CHAPTER 8

KRELIC ET AL. v. MUTUAL PHARMACEUTICALS CO., INC.

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I. Why It Made the List

Generic pharmaceuticals provide a low-cost alternative to high-price brand drugs to the American public. Thanks in part to streamlined application processes under the Hatch-Waxman Amendments, generic pharmaceuticals make up at least 80 percent of the drug market. Under this regime, generic drug companies need not incur the expense of extensive clinical trials but must provide a product that is bioequivalent to, and the same in all major respects as, its brand-name counterpart. Strict labeling provisions require that the generic drug product's label be the same as the approved brand label. This means that the generic drug manufacturer may not make any substantial changes to its label (e.g., active ingredients and warnings must be the same).

This is the statutory landscape that many plaintiffs find themselves up against as they attempt to bring state failure-to-warn claims against generic drug manufacturers. However, the United States Supreme Court in *PLIVA, Inc. v. Mensing*,[1] held that federal laws and regulations preempted state failure-to-warn claims because it would be impossible

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* The authors would like to disclose that their law firm represents Morton Grove Pharmaceuticals, Inc. and Wockhardt USA, LLC in the *In re Reglan/Metoclopramide Litigation* pending before the Pennsylvania Supreme Court on a similar preemption issue.

1 131 S. Ct. 2567 (2011).

for generic manufacturers to fulfill their state-law duties to warn without violating the federal-law requirement that the labeling be the same as the approved brand drug.

Krelic et al. v. Mutual Pharmaceutical Co., Inc.,[2] is one of the latest in a line of cases after *Mensing* relating to federal preemption of state failure-to-warn claims against generic drug manufacturers. The Krelics attempted to distinguish their case from *Mensing* based on the Different Manufacturers Exception to the labeling requirement, which in essence allows changes to the labels for manufacturers other than the branded company. The court relied on *Mensing* as well as the Food and Drug Administration's (FDA's) interpretation of the statutes and regulations to dismiss all of the Krelics' failure-to-warn claims.

Mensing, *Krelic*, and other similar failure-to-warn preemption cases have started a conversation between the public and FDA regarding the differences between the duties to warn as a branded drug company and a generic drug manufacturer. It is in light of these cases that FDA has recently proposed new rules that would make generic manufacturers' duties more in line with the duties of the branded drug company and potentially open them to more liability.

II. Facts of Case

Plaintiffs Curt and Diane Krelic, husband and wife, alleged a number of state tort failure-to-warn claims against generic drug manufacturer Mutual Pharmaceuticals Company, Inc. ("Mutual") relating to the drug prednisone.[3]

Mr. Krelic was prescribed the drug prednisone at a dose of 40 mg a day for a thyroid condition by his treating physician on March 7, 2006, which he began using that same day.[4] Prednisone is a corticosteroid and is only available in the United States by prescription.[5] The prednisone that Mr. Krelic was given was manufactured by Mutual.[6] On March 18, 2006, Mr. Krelic went to the hospital, because he was seeing green spots in his eyes, as well as other symptoms, such as discoloration of light backgrounds, seeing different sizes with each eye, blisters on his retina, straight line distortion, water spots, fuzziness, distortion, blurriness, bright light sensitivity, and so forth.[7] Mr. Krelic was referred to a retina specialist and diagnosed with Central Serous Chorioretinopathy (CSR) from taking steroids.[8] Mutual's label stated that corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and

2 Krelic et al. v. Mutual Pharmaceuticals Co., Inc., C.A. No. GD-08-024513, 161 P.L.J. 329 (C.P. Allegheny Apr. 11, 2013).

3 *Id.* at 329.

4 *Id.* (First Am. Compl. at 4).

5 *Id.* (First Am. Compl. at 4, 9).

6 *Id.* (First Am. Compl. at 4).

7 *Id.* (First Am. Compl. at 5).

