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IN THE COURT OF APPEAL OF THE STATE OF CALIFORNIA

SECOND APPELLATE DISTRICT

DIVISION THREE

RISPERDAL AND INVEGA PRODUCT LIABILITY CASES	B284315, B284002, B284317 (Los Angeles County Super. Ct. Nos. BC562540, BC583302, BC604937) (JCCP No. 4775)

APPEALS from judgments of the Superior Court of Los Angeles County, William E. Highberger, Judge. Affirmed in part and reversed in part.

Bernstein Liebhard and Daniel C. Burke for Plaintiff and Appellant C.S.

Law Office of Martin N. Buchanan, Martin N. Buchanan; Engstrom, Lipscomb & Lack and Ann Howitt for Plaintiffs and Appellants J.D. and J.T.

Drinker Biddle & Reath, Rodney M. Hudson, William A. Hanssen; Faegre Drinker Biddle & Reath and Rodney M. Hudson for Defendants and Respondents.

C.S., J.D., and J.T. (collectively plaintiffs) were adolescents who were prescribed the antipsychotic drug risperidone after it was approved by the Food and Drug Administration (FDA) to treat behavioral symptoms in children with autism. They allege that risperidone caused them to develop gynecomastia, a condition characterized by the enlargement of male breast tissue. Plaintiffs sued risperidone's manufacturers and distributors, Janssen Pharmaceuticals, Inc.; Janssen Research and Development, LLC; Johnson & Johnson; and McKesson Corporation (collectively and interchangeably, Janssen) for failure to adequately warn of the risk of gynecomastia on the drug's label. Janssen moved for summary judgment on federal preemption grounds against plaintiffs. Janssen also moved for summary judgment against the individual plaintiff, C.S., on the ground that he could not raise a triable issue of fact under New York's proximate cause standard, which requires the patient to show that the treating physician would have changed her prescribing behavior had she had an adequate warning. The trial court granted both motions. For the reasons set forth below, we affirm the summary judgment against C.S., but reverse the summary judgment decided on preemption grounds.

BACKGROUND

I. Janssen researches a pediatric indication for risperidone

Risperidone[1] is an antipsychotic medication that was first approved by the FDA in 1993 for managing manifestations of psychotic disorders in adults. Risperidone elevates blood levels of prolactin, a hormone produced by the pituitary gland. Elevated

[1] Risperdal is the brand name for risperidone.

levels of prolactin (hyperprolactinemia) are associated with gynecomastia.

After risperidone was approved for use in adults, Janssen sought a pediatric indication to treat irritability associated with autism in children. Before it sought FDA approval for pediatric use, Janssen conducted five studies of prolactin levels and prolactin-related side effects in 592 children who took risperidone for disruptive behavior disorders. The combined results of these five studies showed that the prolactin levels of children elevated quickly after being put on risperidone, peaked during weeks four through seven, then gradually declined. At weeks four through seven, 70.5 percent of children had elevated prolactin levels. Thirty of the 592 children, or five percent, developed prolactin-related side effects, with gynecomastia being the most common.

The largest of the pediatric studies was an open label risperidone only use study known as RIS-INT-41 (study 41). (Croonenberghs et al., *Risperidone in Children With Disruptive Behavior Disorders and Subaverage Intelligence: A 1-Year, Open-Label Study of 504 Patients* (Jan. 2005) 44 Journal of the American Academy of Child and Adolescent Psychiatry 64.) It followed 504 children between the ages of five and 14 who used risperidone over the course of one year. The results of study 41 showed that 5.5 percent of the boys in the study developed gynecomastia. Janssen also conducted an extension study of study 41 that followed 48 of the children who continued to take risperidone for a second year known as RIS-INT-70 (study 70). (Reyes et al., *Long-Term Use of Risperidone in Children with Disruptive Behavior Disorders and Subaverage Intelligence: Efficacy, Safety, and Tolerability* (2006) 16 Journal of Child and

Adolescent Psychopharmacology 260.) Study 70 showed that 14.3 percent of the children developed gynecomastia.

The pooled results of the five pediatric studies were published in a 2003 article in the Journal of Clinical Psychiatry. (Findling et al., *Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents* (Nov. 2003) 64 Journal of Clinical Psychiatry 1357.) The purpose of the article was to investigate prolactin levels in children taking risperidone and to explore any relationship to "side effects hypothetically attributable to prolactin" or "SHAP", which included gynecomastia.[2] For the article, Janssen commissioned a statistical analysis of the five pediatric studies that generated a number of tables. One of those tables was table 21, which compared subjects with elevated prolactin levels and those with normal prolactin levels for different study time periods. For children prescribed risperidone for a period of eight to 12 weeks, table 21 showed that those with elevated prolactin levels were 2.8 times more likely to have suffered prolactin-related side effects, particularly gynecomastia.

