Wagner, Appellant, v. Roche Laboratories et al., Appellees.

[Cite as *Wagner v. Roche Laboratories* (1996), _____ Ohio St.3d _____.]

Civil procedure -- Motion for directed verdict -- Civ.R. 50(A)(4) interpreted and applied.

(No. 95-1209 -- Submitted May 22, 1996 -- Decided November 13, 1996.)

Appeal from the Court of Appeals for Lucas County, Nos. L-93-277 and L-93-187.

On November 8, 1982, plaintiff-appellant, Josephine Wagner, was prescribed the drug Accutane (isotretinoin) for treatment of cystic acne on her face by her dermatologist, Dr. Craig Burkhart. Dr. Burkhart had previously prescribed the antibiotic Minocin (minocycline), a tetracycline derivative, for appellant's acne problem, and continued appellant on the Minocin prescription in addition to the newly prescribed Accutane.

On December 30, 1982, appellant reported vision problems and headaches to Dr. Burkhart, who immediately discontinued the prescriptions and referred appellant to an ophthalmologist. The ophthalmologist diagnosed appellant with papilledema (swelling of the optic nerve caused by increased pressure on the brain) and referred appellant to a neurologist. The neurologist diagnosed appellant with pseudotumor cerebri ("PTC"), also called benign intracranial hypertension, a serious condition involving swelling of the brain. PTC is accompanied by effects

often associated with a brain tumor (such as papilledema, vision problems, nausea, and severe headaches), but no tumor is actually present.

Steroids were prescribed to treat the PTC effects. As a result of the steroid therapy, appellant experienced avascular necrosis, which involves diminished blood flow to the heads of bones, eventually leading to destruction of the bone ends. Appellant underwent several surgeries to replace both hip joints and a shoulder joint.

According to the court of appeals' opinion, appellant filed a medical malpractice suit against Dr. Burkhart on August 26, 1986. On August 23, 1988, Dr. Burkhart joined appellees Roche Laboratories and Hoffman-La Roche, Inc. ("Roche") as third-party defendants. Appellant amended her complaint to include a product liability claim against Roche, the developers of Accutane. On August 2, 1991, appellant settled her malpractice suit against Dr. Burkhart for $185,000 and soon after dismissed her complaint against Roche without prejudice pursuant to Civ.R. 41(A)(1)(a).

On February 24, 1992, appellant instituted the present action by refiling her complaint against Roche, reasserting the product liability claims. Appellant

claimed that the Accutane and Minocin worked in combination to cause her PTC, which necessitated the steroid treatments, which ultimately resulted in the avascular necrosis, which necessitated the joint replacements. Appellant alleged that Roche had failed to provide warnings in the Accutane package insert that Accutane could cause PTC and also that Accutane should not be taken in combination with some drugs, such as Minocin. Appellant alleged that her PTC and associated problems were proximately caused by appellees' failure to provide the warnings.

The case proceeded to a jury trial. Testimony at trial established that Accutane was approved by the federal Food and Drug Administration for treatment of severe cystic acne in May 1982 and that Accutane was first marketed in September 1982, shortly before Accutane was prescribed for appellant by Dr. Burkhart.

Accutane is a synthetic derivative of Vitamin A, and both belong to the same family of drugs, called retinoids. Accutane is a very effective acne treatment, but its use is restricted to severe cases of cystic acne that are resistant to other standard methods of treatment due to concerns about Accutane's side effects

and toxicity. The chemical structures of Accutane and Vitamin A are similar, and due to that similarity, the two produce some similar biological effects when ingested.

Hypervitaminosis A syndrome is a symptom complex associated with the ingestion of large dosages of Vitamin A often prescribed to treat acne. One of the symptoms of hypervitaminosis A is PTC. Appellant's theory of recovery at trial was premised on her presentation of expert testimony that Accutane is so similar chemically to Vitamin A that appellees either were aware, or should have been aware, that Accutane also had the potential to cause PTC, and that appellees should have included a warning of that potential effect in the Accutane package insert. Appellant further presented expert testimony questioning the testing process conducted by appellees prior to the FDA approval of Accutane, and alleged that deficiencies in the testing protocol had prevented appellees from gathering information on the connection between Accutane and PTC.

