a question of fact that cannot be resolved on summary judgment unless the moving party establishes it was *not* negligent beyond "a reasonable doubt." (*Johnson & Johnson Talcum Powder Cases* (2019) 37 Cal.App.5th 292, 323.)

"A brand-name pharmaceutical manufacturer has a duty under federal law to draft, update, and maintain the warning label so that it provides adequate warning of the drug's potentially dangerous effects." (*T.H.*, *supra*, 4 Cal.5th at p. 166, citing 21 U.S.C. § 352(f)(2).) Thus, the pertinent "breach" question is whether there were "deficiencies present in the [Brethine] warning label prior to [Novartis's] sale" of Brethine to its successor, aaiPharma. (*T.H.*, *supra*, 4 Cal.5th at p. 192.)

To assess that question, Plaintiffs asked Dr. Kessler, a former FDA Commissioner, to review this case. Kessler opined that Novartis breached its federal regulatory duties in at least two fundamental ways, as discussed below. At a minimum, this testimony creates a triable issue of fact as to whether Novartis breached a duty here.

A. Novartis breached its duty to raise Brethine from pregnancy-risk category "B" to "C," and issue a "Dear Doctor" letter to notify doctors of that change.

First, Novartis breached its duty of care by failing to raise the pregnancy category on the Brethine label from "B" to "C" (PUMF 56), and—more importantly—by not including a statement on the drug label that animal studies had shown that administering terbutaline to pregnant rats results in abnormal brain development in the exposed offspring.

Under federal regulations, manufacturers must provide adequate warnings about a drug's potential for "[t]eratogenic effects" (i.e., disturbances in the development of the embryo or fetus) by giving the drug a pregnancy-risk category (e.g., "A," "B," "C," "D," or "X"). (21 C.F.R. § 201.57(f)(6).)[3]

[3] The 2001 version of this regulation is available at Exhibit 3 to Plaintiffs' Notice of Lodgment.

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As noted above, when Novartis sold Brethine to aaiPharma, the label carried a pregnancy-risk category "B" rating. This served as a warranty to the public that animal studies have shown "no evidence of … harm to the fetus." (21 C.F.R. § 201.57(f)(6)(b); PNOL 0064.) But as Kessler points out, there was actually significant evidence that Brethine might pose a risk of harm to the fetus: **Six** peer-reviewed, published animal studies available before December 2001 that, in the FDA's own words, demonstrated that "pregnant rats that received terbutaline … showed abnormal brain development in exposed offspring." (PUMF #48.)

Kessler noted that these studies had even greater significance in light of **six** studies reporting similar findings for other beta-agonists. (PUMF #56.) Novartis's purported FDA "guideline" agrees: "Similar findings in the animal studies for the … product compared to the class would be *cause for more concern*." (Def. Ex. 84, p. 12, italics added.)

- A 1988 study that showed giving the beta-agonist "isoproterenol" to pregnant rats resulted in an "immediate decline … in the formation of new brain cells" in the offspring.
- A 1992 study that showed that giving other beta-agonists to pregnant rats resulted in "long-term biochemical, morphological, behavioral and electrophysiological effects" in the brains of the exposed offspring.
- A 1992 study that showed nerve cells in immature rat brains are sensitive to the beta-agonist "isoproterenol," a sensitivity that laid "the groundwork for potential lasting adverse functional effects" in exposed offspring.
- A 1993 study involving beta-agonists similar to terbutaline, which concluded that "all drugs acting [on beta-receptors] may indeed have functional teratogenic potential."
- A 1993 study involving administration of the beta-agonist clenbuterol that concluded that "chronic postnatal activation of beta-adrenoceptors by clenbuterol treatment" in rat pups "causes changes in the setting of the neurochemical parameters investigated in the frontal cortex."
- A 1994 study that showed administration of isoproterenol to two-day-old rat pups resulted in "inappropriate hyperstimulation of beta-adrenergic receptors in the developing brain and subsequent, adverse functional deficits."

(PUMF #49.)

Based on this overwhelming animal data, Kessler opined that rather than a category "B" rating, Novartis should have reclassified Brethine a pregnancy-risk category "C." (PUMF #56.)

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But there's more: Perhaps more important than merely reclassifying the pregnancy rating, federal regulations required Novartis to include "a description of the animal studies" justifying the "C" rating. (21 C.F.R. § 201.57(f)(6)(i)(c).) In other words, Novartis should have included a statement in the Brethine label that "[p]ublished animal studies show that rat offspring" exposed to terbutaline in utero "exhibit alterations in behavior and brain development." (PUMF #45, 57.)

Finally, Kessler opined that, in addition to making these changes to the label, Novartis should have notified OB/GYNs of these changes by issuing a "Dear Doctor" letter or its equivalent (PUMF #59), just as the FDA did when it made these changes. (PUMF #44, 46–47.) Here, Kessler's opinions were based, in part, on Novartis's awareness of—and, indeed, its role in promoting—the widespread use of terbutaline for tocolysis. (PUMF #59),

Novartis offers two arguments in response; both fail.