A July 2002 draft manuscript of the article circulated internally within Janssen referred to the statistically significant association between elevated prolactin in risperidone users and prolactin related adverse events during weeks eight through 12. In internal emails, Janssen officials expressed concerns about how to deal with the table 21 statistics. One Janssen representative stated, "I think we need to include the lack of association between . . . [prolactin] level or SHAP, as our advisors tell us that this is one serious concern about prolactin. If we can

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[2] SHAP is an acronym invented by Janssen. Gynecomastia is the only prolactin-related side effect in males.

demonstrate that the transient rise in [prolactin] does not result in abnormal maturation or SHAP, this would be most reassuring to clinicians." Another Janssen representative stated, "Key message—prolactin rise is transient and not related to side effects hypothetically attributed to prolactin." Janssen then commissioned a revised statistical analysis, which excluded all findings of prolactin-related side effects in males 10 years or older. With the revised data set, Janssen created a new table, which was similar to table 21; however, it no longer showed any statistical significance for prolactin-related side effects at weeks eight through 12.

In October 2002, Janssen prepared another draft of the article based on the revised statistics. The draft manuscript claimed that there "was no statistical difference in the percentage of patients who reported SHAP for any analysis time period, whether or not prolactin levels were normal or above the ULN [upper limit of normal] (range)." The final published version of the article again omitted all prolactin-related side effects in boys 10 years of age or older, and did not mention or include the original analysis results for weeks eight through 12. Table 21 was not disclosed by Janssen to the outside authors of the article.

II. The FDA approves risperidone's label and pediatric indication

In 2003, Janssen submitted a supplemental new drug application seeking a pediatric indication for risperidone to treat children with autism. Janssen submitted the pooled pediatric safety data to the FDA. Janssen described the data pooling portion of Janssen's proposed statistical analysis plan, which included data from autism studies as well as data from pediatric

disruptive behavior disorder studies. Janssen did not submit table 21 as part of its application.

In July 2006, the FDA sent Janssen an approvable letter for its application and attached proposed labeling that included language describing the method for pooling pediatric safety data.[3] The FDA requested that Janssen specify the number of pediatric patients in the studies. Janssen responded with two proposals for calculating the number of patients for adverse event purposes. The FDA found discrepancies in Janssen's calculation, noting that the "proposed labeling uses 1348 as the denominator for the calculation of the rate of . . . (. . . adverse events) in pediatric clinical trials" while the other events observed during the premarketing evaluation of risperidone section states that risperidone was studied in 1,923 children. The FDA asked Janssen to clarify the total number of patients exposed to risperidone and to provide an updated percentage for gynecomastia.

Janssen explained that the number of risperidone-treated subjects across all studies of children and adolescents with autism or disruptive behavior disorders was 1,348. The FDA asked Janssen to include any new serious adverse events experienced by children to the list of events observed during premarketing evaluation and to include all pediatric studies beyond autism and disruptive behavior disorders. These

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[3] An approvable letter is a written communication to an applicant from the FDA stating that the agency will approve the application if specific additional information or material is submitted or specific conditions are met. (21 C.F.R. § 314.110(a) (2019); see *id.* § 814.44(e)(2019) [describing approvable letters for medical devices].)

additional studies brought the total number of risperidone-treated subjects to 1,923.

The FDA's revised label included 1,923 patients as a denominator and a proposed calculation for the reported incident rate specific to gynecomastia in the label. The FDA revised the reported rate of gynecomastia from .03 percent to 2.7 percent. Janssen responded to the FDA's proposal by explaining that 1,923 pediatric patients was an accurate number; however, 38 patients were in an ongoing clinical study and full safety data were not yet available. Janssen proposed a rate based on 1,885 patients, excluding the 38 patients from the ongoing study. This brought the rate of gynecomastia to 2.3 percent. The 2.3 percent rate included the results from studies 41 and 70.

In October 2006, the FDA approved the pediatric use of risperidone for irritability associated with autistic disorder with an updated label. Under the precautions section for pediatric use, the label stated, "The efficacy and safety of [risperidone] in the treatment of irritability associated with autistic disorder were established in two 8-week, placebo-controlled trials in 156 children and adolescent patients, aged 5 to 16 years. . . . Additional safety information was also assessed in a long-term study in patients with autistic disorder, or in short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight, and who received similar dosages of [risperidone] as patients . . . treated for irritability associated with autistic disorder."

The precautions section also contained a section on hyperprolactinemia, stating, "As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin

levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. [¶] . . . [G]ynecomastia . . . ha[s] been reported in patients receiving prolactin-elevating compounds." The label went on to state that "[r]isperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS—Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years), 49% of patients who received risperidone had elevated prolactin levels compared to 2% of patients who received placebo. [¶] In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, . . . gynecomastia was reported in 2.3% of risperidone treated patients. [¶] The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated." Under adverse reactions and other events observed during the premarketing of risperidone, the label stated that during premarketing assessment, risperidone was administered to 2,607 adult patients and 1,923 pediatric patients. That same section listed gynecomastia as "rare" and defined rare events to mean those occurring in fewer than one in 1,000 patients.

III. Citizens petition

In July 2012, Sheller P.C. (Sheller), a law firm representing hundreds of individuals who had taken risperidone, petitioned the FDA to immediately revoke the pediatric indication for risperidone unless and until the long-term safety of the drug could be demonstrated, or in the alternative, require that the risperidone label include a box warning based on the lack of

sufficient safety data (citizens petition).[4] The citizens petition alleged that the risperidone label did not reflect the long-term safety data used to support risperidone's pediatric indications and it did not reflect the true risks posed by the drug. The citizens petition alleged that the portion of the risperidone label stating that gynecomastia was reported in 2 to 3 percent of risperidone-treated patients was misleading and that the actual rate of gynecomastia was five percent. The citizens petition also alleged that the risperidone label failed to recommend that physicians should closely monitor their adolescent patients' prolactin levels, routinely examine them for abnormal breast growth, and discontinue risperidone use at the first sign of any of those symptoms.