8 *Id.*

may enhance the establishment of secondary ocular infections due to fungi or viruses.[9] Mutual's label did not list CSR as a side effect for its prednisone tablets.[10]

III. Court Ruling

The court dismissed all of the Krelics' claims that required a showing of failure to warn.[11] In doing so, the court found that the Different Manufacturers Exception to FDA's regulation on generic drug labeling did not permit different warnings as to safety and efficacy.[12] "The Different Manufacturers Exception refers to changes 'required' because the manufacturers are different . . . The active ingredients of a generic and a brand-name drug are identical, so changes are not 'required' with respect to warnings and other safety-related information concerning the active ingredient."[13]

IV. Rationale for Decision

The *Krelic* decision is one of the latest in a line of cases since the United States Supreme Court's decision in *Mensing*, which held that failure-to-warn claims against generic drug manufacturers were federally preempted.[14]

The court acknowledged that, as in *Mensing*, it is established that federal law requires a manufacturer to prove that a new drug is safe and effective and that the proposed label is accurate and adequate.[15] However, a generic drug manufacturer must only show equivalence to a listed or brand-name drug that has already been approved by FDA.[16] Such a generic drug manufacturer must also show that the safety and efficacy labeling it proposes is the same as the brand-name drug's labeling.[17] As opposed to brand-name manufacturers, federal legislation and regulations only permit generic drug manufacturers to change their labeling to match an updated brand-name label.[18] The court also noted that "[u]nder FDA interpretations, changes unilaterally made to strengthen a generic drug's warning label would violate federal legislation and regulations requiring a generic drug's label to match its brand-name counterparts."[19]

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9 *Id.* (First Am. Compl. at 9)
10 *Id.*
11 *Id.* at 332.
12 *Id.*
13 *Id.* at 331.
14 *Id.* at 330.
15 *Id.*
16 *Id.*
17 *Id.* (citing *Mensing*, 131 S. Ct. at 2574).
18 *Id.*
19 *Id.* (citing *Mensing*, 131 S. Ct. at 2575).

Here, however, the plaintiffs asserted that the Different Manufacturers Exception would apply to Mutual and, therefore, *Mensing's* preemption rulings would not govern. The court quoted the Different Manufacturers Exception, which reads as follows:

> An abbreviated application for a new drug shall contain . . . information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) *except for changes required* because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers.[20]

The court noted that neither the *Mensing* opinion nor its dissenting opinion mentioned the Different Manufacturers Exception. However, the court was not persuaded that this fact alone permits a generic manufacturer to comply with state tort law regarding safety and efficacy labeling over federal labeling laws and regulations.[21] Instead, the court was persuaded by the PLIVA, Inc. brief filed in the United States Supreme Court, which stated that:

> Of course, certain labeling differences are unavoidable. Petitioners' generic versions of Wyeth's Reglan® cannot, for instance falsely represent that they too are manufactured by Wyeth. *See* 21 U.S.C. § 331 (b); *id.* § 321(n). Hatch-Waxman therefore authorizes labeling variances where "'the [generic] drug and the [brand-name] drug are produced or distributed by different manufacturers.'" 21 U.S.C. § 355(j)(2)(A)(v). FDA has interpreted this language to permit differences
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> > In expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity.
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> 21 C.F.R. § 314.94(a)(8)(iv). The regulation pointedly does not authorize divergent product warnings.
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> That is no accident. *FDA received dozens of comments when it proposed the regulation, including two submissions proposing that it "be revised to permit ANDA applicants to deviate from the labeling for the [branded] drug to add contraindications, warnings, precautions, adverse reactions, and other safety-related information.* 57 Fed. Reg. at 17961, Pet. App. 108a (emphasis added). *FDA rejected the proposal:*

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[20] *Id.* (quoting 21 U.S.C. § 355(j)(2)(A)(v)) (emphasis added by the court).

[21] *Id.*

> FDA disagrees with the comments. Except for labeling differences under section 505(j)(2)(v) of the act, *the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval.* Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart.