First, Novartis claims that Slotkin's studies were not true "animal reproduction studies" because they were not done according to "guidelines" in Novartis' lodgment that, *according to Novartis*, supply the *exclusive* definition of "animal reproduction study" relevant to the pregnancy-risk categories. (Def. Br. at 19–20.)

But this claim lacks factual support. The pertinent regulation—21 C.F.R. § 201.57(f)(6)(i)—does not cross-reference Novartis's proffered "guidelines" for its definition of "animal reproduction study," nor do the "guidelines" purport to supply one. Novartis *might* have filled that foundational gap with an expert, but it failed to do so. Not coincidentally, Novartis's retained regulatory expert conceded that "an animal reproduction study that was done that actually showed neurodevelopmental functional changes, but didn't meet standards from the FDA, may still compel labeling change." (PNOL 1056–1057, 1063–1064; PUMF #53.)

Novartis's attack on the animal studies is also foreclosed by Kessler's testimony that Slotkin's studies required a change to pregnancy-risk category "C." (PUMF #57.) That opinion is corroborated by the FDA itself: Indeed, of the 15 studies, the FDA cited as justification for raising Brethine's pregnancy-risk category from "B" to "C," **13** were Slotkin's studies, including the five that pre-dated December 2001. (PUMF #40.) As an FDA Commissioner, Kessler's interpretation of the FDA regulations is certainly sufficient to defeat summary judgment.

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But even if Novartis's "guidelines" were valid, Slotkin's studies are still relevant.

Although Novartis claims that Slotkin's studies did not allow any of the rat subjects "to survive to maturity to assess long-term developmental issues" (Def. Br. at 20), Slotkin's studies in fact "encompassed both immediate effects during the terbutaline exposure as well as the longitudinal, functional consequences of these effects carried out through juvenile and adolescent stages, and into full adulthood." (PNOL 0718 [¶ 11].)

Nor is it true Slotkin's "studies used doses up to 2,000-3,000 time[s] the equivalent human dose." (Def. Br. at 21.) As the FDA noted, Slotkin's studies used "doses 24 to 48 times the recommended human dose." (FDA Response to Reichmann, p. 11; Slotkin Dec. ¶¶ 6–11.) Indeed, the dosages in Slotkin's studies were far closer to the recommended human dose for terbutaline than the "animal reproduction studies" on which Brethine's pregnancy-risk "B" rating was based. (See PNOL 0285 [rat study using "approximately 810 times the maximum recommended daily sc dose for adults" and rabbit study using "approximately 1,600 times the maximum recommended daily sc dose for adults"].)

Nor do Slotkin's studies merely "hypothesize" that terbutaline is neurotoxic because their conclusions were qualified with "may." (Def. Br. at 19.) In peer-reviewed scientific literature, "may" is an acknowledgment that "science can never be 100% certain." (PNOL 0719–0720 [¶¶ 16–17].) But peer-review standards nonetheless required Slotkin to be 95% certain of the association between terbutaline and the effects he described. (*Ibid.*) Thus, rather than "hypothesize," Slotkin's studies "drew the *conclusion* that terbutaline was, more likely than not, a developmental neurotoxicant." (*Ibid.*)

Second, Novartis errs in suggesting there was insufficient animal data to warrant a change to pregnancy-risk category "C" in December 2001 because the FDA's decision to make that change came "after *an additional ten years of research and study*." (Def. Br. at 21.)

That claim is not factually accurate: Of the 10 animal studies published after 2001 that the FDA cited as justification for raising Brethine's pregnancy-risk category, the last was from **2007**, only *six years* after Novartis sold Brethine to aaiPharma. (PNOL 0292.)

Moreover, the fact that there may have been *more than enough* evidence of an association

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between terbutaline and "abnormal brain development in exposed offspring" by the time the FDA intervened in 2011 does *not* support an inference that there was insufficient evidence to warrant a change in 2001.

Drawing such inferences is forbidden as a general matter. (*Aguilar v. Atlantic Richfield Co.* (2001) 25 Cal.4th 826, 843.) And here, the pertinent federal regulations cut against that very inference by suggesting that the threshold for a change to the pregnancy category is relatively low: Under the regulations, a category "B" designation is warranted only if animal studies have shown "*no evidence* of … harm to the fetus." (21 C.F.R. § 201.57(f)(6)(i)(b), italics added) And a drug slips into category "C" as soon as "animal reproduction studies have shown an adverse effect on the fetus." (21 C.F.R. § 201.57(f)(6)(i)(c).) On its face, this language shows that a category "C" rating was already overdue when Novartis sold Brethine to aaiPharma in December 2001.

Indeed, Novartis's own regulatory expert rejected the premise that "there is a certain number" of studies needed to inform a pregnancy-risk category, and stated that even **two** studies could inform the pregnancy-risk category, whether or not they were done according to the "guidelines" on which Novartis relies. (PUMF #53–54.)

B. Novartis breached its duty of care by failing to seek a "boxed warning" for the Brethine label contraindicating its use for maintenance tocolysis.