In addition to requests for a box warning and revocation of the pediatric indication, the citizens petition indicated that Janssen was in possession of documents that substantiated the allegations. However, those documents were subject to confidentiality orders in other risperidone litigation and petitioners were unable to supply those documents to the FDA. The petition requested that the FDA obtain the documents directly from Janssen or to release petitioners from the confidentiality orders. In response, the FDA requested Janssen to submit any data in its possession relevant to the use of risperidone in children and adolescents that it had not previously provided. Janssen responded that it had not identified any data

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[4] The FDA generally requires special problems with a drug, particularly those that may lead to death or serious injury, to be placed in a prominently displayed box on the label. (21 C.F.R. § 201.80(e) (2019).)

that it was required to submit pursuant to its statutory and regulatory obligations.

The FDA denied the citizens petition, disagreeing with the assertion that a lack of long-term safety data is a basis for either revoking the pediatric indications for risperidone or adding a new boxed warning. The FDA was concerned that revoking risperidone's pediatric indications until long-term safety could be demonstrated "would be tantamount to a long-term or permanent withdrawal, thereby removing an important and beneficial therapeutic option for many children and adolescents with these disorders." The FDA stated that based on reviews of clinical data submitted by Janssen, published literature, and postmarketing surveillance, there was no evidence that risperidone was unsafe or anything else that warranted revoking the pediatric indication of the drug. The FDA also stated, "Gynecomastia is a common clinical manifestation of hyperprolactinemia, regardless of cause,[fn. omitted] and does not represent a serious adverse event" as defined in 21 Code of Federal Regulations, section 312.32 (a) (2019).[5]

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[5] "An adverse event . . . is considered 'serious' if . . . it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." (21 C.F.R. § 312.32 (a) (2019).)

Further, the FDA found no basis for requiring a box warning about the lack of long-term safety data associated with pediatric use of risperidone. In response to the petitioner's box warning request, the FDA noted that risperidone is "known to elevate blood levels of prolactin, a naturally occurring hormone produced by the pituitary gland in the brain. Elevated levels of prolactin (hyperprolactinemia) from any cause can be associated with a number of clinical effects, including breast enlargement (also called gynecomastia)." "The risk of hyperprolactinemia associated with certain antipsychotics has been basic textbook knowledge in psychiatry for many years."

In its denial, the FDA noted that it was not responding to any labeling requests other than the request for a box warning and the revocation of the pediatric indication. "Although your petition includes an extensive discussion of the current labeling of [risperidone], you do not make specific labeling requests other than . . . that FDA require a new boxed warning for Risperdal and all generic versions of risperidone. We therefore do not respond to your specific contentions regarding the current labeling of these products."

IV. C.S.

C.S. is a New York resident who was diagnosed with autism and attention deficit hyperactivity disorder as a child. He exhibited aggressive behavior including screaming, tantrums, and physical aggression. C.S. and his mother consulted a child psychiatrist to treat these behavioral symptoms. The psychiatrist prescribed risperidone to C.S. from April 2009 to July 2010.

Before prescribing a particular medication, the psychiatrist's practice was to review the risks and benefits with

her patients. At the time she prescribed risperidone to C.S., her custom was to mention gynecomastia in "passing" but she did not "delve into" it the way she would have with other side effects. When presented with the results of study 70 which showed a gynecomastia rate of 12.5 percent, the psychiatrist stated she would have emphasized gynecomastia as a side effect to C.S.'s mother and would have included it as part of her risk-benefit analysis. She currently informs her patients that gynecomastia is a potential side effect of risperidone use, but still emphasizes other side effects more.

The psychiatrist's records do not indicate that she mentioned gynecomastia to C.S.'s mother or observed the condition in C.S. The psychiatrist would have noted gynecomastia in C.S.'s medical records if she had observed the condition, or if either C.S. or his mother had mentioned it. Indeed, C.S.'s medical records do not mention gynecomastia, breast growth, or elevated prolactin during risperidone use. A few months after C.S. stopped using risperidone, another physician examined C.S. and found his chest to be " 'normal contour, normal shape and expansion, clear to auscultation' " and made the same observation five months later.

Two months after discontinuing risperidone, C.S. was prescribed, haloperidol, another antipsychotic associated with elevated prolactin. Haloperidol's prescribing information in effect at the time stated, "[a]ntipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration." C.S. used haloperidol from September 2010 through 2016. In November 2011, over a year after C.S. discontinued risperidone, a physician noted C.S. had abnormal breast growth. In February 2015, C.S. was diagnosed with idiopathic gynecomastia.

V. Procedural history

Plaintiffs, along with thousands of other individuals sued Janssen, alleging that they developed gynecomastia from their use of risperidone and that Janssen failed to adequately warn of the risk. The complaints were coordinated and assigned to a single trial court.