Id., Pet. App. 109a (emphasis added; citing 21 U.S.C. § 355(j)(2)(A)(v); *see also id.* at 17953, Pet. App. 104a ("As for accepting ANDA's with additional warnings or precautions . . . the act requires that the applicant's proposed labeling be the same as that of the [branded] drug.") (citing 21 U.S.C. § § 355(j)(2)(A)(v), (j)(3)(G)).[22]

The *Krelic* court, therefore, found that "[t]he only explanation for the failure of the briefs to support plaintiffs or the Supreme Court's opinions in *PLIVA* to discuss the Different Manufacturers Exception is that the exception does not permit different labeling as to safety and efficacy."[23]

The Court also noted that:

> The Different Manufacturers Exception refers to changes "required" because the manufacturers are different. The use of the word "required" refers to changes to the label of the generic manufacturer that are triggered by the manufacturer of the generic drug not being the same as the manufacturer of the brand-name drug. The active ingredients of a generic and a brand-name drug are identical, so changes are not "required" with respect to warnings and other safety-related information concerning the active ingredients.[24]

In addition, the Court commented that most of the drugs on the market are generic; therefore, the Krelics' view of the Different Manufacturers Exception would render the labeling provisions in the FDA regulations "almost meaningless."[25] The Krelics provided no reasoning for "why this is what Congress intended."[26]

Accordingly, the court turned to FDA's interpretation of the Different Manufacturers Exception, since *Mensing* established that such interpretations are "controlling unless plainly erroneous or inconsistent with the regulations or where there is another reason to doubt that these views reflect the FDA's fair and considerate judgments."[27] According

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22 *Id.* at 332 (some emphasis in original some added by court).

23 *Id.*

24 *Id.* at 331.

25 *Id.*

26 *Id.*

27 *Id.* (citing *Mensing*, 131 S. Ct. at 2575).

to 21 C.F.R. § 314.94(a)(8)(iv), which "sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers,"[28] the Different Manufacturers Exception does not include any differences relating to the active ingredient:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. *Such differences between the [generic] applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 5050)(5)(F) of the act.*[29]

Therefore, FDA has "interpreted the difference-due-to-manufacturer exception to apply when the ANDA [Abbreviated New Drug Application] differs in an aspect that is not required by the statute or regulation to be the same as the RLD [reference listed drug] (e.g. a difference in inactive ingredients)."[30]

Ultimately, the court found that "active ingredients of the generic drug and the brand-name drug must be the same. Thus, the warnings as to the side effects and safety of the active ingredients must be the same."[31] As a result, the court dismissed all of the Krelics' claims that relied upon a showing of failure to warn.[32]

V. Impact of Decision

In recent years, a number of plaintiffs have brought claims against generic drug manufacturers based on state tort laws, mostly for failure to warn about potential side effects of their drug products. As mentioned above, the *Mensing* case set a precedent that all such failure-to-warn claims were preempted by federal laws and regulations. *Krelic* is one of the latest in this line of cases. As a result of the *Mensing* line of cases, FDA has

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28 *Id.* (quoting Letter from Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, Docket No. FDA-2011-P-0702 (Feb. 8, 2012)).

29 *Id.* (quoting 21 C.F.R. § 314.94(a)(8)(iv)) (emphasis added by court)

30 *Id.* (quoting Letter from Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, Docket No. FDA-2011-P-0702 (Feb. 8, 2012)).

31 *Id.*

32 *Id.* at 332.

recently published new proposed rules on labeling that would change the landscape of potential liability for generic drug manufacturers.

Historically, the Drug Price Competition and Patent Term Restoration Act, more commonly known as the Hatch-Waxman Amendments, provided an avenue for generic drug manufacturers to submit more streamlined drug applications that no longer required expensive and lengthy clinical trials for generic drug products. Instead, the generic drug manufacturer had to prove that the drug was the same as the branded drug. This is the hallmark of the Hatch-Waxman Amendments: sameness. The law requires, therefore, that generic drugs have the "same" active ingredients, the "same" dosage form and strength, the "same" therapeutic effect, and use the "same" route of administration as the branded drug.[33] Minor differences, like color and inactive ingredients, are allowed, but in all other respects the generic drug must be the "same" as the branded drug.