In addition to raising Brethine's pregnancy-risk category from "B" to "C," Kessler opined that Novartis should have sought to add a "boxed warning" to the Brethine label contraindicating Brethine for maintenance tocolysis. (PUMF #58.)

Federal regulations state that a drug manufacturer may be expected to address "[s]pecial problems, particularly those that may lead to death or serious injury" with a warning "placed in a prominently displayed box." (21 C.F.R. § 201.57(e).) Under federal regulations, "a congenital anomaly/birth defect" is regarded as a "serious" hazard. (21 C.F.R. § 314.80.)

Kessler opined that a boxed warning was warranted in 2001 given (1) the animal data showing that administration of terbutaline resulted in abnormal brain development in exposed offspring, and (2) the fact that Novartis not only knew terbutaline was widely used for maintenance tocolysis, but had in fact promoted it as such, thus requiring corrective action. (PUMF #5, #58.)

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Novartis's counterarguments all fail.

First, Novartis implies that it adequately discouraged the tocolytic use of terbutaline by placing a sentence in the label that "Terbutaline has not been approved and should not be used for tocolysis." But "the adequacy of a warning is a question of fact for the jury," *not* summary judgment. (*Oxford v. Foster Wheeler LLC* (2009) 177 Cal.App.4th 700, 717.)

And here there is evidence Novartis knew this warning was being widely disregarded: Indeed, although the statement that terbutaline "should not be used for tocolysis" was added to the label in 1991 (Def. Ex. 17), over **260,000** women received terbutaline for tocolysis in the United States (PUMF #22), and **65%** of Brethine prescriptions were for pre-term labor." (PUMF #10.)

Second, Novartis claims it has "clear evidence" the FDA would have rejected an effort to add a boxed warning to the Brethine label in December 2001. Here, Novartis cites the fact that, in 1998, the FDA purportedly rejected Novartis's effort "to place the entire tocolysis precautions section in bold font for emphasis." (Def. Br. at 25.)

But the only evidence the FDA deemed that effort "unwarranted" is an email by a Novartis employee relating a purported statement by an FDA officer. This is classic hearsay. (*People v. Sanchez* (2016) 63 Cal.4th 665, 674.)

Moreover, the "authority" on which Novartis relies for its "clear-evidence" defense confirms that an inference the "FDA determined a label change was unjustified" applies only "if FDA declines to require a label change *despite having received and considered information regarding a new risk*." (*Merck Sharp & Dohme Corp. v. Albrecht* (U.S. 2019) 139 S.Ct. 1668, 1684 (conc. opn. of Alito, J.), italics added.) But unlike the detailed petition that ultimately persuaded the FDA to change the Brethine label, there is absolutely no evidence that Novartis attempted to support that proposed label change with any scientific evidence of neurotoxic risk to fetal health. Novartis is not entitled to an inference that an effort to add a boxed warning supported by scientific evidence would have failed simply because its *unsupported* effort to use boldface type was (purportedly) rejected.

Indeed, the evidence shows that Novartis failed to keep the FDA informed of the animal studies showing that terbutaline resulted in abnormal brain development in exposed offspring despite a duty to do so. Novartis's own regulatory expert confirmed that Novartis had a duty under federal

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law to know about the pre-December 2001 animal studies the FDA cited as justification for changing Brethine's pregnancy-risk category. (PUMF #55.) And yet, of the five pre-December 2001 animal studies the FDA cited as justification for changing Brethine's pregnancy-risk category (PNOL 0292), Novartis only reported *one* to the FDA. (See Def. Ex. 20.)

Finally, the FDA's purported reluctance to emphasize an existing "precaution" in the Brethine label regarding *all forms of tocolysis* does *not* support an inference that the FDA would have rejected a narrower boxed warning against *maintenance tocolysis in particular*. Indeed, as recounted in the "Background" section of this brief, the FDA acknowledged terbutaline had value for "acute tocolysis," but strongly opposed the use of terbutaline for maintenance tocolysis. The boxed warning against maintenance tocolysis that Kessler proposed (and which the FDA added) reflected a more tailored, effective approach to this nuanced issue than simply throwing boldface at a "precaution" against tocolysis generally.

Third, Novartis emphasizes that the FDA's decision to add a boxed warning against maintenance tocolysis was based on maternal health risks in addition to the animal data showing neurotoxic risks to the fetus. While it's true the FDA's decision to add a boxed warning in 2011 was based on 16 maternal deaths involving terbutaline used for tocolysis (PUMF #42), there had already been "**thirteen** maternal deaths have been reported to the FDA in patients using terbutaline sulfate for tocolysis" in 1999, two years before Novartis sold Brethine. (PUMF #32, boldface added.) Novartis's failure to add an adequate warning to address serious fetal health risks is hardly made less negligent simply because, by withholding that warning, Novartis *also* negligently failed to prevent maternal deaths.