The trial court divided the cases into four separate groups: individuals who used risperidone as children before the October 2006 label change; individuals who used risperidone as children after the October 2006 label change; individuals who used risperidone as children before and after the October 2006 label change; and individuals who used Invega, but not risperidone.[6] Plaintiffs are from the second group of individuals who used risperidone after the October 2006 label change.

Janssen moved for summary judgment against six of the plaintiffs who took risperidone after the 2006 label change, including J.D., J.T., and C.S. Janssen asserted that their claims were preempted by federal law governing prescription medication. Janssen also moved for summary judgment on nonpreemption grounds against C.S, arguing that C.S. could not raise a triable issue of fact under New York's proximate cause standard. The trial court granted both motions.

J.D., J.T., and C.S. filed individual appeals. We consolidated the appeals, ordered J.D. and J.T. to file joint briefing on the preemption issue, and allowed C.S. to join in that briefing and to file separate briefing on the nonpreemption issues raised in the case-specific motion for summary judgment. After

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[6] Invega is a risperidone-related drug. Individuals who took Invega are not the subject of this appeal.

the appeals were fully briefed, the United States Supreme Court decided *Merck Sharp & Dohme Corp. v. Albrecht* (2019) ___ U.S. ___, ___ [139 S.Ct. 1668] (*Merck Sharp*), addressing the same preemption question at issue here. Janssen, J.D., and J.T. filed supplemental briefs discussing *Merck Sharp*.

DISCUSSION

As noted above, there are two motions for summary judgment at issue: one entered against a group of plaintiffs who used risperidone after the FDA approved the 2006 label and another on case-specific grounds against C.S. Regarding the preemption issue, the parties dispute whether the trial court had authority to determine the preemption question as matter of law or whether it was required to submit underlying factual disputes to a jury. On the merits, the parties contest whether Janssen met its burden to show that plaintiffs' claims were preempted. With respect to the case-specific summary judgment against C.S., the parties dispute whether there is a triable issue of fact that risperidone's label proximately caused C.S. to develop gynecomastia. We address each issue in turn.

I. Preemption

A. *Preemption is decided as a matter of law*

The parties' first dispute is whether the trial court had authority to decide the preemption issue as a matter of law. Plaintiffs argue that the trial court overstepped its authority by deciding the preemption issue in the face of underlying factual disputes that should have been submitted to a jury. However, the United States Supreme Court in *Merck Sharp*, *supra*, 139 S.Ct. 1668 rejected this argument. "[J]udges, rather than lay juries, are better equipped to evaluate the nature and scope of an

agency's determination. Judges are experienced in '[t]he construction of written instruments,' such as those normally produced by a federal agency to memorialize its considered judgments. [Citation.] And judges are better suited than are juries to understand and to interpret agency decisions in light of the governing statutory and regulatory context. [Citations.] To understand the question as a legal question for judges makes sense given the fact that judges are normally familiar with principles of administrative law." (*Id.* at p. 1680.) *Merck Sharp* acknowledged that "brute facts will prove relevant to a court's legal determination about the meaning and effect of an agency decision"; however, these factual questions are "subsumed within an already tightly circumscribed legal analysis." (*Ibid.*) They do not "warrant submission alone or together with the larger pre-emption question to a jury." (*Ibid.*) Accordingly, the trial court was correct to decide the issue without submitting any purported underlying factual questions to a jury.

B. *Plaintiffs' claims are not preempted*

Although the trial court had authority to decide the issue, in light of *Merck Sharp*, it came to the wrong conclusion. Janssen did not meet its burden to establish its preemption defense.

To understand plaintiffs' theory of the case and Janssen's preemption defense, we provide an overview of FDA regulations and the process followed by drug manufacturers to appropriately label their drugs. "The FDA regulates the safety information that appears on the labels of prescription drugs that are marketed in the United States. [Citation.] Although we commonly understand a drug's 'label' to refer to the sticker affixed to a prescription bottle, in this context the term refers more broadly to the written material that is sent to the physician

who prescribes the drug and the written material that comes with the prescription bottle when the drug is handed to the patient at the pharmacy. [Citation.] These (often lengthy) package inserts contain detailed information about the drug's medical uses and health risks." (*Merck Sharp*, *supra*, 139 S.Ct. at pp. 1672–1673.)

Federal regulations set out the requirements for the content, format, and order of the safety information on a drug's label. (21 C.F.R. § 201.57(c) (2019).) The labels must include: "(1) prominent 'boxed' warnings about risks that may lead to death or serious injury; (2) contraindications describing any situation in which the drug should not be used because the risk of use outweighs any therapeutic benefit; (3) warnings and precautions about other potential safety hazards; and (4) any adverse reactions for which there is some basis to believe a causal relationship exists between the drug and the occurrence of the adverse event." (*Merck Sharp*, *supra*, 139 S.Ct. at p. 1673.) The section where a particular risk appears on a drug label is an indicator of the likelihood and severity of the risk, ensuring that less important information does not overshadow more important information. (*Ibid.*) It prevents over exaggeration of risk and excludes speculative or hypothetical risks such that appropriate use of an otherwise beneficial drug is discouraged. (*Ibid.*)

A "central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times." (*Wyeth v. Levine* (2009) 555 U.S. 555, 570–571.) While drug manufacturers work with the FDA to develop an appropriate label when they apply for approval of a new drug, the drug manufacturer, not the FDA, is responsible for crafting an adequate label and ensuring that the warnings remain adequate

while the drug is on the market. (*Ibid*.; 21 U.S.C.S. § 355(a), (b), & (d); 21 C.F.R. § 314.125(b)(6) (2019).) The drug manufacturer has a duty to conduct postmarket surveillance and revise the label as soon as there is reasonable evidence of an association of a serious hazard with a drug. (21 C.F.R. §§ 201.80(e) (2019), 314.80(b) (2019).)