In addition to presenting testimony on the association of Vitamin A and PTC, appellant also presented expert testimony that Minocin, the antibiotic appellant was receiving at the time the Accutane was prescribed, also is associated

with an increased risk of PTC. Appellant's experts testified that when two drugs each tend to cause a particular effect when taken separately, the threat of that effect will predictably be magnified if the two drugs are taken concomitantly. Appellant alleged that in her case the Minocin and Accutane had a synergistic effect, greatly increasing her risk of PTC, and that appellees knew of, or should have known of, that increase in risk, and should have included a warning on the Accutane package insert to discontinue certain other drugs, such as Minocin, when Accutane was prescribed.

Appellees argued throughout the trial that the warnings provided on the Accutane package insert were adequate, and presented expert testimony to support the sufficiency of the protocol behind the Accutane trials which led up to FDA approval.

The trial court having denied appellees' motion for a directed verdict, the jury returned a verdict for appellant and awarded $350,000 in damages. The trial court granted appellees' motion to set off the earlier $185,000 settlement amount appellant received from Dr. Burkhart against the damage award, denied appellant's motion for prejudgment interest, and entered judgment in favor of

appellant for $165,000. The trial court later denied appellees' motions for judgment notwithstanding the verdict and for a new trial.

Appellees appealed to the Court of Appeals for Lucas County, contending that the trial court erred by denying their motion for a directed verdict, by denying their motion for judgment notwithstanding the verdict, and by denying their motion for a new trial. Appellant cross-appealed, urging that the trial court erred in several of its rulings, including granting the setoff and denying prejudgment interest.

The court of appeals, in a split decision, reversed the jury verdict in favor of appellant and determined that the trial court erred by not entering a directed verdict for appellees. The court of appeals found that the evidence revealed "no case reports, no medical literature, and no scientific studies associating Accutane with PTC or associating the concomitant use of Accutane and Minocin with PTC." The court of appeals went on to state that "[r]easonable minds could only conclude the warning provided by Roche for Accutane was adequate, and, therefore, the issue should not have been submitted to the jury."

In light of its holding that the trial court should have directed a verdict for Roche, the court of appeals found the remainder of Roche's appeal and Wagner's entire cross-appeal moot and did not address them.

The cause is now before this court upon the allowance of a discretionary appeal.

Don C. Iler Co., L.P.A., Don C. Iler and *Nancy C. Iler*, for appellant.

Arter & Hadden, *Irene C. Keyse-Walker* and *George Gore*; *Patterson, Belknap, Webb & Tyler, L.L.P.*, and *John Winter*, for appellees.

Alice Robie Resnick, J. This case requires us to interpret Civ.R. 50(A)(4) and to apply the standards contained in that rule to appellant's claims of failure to warn, in order to determine whether appellant created a jury question sufficient to overcome appellees' motion for a directed verdict. For the reasons which follow, we conclude that the trial court properly applied Civ.R. 50(A)(4) and correctly denied appellees' motion for a directed verdict. We reverse the judgment of the court of appeals, and remand this cause to the court of appeals for further proceedings.

Civ.R. 50(A)(4) provides:

"When a motion for a directed verdict has been properly made, and the trial court, after construing the evidence most strongly in favor of the party against whom the motion is directed, finds that upon any determinative issue reasonable minds could come to but one conclusion upon the evidence submitted and that conclusion is adverse to such party, the court shall sustain the motion and direct a verdict for the moving party as to that issue."

In *Strother v. Hutchinson* (1981), 67 Ohio St.2d 282, 284-285, 21 O.O.3d 177, 178-179, 423 N.E.2d 467, 469, this court observed:

"The law in Ohio regarding directed verdicts is well formulated. In addition to Civ.R. 50(A), it is well established that the court must neither consider the weight of the evidence nor the credibility of the witnesses in disposing of a directed verdict motion. *** Thus, 'if there is substantial competent evidence to support the party against whom the motion is made, upon which evidence reasonable minds might reach different conclusions, the motion must be denied. *Kellerman v. J.S. Durig Co.* (1964), 176 Ohio St. 320 [27 O.O.2d 241, 199 N.E.2d 562] ***.' *Hawkins v. Ivy* (1977), 50 Ohio St.2d 114, 115 [4 O.O.3d 243, 244,

363 N.E.2d 367, 368]." See, also, *Ramage v. Cent. Ohio Emergency Serv., Inc.* (1992), 64 Ohio St.3d 97, 109, 592 N.E.2d 828, 837.