Fourth, Novartis resurrects the point that, by the time the FDA added a boxed warning to the Brethine label in 2011, there was more evidence of neurotoxic risk to the fetus than in December 2001. But again, the mere fact there *was more than* enough concern to justify a warning in 2011 does not justify an inference that there *was not* enough back in 2001, particularly on summary judgment. (*Aguilar*, *supra*, 25 Cal.4th at p. 843.) Again, Dr. Kessler, a former FDA Commission has opined that, based on the totality of the science available at the time, a warning was already required in 2001. (PUMF #57.)

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Fifth, in a footnote, Novartis emphasizes that the FDA must approve a boxed warning. (Def. Br. at 24–25, n. 22.) But as Novartis's own regulatory expert points out, the FDA *always* has the final call with respect to added warnings. (PNOL 1055.) And yet, "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." (*Wyeth v. Levine* (2009) 555 U.S. 555, 570–571.) To absolve Novartis of liability for adding necessary warnings to its drug label simply because of the unremarkable fact that it would have to work with the FDA in doing so would turn that rule on its head.

In any event, Novartis—as the party seeking summary judgment—had the burden to establish that it would not have succeed in securing a boxed warning against maintenance tocolysis if it had sought one. As discussed above with reference to Novartis's "clear evidence" defense, it has failed to do so. Indeed, the FDA's willingness to add a boxed warning in response to a petition from a *lay citizen* suggests that effort would have succeeded had Novartis made a similar effort. (PUMF #58.)

III. There are triable issues regarding whether Novartis caused Plaintiffs' injuries.

Novartis next argues that Plaintiffs cannot demonstrate that its negligence was a legal cause of injury to Plaintiffs. Like breach, causation is a highly fact-intensive question that typically "cannot be resolved by summary judgment." (*Lawrence v. La Jolla Beach & Tennis Club, Inc.* (2014) 231 Cal.App.4th 11, 33.)

A. Adequate warnings would have prevented Plaintiffs' exposure to terbutaline.

Novartis claims Plaintiffs would have been exposed to terbutaline as a maintenance tocolytic even if Novartis discharged its duties under federal law. In fact, the evidence shows that Plaintiffs would have avoided their exposure had Novartis *either* (1) added a black-box warning on the Brethine label against maintenance tocolysis, *or* (2) changed the pregnancy-risk information on the label *and* issued a corresponding "Dear Doctor" letter.

1. A boxed warning would have prevented Plaintiffs' exposure.

Dowling—the doctor who prescribed the maintenance tocolysis to Plaintiffs' mother—testified *unequivocally* that he would *not* have prescribed terbutaline to Plaintiffs' mother for maintenance tocolysis if it bore a black-box warning against such use. This occurred at his

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deposition when Dowling was asked that very question: "Doctor, had you received a black box warning or been made aware of a black box warning regarding terbutaline being used as a tocolytic, would you have prescribed it to Mrs. Hamilton?" (PNOL 1033.) Dowling responded: "No." (*Ibid.*) Indeed, Dowling testified that "when that black box warning came out I basically stopped using terbutaline in my practice." (PUMF #86.)

Novartis attempts several counterarguments; all fail.

First, Novartis notes that Dowling did not review the Brethine label. But Dowling nonetheless became aware of the boxed warning when it "was being disseminated through ACOG" (i.e., the American College of Obstetricians and Gynecologists) "and other [a]venues." (PUMF #86.) If a boxed warning had been added in 2001, Dowling would have had *six years* to learn about it before treating Plaintiffs' mother. According to Novartis's own case, if a warning would have deterred the plaintiff's doctor from prescribing the drug at issue, it doesn't matter whether the prescriber would have learned about the warning from the label or some other source. (E.g., *Motus v. Pfizer, Inc.* (C.D. Cal. 2001) 196 F.Supp.2d 984, 997 ["Plaintiff never asked Dr. Trostler what could have been (depending on the answer) the following dispositive question: 'Dr. Trostler, if even without reading the package insert you had become aware that Pfizer itself had disclosed that [whatever is the precise warning regarding suicide that plaintiff considers necessary], would you have prescribed Zoloft to Mr. Motus?'"].)

Second, Novartis suggests that there was no need "to further 'capture physicians' attention'" with a boxed warning because there was already significant information in the public domain that terbutaline was ineffective and dangerous to maternal health when used for maintenance tocolysis. (Def. Br. at 24.) Here, Novartis references bulletins issued by the American College of Obstetrics and Gynecologists, as well as FDA "Dear Colleague" letters. (*Ibid*.) But if that information was sufficient to adequately inform physicians of the downsides of using terbutaline for maintenance tocolysis, the FDA would not have ordered the boxed warning in 2011. As such, Novartis's claim that a boxed warning was unnecessary can be rejected out of hand.

Third, Novartis emphasizes that the boxed warning Kessler says Novartis should have added in 2001—like the boxed warning the FDA actually issued in 2011—might not have specifically

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referenced neurological damage to a fetus.