FDA regulations account for changes to drug safety information changing over time that necessitate revisions to a drug's label. (21 C.F.R. §§ 314.80(c) (2019), 314.81(b)(2)(i) (2019).) Substantive label changes generally require advance FDA approval. However, an FDA regulation called the " 'changes being effected' " or " 'CBE' " regulation permits drug manufacturers to change a label without advanced approval if the change is designed to add or strengthen a warning where there is " 'newly acquired information' " about the " 'evidence of a causal association' " between the drug and a risk of harm. (*Merck Sharp*, *supra*, 139 S.Ct. at p. 1673; 21 C.F.R. § 314.70(c)(6)(iii)(A) (2019).) "Newly acquired information is data, analyses, or other information not previously submitted to the Agency, which may include (but is not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events, or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." (21 C.F.R. § 314.3(b) (2019).) Manufacturers cannot propose a label change that is not based on newly acquired information and supported by reasonable evidence of a causal association with the drug. (21 C.F.R. §§ 314.70(c)(6)(iii)(A) (2019), 201.57(c)(6)(i) (2019).) The FDA reviews CBE submissions and can reject label

changes even after the manufacturer has made them. (See 21 C.F.R. § 314.70(c)(6), (7) (2019).)

The FDA, however, has limited resources and "manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge." (*Wyeth v. Levine*, *supra*, 555 U.S. at pp. 578–579.) To fill the void, "[s]tate tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly." (*Id.* at p. 579.) These lawsuits are a complementary form of drug regulation and offer an important layer of consumer protection. They also support the premise that manufacturers always bear ultimate responsibility for their drug labeling. (*Ibid.*)

In *Wyeth v. Levine*, *supra*, 555 U.S. at page 572, a patient sued a drug manufacturer for a failure-to-warn claim after she developed gangrene and her arm had to be amputated as a result of her use of an antinausea drug. A physician's assistant administered the drug using the "IV-push method" whereby the drug is injected directly into the patient's vein. Using this method greatly increased the risk that the drug could enter a patient's artery and cause irreversible gangrene. (*Id.* at p. 559.) The drug manufacturer argued that the patient's state-law claims were preempted because it would have been impossible to comply with both its state-law duties and federal labeling duties, which require FDA approval of the exact text of a drug label. (*Id.* at p. 568.) The United States Supreme Court observed, however, that while typically, a manufacturer may only change a drug label after it gets FDA approval for the change, the CBE regulation makes an exception, permitting a manufacturer to make certain changes to its label before receiving the FDA's

approval. (*Ibid.*) For example, a manufacturer can "add or strengthen a contraindication, warning, precaution, or adverse reaction" without waiting for the FDA to approve the change. (21 C.F.R. § 314.70(c)(6)(iii)(A) (2019).) Therefore, a drug manufacturer can be held liable for a state law failure-to-warn claim if it could have revised its label using the CBE process but failed to do so. (See *Merck Sharp*, *supra*, 139 S.Ct. at pp. 1677–1678.) *Levine* concluded that state-law failure-to-warn claims concerning prescription drugs are preempted only where there is clear evidence that the FDA would have rejected the proposed label change. (*Levine*, at pp. 571–572.)

" '[C]lear evidence' is evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." (*Merck Sharp*, *supra*, 139 S.Ct. at p. 1672.) In this context clear evidence is not a typical standard of proof. (*Id.* at p. 1679.) "Standards of proof, such as preponderance of the evidence and clear and convincing evidence, have no place in the resolution of this question of law." (*Id.* at p. 1685 (conc. opn. of Alito, J.).) "The underlying question . . . is whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law. And, of course, in order to succeed with that defense the manufacturer must show that the answer to this question is yes." (*Id.* at p. 1678.)

This type of impossibility preemption is a demanding defense. (*Wyeth v. Levine*, *supra*, 555 U.S. at p. 573.) Because the CBE regulation permits changes, "a drug manufacturer will

not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." (*Merck Sharp*, *supra*, 139 S.Ct. at p. 1679.) "[T]he very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept." (*Levine* at p. 570.)

Plaintiffs assert that Janssen could have used the CBE process to revise the risperidone label by: (1) warning of a direct correlation between risperidone use and gynecomastia; (2) adding a recommendation for regular monitoring of prolactin levels and physical examinations of children taking the drug; (3) deleting language on the label referring to gynecomastia as a rare event occurring in fewer than 1/1000 patients; and (4) disclosing the results of studies 41 and 70.

In support of their labeling contentions, plaintiffs argue that table 21, studies 41 and 70 constitute newly acquired information for purposes of the CBE regulation.