"A motion for directed verdict *** does not present factual issues, but a question of law, even though in deciding such a motion, it is necessary to review and consider the evidence." *O'Day v. Webb* (1972), 29 Ohio St.2d 215, 58 O.O.2d 424, 280 N.E.2d 896, paragraph three of the syllabus.

"When a motion for a directed verdict is entered, what is being tested is a question of law; that is, the legal sufficiency of the evidence to take the case to the jury. This does not involve weighing the evidence or trying the credibility of witnesses. *** The 'reasonable minds' test of Civ.R. 50(A)(4) calls upon the court only to determine whether there exists any evidence of substantial probative value in support of [the claims of the party against whom the motion is directed]. *** A motion for a directed verdict raises a question of law because it examines the materiality of the evidence, as opposed to the conclusions to be drawn from the evidence." *Ruta v. Breckenridge-Remy Co*. (1982), 69 Ohio St.2d. 66, 68-69, 23 O.O.3d 115, 116-117, 430 N.E.2d 935, 938.

The standard a drug manufacturer must meet in warning of the dangers of its product is set forth in *Seley v. G.D. Searle & Co*. (1981), 67 Ohio St.2d 192, 21 O.O.3d 121, 423 N.E.2d 831, paragraphs one and two of the syllabus, in which this court, applying Comment *k* to 2 Restatement of the Law 2d, Torts (1965), Section 402 A, regarding strict product liability, held:

"1. A manufacturer of an unavoidably unsafe ethical (prescription) drug is not strictly liable in tort to a consumer who has suffered injury as a result of ingesting that drug where the manufacturer has provided adequate warning to the medical profession of all potential adverse reactions inherent in the use of the drug of which the manufacturer, being held to the standards of an expert in the field, knew or should have known to exist at the time of marketing.

"2. The 'adequacy' of such warning is a question of fact to be determined by a preponderance of the evidence. A warning is adequate where, under all the circumstances, it reasonably discloses all risks inherent in the use of the drug of which the manufacturer, being held to the standards of an expert in the field, knew or should have known to exist."

The *Seley* court adopted the "learned intermediary" theory of adequacy of the warning at paragraph five of the syllabus: "A manufacturer of ethical drugs satisfies its duty to warn of risks associated with use of the product by providing adequate warnings to the medical profession and not to the ultimate user."

Based on *Seley*, it was incumbent on appellant to establish that appellees knew, or should have known, in 1982 when Accutane was marketed, of the association of Accutane to PTC and of the dangers of concomitant use of Accutane and certain antibiotics such as Minocin, and that appellees failed to provide an adequate warning to Dr. Burkhart, through the package insert,[1] based on the knowledge or imputed knowledge.

Appellant contends that whether appellees knew or should have known of the above risks is a question of fact, and that appellant presented sufficient probative evidence to overcome a motion for a directed verdict and to get the issue before the jury. To that end, appellant argues in Proposition of Law No. 1 that a drug manufacturer is not relieved of a duty to warn "simply because cases of those precise adverse reactions [suffered by the plaintiff from taking defendant's new drug] were not reported during limited pre-marketing clinical trials of the drug."

Appellees contend, on the other hand, that appellant failed to put forth substantial probative evidence that appellees' warnings were inadequate, and that therefore the court of appeals correctly found that a directed verdict should have been granted. In support of this position, appellees argue that clinical testing of Accutane showed no association of Accutane to PTC and that the clinical testing was properly designed and executed, so that there was no basis for appellees to know of, and therefore to warn about, the effects of Accutane appellant experienced.

After a thorough review of the record, we agree with appellant that the trial court rightly denied appellees' motion for a directed verdict. Appellant presented evidence of substantial probative value sufficient to create a jury question as to whether appellees failed to provide an adequate warning.[2]

In particular, appellant's expert, Dr. Elias, testified, in part based upon appellees' own documents produced prior to FDA approval of Accutane, that Accutane is similar enough in structure to Vitamin A that appellees should have anticipated that PTC could be associated with Accutane just as PTC is associated with the hypervitaminosis A that can occur with ingestion of therapeutic doses of

Vitamin A to treat acne. Dr. Elias, who was one of the physician investigators who participated in the clinical trials of Accutane, further testified that the testing conducted by appellees prior to FDA approval was deficiently designed, and that if the testing had been done correctly, the link between Accutane and PTC might have been established. Dr. Elias also testified that, due to the similarity of Accutane to Vitamin A,[3] and the known association between an antibiotic such as Minocin and Vitamin A with PTC, appellees should have anticipated and warned of the possible synergistic effect when Accutane is taken in conjunction with therapeutic doses of antibiotics such as Minocin.