But the FDA's decision to add a boxed warning against maintenance tocolysis was undoubtedly motivated by the animal studies showing neurologic damage to offspring. (PUMF #43.) In its 2011 response to the Reichmann citizen's petition urging the FDA to update the Brethine label, the FDA stated that it considered "the animal data regarding neurotoxic risks to be 'new safety information,'" then stated in the very next sentence: "*Based on this new safety information … , we conclude that a contraindication and boxed warning are warranted regarding the use of terbutaline sulfate for prolonged or maintenance tocolysis*." (PNOL 0294; see also PNOL 0308 ["The decision to require a Boxed Warning and Contraindication is based on the FDA's review of … animal data suggesting potential risks."].)

If the FDA (and Kessler) felt the potential for neurological damage to the fetus contributed to the need for a boxed warning, why not reference that risk in the box? Because when it comes to curbing a particular prescribing practice, the *fact of* a black-box warning is far more important than the language used in the warning itself. (PUMF #60.)

As Kessler explained, "Once there's a black box warning, it's a whole different—there are different implications for the doctor, and it certainly, you know, changes practice." (PNOL 0731.) Dowling agreed that a black-box warning "rises to a completely different level than a manufacturer's letter or anything else," and that "from a doctor's perspective, you know, we hear that [] loud and clear if an FDA black box warning comes." (PNOL 1043.) Indeed, Dowling testified that "I've never prescribed a drug that had a black box warning before" (*ibid.*), and that "when that black box warning came out I basically stopped using terbutaline in my practice." (PNOL 1031; see also PUMF #81, 86.)

Ultimately, the evidence shows (1) that the animal studies showing neurotoxic effects on the fetus justified a black-box warning against using terbutaline for maintenance tocolysis, and (2) a black-box warning against using terbutaline for maintenance tocolysis would have deterred Dowling from prescribing terbutaline to Plaintiffs' mother for maintenance tocolysis altogether. Nothing more is required from a causal perspective.

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2. A "Dear Doctor" letter would have prevented Plaintiffs' exposure.

As noted above, Kessler also opined that Novartis should have raised Brethine's pregnancy-risk category from "B" to "C," and—critically—added a statement on the label that "[p]ublished animal studies show that rat offspring" exposed to terbutaline in utero "exhibit alterations in behavior and brain development." (PUMF #56–57.) In addition, Kessler opined that Novartis should have notified OB/GYNs of this information with a "Dear Doctor" letter or an equivalent communication, as the FDA did in 2011. (PUMF #59.)

Novartis claims "Plaintiffs have presented no evidence" these efforts would have "changed" Dowling's "decision to prescribe terbutaline as a tocolytic here." (Def. Br. at 28.) But at his deposition, Dowling was asked whether he would have "considered" a "dear doctor letter from the manufacturer of terbutaline sulfate that said there's potential for neurotoxic injury to the developing fetal brain" before prescribing terbutaline for tocolysis. (PNOL 1041.) Dowling responded, "Yes. Yes." (PNOL 1042.) Dowling was then asked, "Would you have communicated that risk insofar as informing the patient?" (PNOL 1042.) Again, he responded, "Yes." (*Ibid.*) Plaintiffs mother said this information would have caused her to refuse to use terbutaline, particularly for prolonged tocolysis. (PUMF #91.)

The fact Dowling prescribed other category "C" drugs does not justify summary judgment.

First, the assumption that Dowling would have disregarded terbutaline's status as a category "C" drug simply because he prescribed other category "C" drugs can only be accomplished by drawing inferences in Novartis's favor, which is contrary to the rules. (*Aguilar v. Atlantic Richfield Co.* (2001) 25 Cal.4th 826, 843.)

Second, as Novartis's own document explains, the "pregnancy category" a particular drug falls into is less important "*than the underlying information that informed the assessment of the pregnancy category*." (Ex. 85 of Def. NOL, quoted at Def. Memo., p. 21, n. 17.) Here, the information underlying terbutaline's pregnancy-risk "C" designation was the fact that "[p]ublished animal studies show that rat offspring" exposed to terbutaline in utero "exhibit alterations in behavior and brain development." (PUMF #57.) And we know Dowling would have considered *that* information because, again, he said as much at his deposition, as just discussed.

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B. Novartis's negligence was the proximate cause of Plaintiffs' terbutaline exposure.

Citing the fact that Novartis sold Brethine to aaiPharma before Plaintiffs' mother was given terbutaline, Novartis claims that Plaintiffs cannot establish proximate causation without showing that Novartis's failure to update the label somehow influenced "aaiPharma's decision to not change its label in the intervening six years it owned the Brethine NDA." (Def. Br. at 26.)

But as the Supreme Court explained, "a successor drug manufacturer's negligent conduct can be 'derivative of [the brand-name drug manufacturer's] allegedly negligent conduct'" if the "successor drug manufacturer [was] sufficiently likely to continue using the warning label it inherited from the prior brand-name manufacturer, even when that label was deficient at the time the NDA was transferred." (*T.H.*, *supra*, 4 Cal.5th at p. 183, quoting *Kesner v. Superior Court* (2016) 1 Cal.5th 1132, 1148.) This rule is necessary "to provide appropriate incentives for the brand-name manufacturer to update the warning label at the earliest possible time." (*T.H.*, *supra*, 4 Cal.5th at p. 186.)