As an initial matter, we do not agree with plaintiffs that studies 41 and 70 constitute newly acquired information. By definition, newly acquired information is "information not previously submitted to the [FDA]." (21 C.F.R. § 314.3(b)(4) (2019).) The plaintiffs do not dispute that Janssen submitted the results of both studies to the FDA as part of its application for a pediatric indication. Thus, because the FDA had the results of studies 41 and 70, they cannot serve as the basis for a CBE submission. Further, to the extent plaintiffs argue that the results of these studies demonstrated a higher rate of gynecomastia than the 2.3 percent indicated on the label, the FDA made clear in its discussions with Janssen during the labeling process that it wanted adverse events, such as

gynecomastia, to be calculated from all sources and pooled to ensure that all events across multiple studies were captured. Because the FDA had studies 41 and 70, and it expressly asked for the rate of gynecomastia to be calculated using pooled results from all studies (not just the select few identified by plaintiffs), there is clear evidence that the FDA was fully informed and required Janssen describe the risk of gynecomastia in the manner that it did.

Plaintiffs' argument that the risperidone label was inadequate because a section listed gynecomastia as a rare event occurring in less than one in 1,000 patients, thus contradicting the results of the pediatric studies, is also without merit. The term "rare" appears in the section, other events observed during the premarketing evaluation of Risperdal which states that Risperdal was administered to 2,607 adult patients and 1,923 pediatric patients. The section goes on to state that events are categorized by body system and listed in order of decreasing frequency according to the following definitions: "frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo–controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients." Thus, it appears this gynecomastia rate was in reference to all patients, not just children. Plaintiffs have cherrypicked this language as well as the pediatric studies to create a purported discrepancy in the reported rate of gynecomastia on the risperidone label.

We are thus left with table 21 as a basis to support a potential label change via the CBE regulation. It is undisputed that Janssen did not submit table 21 during the application or

labeling process.[7] Nevertheless, Janssen offers several arguments why table 21 does not preclude its preemption defense. First, table 21 is not newly acquired information because it did not reveal risks of a different type or greater severity or frequency and the analysis was based on the studies submitted to the FDA. Janssen argues that the label warned of the exact type of risk, gynecomastia, and table 21 does not change the 2.3 percent rate. While it is true that table 21 does not change the rate of gynecomastia reported on the label, Janssen's position overlooks the fact that table 21 provided additional information with respect to elevated prolactin levels during different time periods. Specifically, table 21 tended to show that children who had elevated prolactin after taking risperidone for eight to 12 weeks were 2.8 times more likely to develop prolactin-related side effects, including gynecomastia. As the risperidone label made no mention of the likelihood of developing side effects related to elevated prolactin levels for different time periods, this information demonstrated a risk of greater frequency then reported on the label.

Second, Janssen argues that table 21 is not new and does not support a label change because the FDA confirmed that Janssen submitted all the necessary data and information to conclude that risperidone was appropriately labeled. In support, Janssen refers to the FDA's statement in a reply brief filed in a separate litigation between the FDA and Sheller, the law firm that filed the citizens petition. The statement is of little value here. Sheller sued the FDA, asserting it had to expend unnecessary resources in various forums where it was suing Janssen for risperidone-related injuries. The primary issue in

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[7] The FDA did not receive table 21 until October 2015.

the brief cited by Janssen was whether the law firm had standing to sue the FDA for denying the citizens petition. This statement is not clear evidence that the FDA would have rejected a CBE submission based on table 21. Not only was it made in a wholly different context, but "the only agency actions that can determine the answer to the pre-emption question, . . . are agency actions taken pursuant to the FDA's congressionally delegated authority." (*Merck Sharp*, *supra*, 139 S.Ct. at p. 1679.) The FDA can communicate its disapproval of a warning by means of notice-and-comment rulemaking setting forth labeling standards, (see, e.g., 21 U.S.C.S. § 355(d); 21 C.F.R. §§ 201.57 (2019), 314.105 (2019)); by formally rejecting a warning label that would have been adequate under state law, (see, e.g., 21 C.F.R. §§ 314.110(a) (2019), 314.125(b)(6) (2019)); or with other agency action carrying the force of law (cf., e.g., 21 U.S.C.S. § 355(o)(4)(A)). The FDA's reference in a reply brief filed in a separate lawsuit in which the agency is seeking to avoid liability, is not the type of official action required by *Merck Sharp*.

Third, Janssen contends that, to the extent table 21 supports a monitoring recommendation, the CBE process does not allow Janssen to unilaterally change an FDA-approved label to make a monitoring recommendation. Janssen reasons that, because monitoring recommendations are included in the highlights section of a drug label (21 C.F.R. § 201.57(b)(2)(v)(C) (2019)) and a change to that section requires prior approval from the FDA, Janssen could not make that change via the CBE process. Janssen's argument misses the mark. Although the highlights section may indicate certain "recommendations for patient monitoring that are critical to safe use of the drug" (21 C.F.R. § 201.57(a)(10) (2019)), it does not have to include all

of the same monitoring recommendations contained in the full prescribing information, which need only be "helpful in following the patient's response or in identifying possible adverse reactions." (21 C.F.R. § 201.57(c)(6)(iii) (2019).) The highlights section includes warnings and precautions and adverse reactions. (21 C.F.R. § 201.57(a)(10), (11) (2019).) Thus, if the CBE process could not be used to add any information that could conceivably be included in the highlights section, the CBE process could never be used to add any new warning, precaution, or adverse reaction without FDA approval. This is contrary to the purpose of the CBE process and the holdings in *Wyeth v. Levine*, *supra*, 555 U.S. 555.