Dr. Elias's explanation of his view on why the testing protocol was inadequate regarding Accutane and PTC was specific enough and of sufficient probative value to create a question of fact as to whether appellees should have known about the risks. Specifically, Dr. Elias testified that appellees were deficient in designing the protocol because they failed to build into it a way of monitoring for neurological toxicity, which could have revealed the association between Accutane and PTC. Dr. Elias testified that, due to the chemical similarity of Accutane and Vitamin A, and due to their similar biological effects, appellees

should have been on the alert when conducting the clinical tests of Accutane for all the effects known to be associated with hypervitaminosis A, including PTC and its accompanying symptoms. Dr. Elias testified that approximately five percent of the patients in the clinical trials exhibited symptoms such as headaches and vomiting that could have alerted appellees to possible PTC problems, but that there was no mechanism built into the testing to specifically follow up and investigate patients who complained of those problems.

Dr. Elias's testimony is by no means the only support for appellant's position in the record. For example, appellant at trial presented as an exhibit a Roche document entitled "Addendum to Schedule 7, Investigational Drug Brochure" for Accutane (dated March 20, 1978), which contains an extensive listing of abnormalities in its "Precautions and Warnings" section reported in patients with "chronic vitamin A intoxication" (hypervitaminosis A). "Papilledema with increased intra-cranial pressure" (PTC) is one of the reported associated abnormalities listed. The document goes on to state: "Because of the chemical and pharmacological similarities between [Accutane], retinoic acid and

retinol [Vitamin A], one should watch for the above adverse reactions in patients taking [Accutane]."

The same document also states: "A review of the clinical studies discussed in this brochure indicates that the adverse reactions seen with the use of orally administered [Accutane] are essentially those of hypervitaminosis A." This document, when considered in light of the testimony of appellant's experts, supports appellant's position that a question of fact was raised on what appellees knew or should have known.

In addition, appellant presented the testimony of Dr. James O'Donnell, a pharmacologist, who testified that, even if no specific instances of PTC were reported in the clinical trials of Accutane, Roche should have predicted the association of Accutane and PTC (and perhaps did predict the association based on the above documents) and should have warned of the possible effect. O'Donnell also testified about synergistic effects of Accutane and Minocin.

Appellees' counterarguments to these points, to the effect that Accutane was not identical to Vitamin A, and was known to be safer than Vitamin A, so that not all effects of hypervitaminosis A were anticipated to also accompany Accutane, do

not as a matter of law establish appellees' nonliability, but instead go toward refuting the factual claims of appellant. Likewise, appellees' argument that its testing protocol was adequate does not establish as a matter of law that appellees should not have been aware of the risks of effects such as those experienced by appellant.

Appellees point out that, as part of the FDA's consideration of appellee's application for approval of Accutane, the FDA reviewed, analyzed, and approved the warning language as it appeared on the package insert in 1982. See Sections 314.50(c)(2)(i) and 314.125(b)(6), Title 21, C.F.R. However, the fact of FDA approval of the package insert as it appeared in 1982 does not insulate appellees from liability. Although the FDA must approve the package insert prior to marketing of the drug, one of appellees' experts agreed with appellant's attorney on cross-examination that the FDA does no tests of its own, but bases its approval on data submitted by the manufacturer. As discussed above, appellant created a question of fact to be resolved by the jury whether appellees adequately warned of the alleged risks associated with Accutane at issue in this case. Appellees' arguments relating to the testing leading up to FDA approval of Accutane go to

the factual question of what information appellees knew or should have known which formed the basis underlying the warnings to be listed on the Accutane package insert. Those arguments have already been rejected by the factfinder in this case, as reflected in the jury verdict in favor of appellant.