Thus, the relevant proximate-causation question is *not* whether Novartis's original negligence affirmatively induced aaiPharma's subsequent negligence. Rather, the "relevant inquiry" is whether it "was reasonably foreseeable" to Novartis "that aaiPharma would be no more conscientious about updating the warning label than Novartis allegedly had been." (*T.H.*, *supra*, 4 Cal.5th at pp. 182–183; *Cline v. Watkins* (1977) 66 Cal.App.3d 174, 180 ["The issue of the proximate causation of damage flowing from … negligence is thus one of foreseeability."].)

And the Supreme Court already answered that question: Crediting the allegation that "[n]early half of all prescriptions for Brethine … were to slow preterm labor," the Supreme Court held that "it was certainly foreseeable that aaiPharma would be no more conscientious about updating the warning label than Novartis had been." (*T.H.*, *supra*, 4 Cal.5th at 182.) If anything, that conclusion is even stronger now: The Supreme Court's opinion rested on the belief that "nearly half" of Brethine prescriptions were for tocolysis, but the real figure is **65%** (PUMF #10), a point Novartis emphasized when courting aaiPharma as a prospective purchaser of the Brethine product line. (PUMF #13; PNOL 0097 ["He wants to have in the memo the fact that 2/3 of sales derive from off label use[.]"].)

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Novartis could have *eliminated* the possibility the Brethine label would persist in a deficient state simply by adding the required warnings before it sold Brethine to aaiPharma. Indeed, under federal law, "a successor brand-name drug manufacturer has no choice but to use the former manufacturer's drug label" (*T.H.*, *supra*, 4 Cal.5th at p. 182) and "cannot remove any aspect of the warning without FDA approval." (*Id.* at p. 186.) And, as just discussed, Novartis knew or should have known that aaiPharma would be reluctant to add the necessary warnings. These premises—which Novartis does not even attempt to rebut—are sufficient to render Novartis's failure to update the Brethine label a proximate cause of Plaintiffs' injuries from terbutaline under California law.

C. Plaintiffs' terbutaline exposure was a substantial factor in their injuries.

Novartis next argues that Plaintiffs cannot establish medical causation, insofar as there is no evidence that terbutaline causes autism in general ("general causation"), or that it caused autism in Plaintiffs specifically ("specific causation"). Novartis is wrong on both counts.

1. There are triable issues regarding "general causation"

a. Animal studies establish terbutaline is neurotoxic to the developing brain.

Regarding general causation, Plaintiffs retained Dr. Slotkin, a neurotoxicologist at Duke University. Slotkin co-authored **13** of the 15 peer-reviewed animal studies on which the FDA relied in raising Brethine's pregnancy category from "B" to "C." (PUMF #10.) Slotkin testified that the many animal reproduction studies involving terbutaline leave "[a]bsolutely no question that terbutaline damages the developing brain" in mammals. (PUMF #112.)

Novartis offers two arguments why those animal studies are inadmissible here; both fail.

First, Novartis claims Slotkin "conceded that animal studies do not establish a causal relationship between terbutaline and autism spectrum disorder." (Def. Br. at 32.) But Slotkin only agreed that animal studies *alone* do not establish a causal relationship between terbutaline and autism, but was clear that the "animal data *in conjunction with* the human data" *does*. (PNOL 0784.) That premise is hardly novel, as Novartis's own case explains:

> Opinions of any kind are derived from individual pieces of evidence, each of which by itself might not be conclusive, but when reviewed in its entirety are the building blocks of a perfectly reasonable conclusion, one reliable enough to be submitted to a jury along with the tests and criticisms cross-examination and contrary evidence would supply.

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(*Siharath v. Sandoz Pharmaceuticals Corp.* (N.D. Ga. 2001) 131 F.Supp.2d 1347, 1359, quoting *Joiner v. General Elec. Corp.*, (11th Cir. 1996) 78 F.3d 524, 531.)

Second, Novartis challenges the admissibility of the animal studies, noting that "[e]xtrapolations from animal studies to human beings generally are not considered reliable in the absence of a credible scientific explanation of why such extrapolation is warranted." (*Siharath*, *supra*, 131 F.Supp.2d at p. 1366, cited at Def. Br. at 32.)

But under California law, the extent to which animal studies can be extrapolated to humans goes to the *weight* of those studies, not their *admissibility*.

Roberti v. Andy's Termite & Pest Control, Inc. (2003) 113 Cal.App.4th 893, is instructive on this point: In that case, a plaintiff alleged his autism was caused by prenatal exposure to pesticide. Like Novartis, the defendant in *Roberti* asked the trial court to exclude "animal studies relied upon by plaintiff's expert toxicologists … for the assertion that Dursban can cause autism in humans" on the theory that "extrapolation of these animal studies to humans is speculative." (*Id.* at pp. 897–898.) The trial court granted the defendant's motion, but the Court of Appeal reversed, holding that the extent to which animal studies "extrapolate to effects of a substance on humans" only "pertains to the weight of the underlying bases for the expert opinion, not its admissibility." (*Id.* at p. 904.)