We also reject Janssen's assertion that the denial of the citizens petition was clear evidence the FDA would have rejected a proposed label change based on the evidence presented in table 21. As stated above, the FDA did not have table 21 when it denied the citizens petition. Impossibility preemption requires the drug manufacturer to show that it fully informed the FDA. Janssen did not. Nevertheless, Janssen argues that, because the FDA rejected similar allegations in the citizens petition, the FDA would have also rejected plaintiffs' claims here. But the citizens petition made a much broader request, asking the FDA to essentially take risperidone off the market or include the risk of gynecomastia in the box warning, the most serious type of warning on the label. (See 21 C.F.R. § 201.57(c)(1) (2019) [requiring contraindications leading to death or serious injury be included in boxed warning].) In contrast, here, plaintiffs' argument is that table 21 could have supported a label change that included a recommendation to monitor prolactin levels at certain periods while a patient was taking risperidone. The fact

that the allegations in the citizens petition were similar and partly based on some of the evidence presented here does not change our conclusion that the claims are distinct. Hypothetical labeling changes and speculative future rejections are not clear evidence of an impossibility preemption defense. (See *Merck Sharp*, *supra*, at p. 1682 (conc. opn. of Thomas, J.).)

Accordingly, Janssen did not meet its burden to show by clear evidence that it fully informed the FDA and, in turn, the FDA rejected a proposed label change. Plaintiffs' claims based on the information in table 21 are not preempted.

II. C.S. cannot establish causation

Turning to the merits of Janssen's case-specific summary judgment against C.S., we find Janssen's argument persuasive. C.S. failed to raise a triable issue of fact with respect to causation because there is no evidence that C.S.'s treating physician would have changed her prescribing behavior had she been given a different warning.

Summary judgment is proper when there are no triable issues of material fact and the moving party is entitled to judgment as a matter of law. (Code Civ. Proc., § 437c, subd. (c).) "The purpose of the law of summary judgment is to provide courts with a mechanism to cut through the parties' pleadings in order to determine whether, despite their allegations, trial is in fact necessary to resolve their dispute." (*Aguilar v. Atlantic Richfield Co.* (2001) 25 Cal.4th 826, 843.)

"A defendant who moves for summary judgment bears the initial burden to show the action has no merit—that is, 'one or more elements of the cause of action, even if not separately pleaded, cannot be established, or that there is a complete defense to [that] cause of action.' [Citation.] Once the defendant

meets this initial burden of production, the burden shifts to the plaintiff to demonstrate the existence of a triable issue of material fact. [Citation.] 'From commencement to conclusion, the moving party defendant bears the burden of persuasion that there is no triable issue of material fact and that the defendant is entitled to judgment as a matter of law.' [Citation.] We review the trial court's ruling on a summary judgment motion de novo, liberally construing the evidence in favor of the party opposing the motion and resolving all doubts about the evidence in favor of the opponent. [Citation.] We consider all of the evidence the parties offered in connection with the motion, except that which the court properly excluded." (*Grotheer v. Escape Adventures, Inc.* (2017) 14 Cal.App.5th 1283, 1292–1293.)

Under New York law,[8] a pharmaceutical "manufacturer's duty is to warn of all potential dangers in its prescription drugs that it knew, or, in the exercise of reasonable care, should have known to exist." (*Martin v. Hacker* (1993) 83 N.Y.2d 1, 8.) This duty to warn applies to the prescribing medical professional, not the individual patient. (*Id.* at p. 9.) The basis for this rule is that the physician acts as a learned intermediary between the manufacturer and the patient, evaluating the patient's needs, assessing the risks and benefits of available drugs, and supervising their use. (*Glucksman v. Halsey Drug Co., Inc.*, (1990) 553 N.Y.S.2d 724, 726.) A plaintiff must demonstrate that the warning was inadequate and that the failure to adequately warn of the dangers of the drug was a proximate cause of his or her injuries. (*Ibid.*) To establish proximate cause, "a plaintiff must demonstrate that had a different, more accurate warning[ ]

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[8] As C.S. is a New York resident, the parties do not dispute that New York law applies.

been given, his physician would not have prescribed the drug in the same manner." (*Alston v. Caraco Pharm., Inc.* (S.D.N.Y. 2009) 670 F.Supp.2d 279, 285.) A defendant is entitled to summary judgment if the evidence establishes "that any given warning would have been futile—either because any such warnings would not have been heeded or because the injury would have occurred, regardless of the given warnings." (*Bee v. Novartis Pharms. Corp.* (E.D.N.Y. 2014) 18 F.Supp.3d 268, 284.)