We are cognizant of appellees' statement that, in order to support the goal that information in a package insert should be concise and not so detailed that it loses meaning, the FDA requires that only information concerning known hazards should be included and warned about. See, *e.g.*, 44 F.R. 37,446-37,447 and 37,453. Appellees urge that the FDA's policy is to discourage "information overload" on package inserts. We recognize that the contents of package inserts must reflect a balance between the need for conciseness and a drug company's temptation to include every potential effect, no matter how remote, on a package insert in order to avoid legal liability for failure to indicate a particular hazard. Nevertheless, however the balance is reached, this FDA policy does not relieve the drug manufacturer from providing a warning of "all potential adverse reactions inherent in the use of the drug of which the manufacturer, being held to the

standards of an expert in the field, knew or should have known to exist at the time of marketing." *Seley*, *supra*, paragraph one of the syllabus.

We are also aware of the dangers that can arise from looking at drug warning cases with the 20/20 hindsight that may come when effects not anticipated at the time a drug is prescribed later manifest themselves. However, appellant presented competent credible evidence that appellees should have known in 1982 of hazards of the type that affected appellant, and should have warned of them. To avoid the temptation of using 20/20 hindsight in this case, the trial court did not allow appellant to place evidence before the jury that, in 1984, both the package insert and the PDR entry for Accutane were supplemented to include a warning that Accutane used concomitantly with tetracycline therapy (*e.g.*, such as Minocin) could be associated with PTC. The trial court excluded this evidence under Evid.R. 407 as a subsequent remedial measure. The jury verdict thus focused on what appellees knew, or should have known, in 1982.

In addition to creating a jury question as to the adequacy of the warnings, appellant also created a jury question as to causation, which the jury also answered in appellant's favor. Appellant presented expert testimony to support her

arguments that the lack of adequate warnings was a proximate cause of her ingestion of Accutane, and that her ingestion of Accutane was a proximate cause of her injury. See *Seley*, *supra*, paragraphs three and four of the syllabus. We reject appellees' contention that they were entitled to judgment notwithstanding the verdict (or to a directed verdict) because appellant did not create a jury question as to causation.

Moreover, we also reject appellees' contention, raised below and implicated by their position here, that the holding of the United States Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.* (1993), 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469, requires a finding that appellant did not create a jury question because the opinions elicited during testimony of appellant's experts were not scientifically valid. Our review of the record of this case in its entirety convinces us that appellant's experts' opinions were sufficiently grounded in credible reasoning and scientific methodology to validly support appellant's theory of recovery.

In her third proposition of law, appellant asks this court to address some of the issues raised in her cross-appeal to the court of appeals, which were found

moot and were not addressed by the court of appeals. Appellant requests that we overturn the trial court decision to deduct the amount appellant received in her settlement with Dr. Burkhart from the jury award against appellees.

We decline to consider this proposition of law, but remand this cause to allow the court of appeals to address appellant's assignments of error raised in her cross-appeal below, which were found moot. Also remaining are the issues underlying appellees' argument that a new trial is warranted, raised in the court of appeals but found moot and not addressed by that court. We remand this cause to the court of appeals for that court to address these remaining assignments of error.

Judgment reversed

and cause remanded.

MOYER, C.J., DOUGLAS, F.E. SWEENEY, PFEIFER, COOK and STRATTON, JJ., concur.

FOOTNOTES:

[1] In addition to the package insert, the Physicians' Desk Reference ("PDR") is another common resource frequently consulted by physicians when prescribing drugs. The PDR is considered an authoritative source for information. Appellant's claim that appellees failed to provide a warning in the package insert would also encompass appellees' alleged failure to provide a warning through the PDR entry for Accutane.

[2] Our conclusion that appellees were not entitled to a directed verdict mandates the conclusion that appellees also were not entitled to judgment notwithstanding the verdict. The standard to be applied in considering a motion for a directed verdict is the same standard to be applied in considering a motion for judgment notwithstanding the verdict. See *Gladon v. Greater Cleveland Regional Transit Auth.* (1996), 75 Ohio St.3d 312, 318-319, 662 N.E.2d 287, 294; *Posin v. A.B.C. Motor Court Hotel, Inc.* (1976), 45 Ohio St.2d 271, 275, 74 O.O.2d 427, 430, 344 N.E.2d 334, 338.

[3] The 1982 PDR entry for Accutane contains the following precaution:

“Because of the relationship of Accutane to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.”