Novartis's three contrary cases are not authority. Two of them—*Soldo v. Sandoz Pharm. Corp.* (W.D. Pa. 2003) 244 F.Supp.2d 434, 441, and *Siharath*, *supra*, 131 F.Supp.2d at p. 1350—are federal cases applying the *Daubert* standard for the admissibility of scientific evidence, which "subjects all expert scientific and technical opinion testimony to a threshold reliability test." (*Roberti*, *supra*, 113 Cal.App.4th at p. 904.) But as *Roberti* explained, "*Daubert* … does not alter California law with regard to admissibility of expert medical opinion testimony." (*Ibid.*)

The one California case Novartis cites—*Lockheed Litigation Cases* (Cal. Ct. App. 2005) 23 Cal.Rptr.3d 762—is not good law. The Supreme Court granted review there (see *Lockheed Litigation Cases* (Cal. 2007) 110 P.3d 289), and the rule at the time was that an opinion "is no longer citable as authority [if] hearing has been granted by the Supreme Court." (*In re Angelica V.* (1995) 39 Cal.App.4th 1007, 1011.)

But even if the extent to which animal studies extrapolate to humans was a proper subject for

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summary judgment, extrapolation is warranted here for at least two reasons.

First, animal studies have not only shown that terbutaline is a neurotoxicant, but have also identified "the mechanism by which that occurs." (PUMF #119.) Specifically, terbutaline "overstimulates" receptors in developing nerve cells, "culminating in the subsequent cell damage and functional loss of nerve cells." (PNOL 0717 [¶ 9].) This same mechanism is "present in the developing brain of every organism that has a brain, including humans" (PNOL 0786), and therefore "[t]here's no reason to think that humans would be different from other species" in this effect. (PNOL 0798.) Even under *Daubert*, "an explanation of the biological and/or pathological mechanism at work" is "[a]n important aspect of the ... reliability analysis." (E.g., *Soldo*, 244 F.Supp.2d at p. 561.)

Second, as Slotkin noted, "[t]he structural defects seen in … postmortem brain examinations of children [with autism] have distinct similarities to those that we see in animal models of terbutaline exposure." (Slotkin Depo., p. 69:10–12.) These *objective* pathological findings render moot the difficulty of *subjective* behavioral comparisons between terbutaline-exposed rats and autistic children. (Def. Br. at 32.)

There is thus no truth to the claim that Slotkin "refuses to state how neurologic damage created in rats can be extrapolated to humans." (Def. Br. at 32.) In fact, Slotkin specifically explained why his studies are "generalizable to the developing human brain." (PNOL 0798.)

Nor is it true that "all of Dr. Slotkin's rat studies utilized non-clinical terbutaline, 'which was almost 50 times the intensity of clinical terbutaline used in humans." (Def. Br. at 32.) In fact, four of Slotkin's studies used terbutaline supplied *by Novartis itself*. (PNOL 0718 [¶ 11].) And Slotkin *vehemently* disputes there is a difference in "intensity" between clinical and non-clinical terbutaline (PUMF #141–142), an opinion the FDA seems to share by citing 13 of Slotkin's studies as justification for raising Brethine's pregnancy-risk designation from "B" to "C." (PUMF #40.)

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b. Human studies show that prenatal terbutaline exposure is strongly associated with autism.

Plaintiffs' general-causation evidence also includes opinions from Dr. Zimmerman (a pediatric neurologist) and Dr. Pollock (an epidemiologist), both of whom testified that terbutaline causes autism. (PUMF #97–99.) In reaching their conclusions, Zimmerman and Pollack relied on animal *and* human data, including:

- A 2005 study of fraternal twins which concluded that "[c]ontinuous terbutaline exposure for 2 weeks or longer was associated with increased concordance for autism spectrum disorders in dizygotic twins." (PNOL Ex. 48.)
- A 2011 epidemiological study ("Croen" study) in which "prolonged maternal exposure to terbutaline … in the third trimester" was associated with a significant increase in "ASD risk." (PNOL Ex. 49.)
- A 2016 epidemiological study ("Gidaya" study) which concluded that the use of beta-agonists (like terbutaline) "during pregnancy was associated with increased risk of ASD" and that "longer" exposure "was associated with … increased risk." (PNOL Ex. 50.)

Novartis attacks the 2005 twins study on the ground that "it is 'not an epidemiological study.'" (Def. Br. at 31.) But according to Novartis's own case, "[e]pidemiological evidence is not the only legally sufficient proof for establishing a prima facie case of medical causation." (*Siharath*, 131 F.Supp.2d at p. at 1358.)