C.S. argues that he is entitled to a heeding presumption, i.e., had Janssen given an adequate warning, C.S.'s physician would have followed it. Janssen counters that New York does not recognize a heeding presumption. The only New York case that is directly on point and contains a lengthy discussion of the heeding presumption is *Castorina v. A.C. & S.* (2017) 49 N.Y.S.3d 238, a decision by the Supreme Court, New York County. *Castorina* at pages 242 and 243 found that the heeding presumption has not been unequivocally recognized as part of New York law and, even if there were a presumption required by state decisional law, there is authority that has restricted its use to where the individual who would have heeded the warnings is not available to testify. As *Castorina* is the only New York case on point, we adopt its rule that where, as here, the physician was available to and actually did testify, plaintiff must prove that an adequate warning would have been heeded.

This leads us to Janssen's argument that C.S. failed to raise a triable issue with respect to whether his treating physician would have heeded a different warning and not prescribed risperidone in the same manner. According to Janssen, C.S. must show that his psychiatrist would not have prescribed risperidone had she been given a different warning.

C.S., on the other hand, suggests that any alteration to his psychiatrist's prescribing behavior is enough. Based on the authorities relied on by both parties, the answer lies somewhere in between.

In another risperidone case, *Chandler v. Janssen Pharms., Inc.* (E.D.N.Y. 2018) 322 F.Supp.3d 314, the trial court granted summary judgment in favor of Janssen. The plaintiff's treating physician testified that he was not sure he would have changed his decision even if he knew the risk of gynecomastia was higher than the rate on the drug label. (*Id.* at p. 328.) Just as testified here, the physician stated he would have done a risk-benefit analysis and considered gynecomastia as a potential risk and weighed it against the potential benefits of keeping his patient on the drug. (*Ibid.*) These statements were not enough to defeat summary judgment.

In contrast, in *Bee v. Novartis Pharms. Corp.*, *supra*, 18 F.Supp.3d 268, the trial court found genuine issues of material fact existed as to whether the patient's prescribing and treating physicians would have acted differently if the drug manufacturer had provided a different warning. There, the patient alleged that he developed osteonecrosis of the jaw (bone death caused by poor blood supply) because the drug manufacturer failed to warn about the risk that tooth extraction, or other forms of invasive dental work, would trigger the condition. (*Id.* at pp. 273, 286.) The physician testified that, since he learned of the drug's side effects, he distributes handouts about the drug, informs his patients about the benefits of the drug, discusses the risk of developing the condition, provides patients with instructions for their dental providers, and warns patients not to undergo dental work until they have stopped taking the drug unless it is an

absolute emergency. (*Id.* at pp. 293–294.) This testimony was sufficient to raise a triable issue of fact with respect to proximate cause as there was a question of whether a different label altered the treating physician's behavior.

In *Davids v. Novartis Pharms. Corp.* (E.D.N.Y. 2012) 857 F.Supp.2d 267, a case involving the same drug as *Bee*, the trial court found a genuine issue of material fact as to whether the patient's treating physician would have prescribed the drug had she been given a different warning. Again, the treating physician testified that she would have referred the patient to a dental specialist to evaluate his dental health before making her prescribing decision. (*Davids*, at p. 288.)

In *McDowell v. Eli Lilly and Co.* (S.D.N.Y. 2014) 58 F.Supp.3d 391, the trial court granted summary judgment in favor of the drug manufacturer finding that the discontinuation warning on the label of an antidepressant was not the proximate cause of the plaintiff's injuries. The plaintiff's treating physician stated that he preferred that particular antidepressant over other medications used to treat the same conditions. He also testified that knowing incident rates of certain withdrawal symptoms would not have changed his decision to prescribe the drug. The only thing that the doctor would have changed was that he would have emphasized the withdrawal symptoms. This was not enough to raise a triable issue under New York's proximate cause standard.

We find the above district court cases instructive and conclude that the psychiatrist's testimony dooms C.S.'s claim. When presented with the results of the individual studies that showed a higher rate of gynecomastia among pediatric patients, the psychiatrist did not indicate whether her decision to prescribe

risperidone would have changed. Rather, the psychiatrist equivocated, stating that, while she would include the higher rate in her risk-benefit analysis, risperidone may have still been the best choice for C.S. At the time, there were only two medications on the market approved to treat C.S.'s symptoms. The psychiatrist stated that she would still have to balance the side effects of risperidone with the only other available drug that had the side effect of making "kids feel[ ] like they're jumping out of their skin." When presented with the results of study 70, the psychiatrist said, "[i]t may or may not have changed the choice of medicine." The psychiatrist acknowledged that she "was treating a really sick kid and I felt I did right by that kid, so I just don't want to mix things up. I didn't know—I didn't know this information at the time. But I was aware that gynecomastia could be a side effect." The psychiatrist's statements are not enough to raise a triable issue of fact with respect to whether she would have altered her behavior. C.S. had to show something more than the psychiatrist's ambiguous statements that she may have still prescribed risperidone and would have spent more time explaining gynecomastia as a side effect.

C.S. failed to carry his burden to establish that his physician would have heeded the warning. Therefore, summary judgment was correctly entered against C.S.

DISPOSITION

The judgments entered against J.D. and J.T. are reversed. The judgment entered against C.S. is affirmed. The parties are to bear their own costs on appeal.

NOT TO BE PUBLISHED.

DHANIDINA, J.

We concur:

LAVIN, Acting P. J.

EGERTON, J.