Novartis attacks the 2011 Croen study on the ground that it "does not offer evidence linking [beta-agonist] exposure in pregnancy with autism risk." (Def. Br. at 30.) That quote is accurate, but misleading: The Croen study did not draw an association between autism and beta-agonists *generally* because there were an insufficient sample of beta-agonists outside of terbutaline and albuterol. (PNOL 0526.) But it *did* show that "prolonged maternal exposure to terbutaline" during "the third trimester" was associated with a four-fold increase in "ASD risk." (PNOL 0527.) Nor does the "may" qualifier in that study's conclusion detract from its value. Again, "may" in peer-reviewed scientific literature still connotes a confidence interval that exceeds the more-likely-than-not standard. (PNOL 0719–0720 [¶¶ 16–17].)

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Novartis attacks the 2016 Gidaya study by falsely claiming that "[t]he authors conceded in the text that the purported association" between autism and beta-agonist use "disappeared once the researchers controlled for asthma, … demonstrating that the weak association was likely due to 'imperfect cofounder control.'" (Def. Br. at 31.) In fact, the text states that the association between beta-agonists and autism persisted "*even after adjustment for maternal asthma and other covariates*." (PNOL 0532.)

Ultimately, a jury will have to determine whether these studies, combined with the animal data, are sufficient to support the belief that, more likely than not, terbutaline causes neurological damage associated with autism. But, at this juncture, this evidence—viewed in a light most favorable to Plaintiffs—is sufficient to foreclose summary judgment.

2. There are triable issues regarding "specific causation."

Novartis next argues that Plaintiffs cannot establish that their prolonged prenatal exposure to terbutaline was the most likely cause of their autism. Here, Novartis cites genetics and a litany of other potential causes that, according to Novartis, Plaintiffs' experts have failed to "rule out."

But as a threshold matter, as the party seeking summary judgment, it was Novartis's burden to *rule out* terbutaline as a substantial factor in Plaintiffs' injures, which it failed to do in the scant three pages of its brief dedicated to that issue. That alone is fatal to Novartis's motion.

In any event, Dr. Brown, an expert on the genetics of autism, testified regarding whether genetics caused Plaintiffs' autism. According to Brown, the state of the art genetic tests for autism are the "Fragile X" test and the "Chromosomal Microarray." (PUMF #64.) Nonetheless, Plaintiffs also underwent a *third* test known as "Whole Exome Sequencing." (PUMF #65.) These tests showed that Plaintiffs were free of all known genes associated with autism. (PUMF #65.) With that evidence in mind, Brown opined that, to a reasonable degree of medical certainty, Plaintiffs' autism was not due to genetics. (PUMF #65–67; PNOL 0708 [¶ 10].)

Novartis claims Brown's opinion is inadmissible because current genetic testing cannot identify *every* gene that might be associated with autism. (Def. Br. at 34.) But "California has rejected the notion that an expert must exclude all possibilities in reaching a specific causation opinion." (*Cooper v. Takeda Pharmaceuticals America, Inc.* (2015) 239 Cal.App.4th 555, 585–586.)

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Thus, the fact that there "may be scientifically unknown causes" of a disease "that [an expert] could not rule out" is "not a proper basis for the court to exclude [the expert's] testimony." (*Id.* at p. 585.)

Moreover, Novartis's argument wrongly assumes autism is *either* genetic *or* has some other cause. But as Dr. Brown explained, autism is likely "a combination of heritability and environmental effects" in that terbutaline likely causes autism when "a genetically susceptible individual" is exposed to it in utero. (PNOL 0860; PUMF #68.) Thus, the possibility Plaintiffs have an as-yet unknown gene that may be associated with autism does not even remotely eliminate their prenatal exposure to terbutaline as a substantial factor in their injuries.

The same can be said for the litany of other "possible" causes of autism Novartis lists in its brief. Again, Plaintiffs' causation theory is that Plaintiffs' prolonged terbutaline exposure in utero "[i]s a major substantial cause, *not the only cause*." (PNOL 0914.) But the fact remains that whatever else *might* have contributed to it, Plaintiffs experts have testified that Plaintiffs autism would not have occurred but for the exposure. (PUMF #159–160.)

The evidence certainly supports the premise that Plaintiffs' prolonged prenatal exposure played at least a substantial role, and likely the *predominant* role in their autism: Indeed, according to Pollock, the science indicates that such exposure increases the risk of developing autism by over **580%**. (PUMF #97.) But even though Novartis's epidemiologist was aware of all the same factors Novartis cites its brief as possible causes of Plaintiffs' autism, she could not think of any other risk factor relevant to Plaintiffs that even came close. (PUMF #98; PNOL 0934–0935.)

While Novartis no doubt has much to say about the relative *weight* of the epidemiological evidence, it must save those arguments for trial: It is well settled that, in reviewing a motion for summary judgment, "[t]he trial court may not weigh the evidence in the manner of a factfinder to determine whose version is more likely true." (*Binder v. Aetna Life Ins. Co.* (1999) 75 Cal.App.4th 832, 840.) Instead, for present purposes, the scientific evidence must be viewed in a light most favorable to Plaintiffs. And, when it is, it becomes evident Novartis has failed to carry its burden to establish that Plaintiffs' terbutaline exposure was not a substantial factor in their autism.

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CONCLUSION

For the foregoing reasons, Novartis's motion for summary judgment must be **denied**.

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