The provision that comes up most frequently in the *Mensing* line of cases is the labeling provision of the Federal Food, Drug, and Cosmetic Act (FDCA). This provision requires that the generic drug manufacturer's proposed labeling "is the same as the labeling approved for the listed drug."[34] Again, this provision emphasizes the "sameness" of the branded and generic drugs. It is these labeling provisions, along with the other Hatch-Waxman Amendments, that allow generic drug products to be "substituted" for the higher-priced branded drugs at the pharmacy.[35] And it is the language of this provision, along with the other Hatch-Waxman Amendments, that form the basis for the *Mensing* and *Krelic* line of decisions. Because of the sameness requirements, the *Mensing* court and other courts have determined that it would be impossible for generic manufacturers to fulfill their state-law duties to warn without violating the federal-law requirement that the labeling be the same as the approved brand drug.

Up until recently, FDA has stood its ground with respect to these "sameness" labeling requirements. In fact, as the court in *Krelic* discussed, FDA has interpreted the labeling provisions to require that every aspect of the label be the same, except for minor differences, such as "*expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act.*"[36]

Just as the branded drug manufacturers have a duty to comply with both state and federal obligations with respect to labeling (based on an FDA regulation that allows them to make certain changes to their labels prior to receiving FDA approval),[37] FDA has proposed new rules that would "allow[] generic drug makers to use the same process

33 21 U.S.C. § 355(j)(2)(A)(i)-(iv).

34 *Id.* at § 355(j)(2)(A)(v).

35 *Mensing*, 131 S. Ct. at 2574.

36 *Id.* (quoting 21 C.F.R. § 314.94(a)(8)(iv)) (emphasis added by court).

37 Wyeth v. Levine, 555 U.S. 555, 568 (2009).

as brand drug manufacturers to update safety information in the product labeling."[38] In an effort to "speed the dissemination of new safety information about generic drugs," under this proposal generic drug manufacturers would be permitted to "independently update product labeling . . . with newly-acquired safety information before FDA's review of the change."[39] FDA's ultimate decision on these proposed labeling changes would affect both the branded and generic drug label, making sure that the branded and generic drug labeling information ultimately stay the "same" as each other.[40] FDA argues that "the changing prescription drug landscape, in which 80% of the drugs dispensed are generic, has altered the risk-benefit balance between clarity and consistency on the one hand, and speedier access to safety information on the other."[41] The proposed rule, says FDA, "would create better parity between brand-name drug manufacturers and generic companies."[42]

Reactions by commentators fall on both sides of the issue. For example, these proposed changes could "open generic manufacturers to potentially massive legal liabilities" under failure-to-warn statutes like those in the *Mensing* line of cases.[43] These changes could also lead to "confusing differences between branded drugs and their generic competitors,"[44] since the proposal would result in "a temporary multiplicity of labels for the 'same' drug."[45] On the other hand, many postmarketing studies show dangerous side effects years after the generic drug has hit the market, and the generic manufacturer has no means to warn the public about these risks under the current regulations.[46] Other commentators say that the proposed changes are "common sense" and "a necessary fix for a system that they say is unfair to patients who take generic medicines."[47] While the proposed change could provide patients with additional safety information and give

38 FDA News Release, FDA takes action to speed safety information on generic drugs (Nov. 8, 2013), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm374171.htm (last accessed Jan. 9, 2014).

39 *Id.*

40 *Id.*

41 Hyman, Phelps & McNamara, P.C., *FDA Proposes a Rule that Would Undercut Generic Drug Preemption*, FDA Law Blog (Nov. 12, 2013), *available at* http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/11/fda-proposes-a-rule-that-would-undercut-generic-preemption.html (last visited Jan. 9, 2014).

42 Katie Thomas, *Label Updates May Be Allowed for Generics*, N.Y. Times, Nov. 8, 2013, *available at* http://www.nytimes.com/2013/11/09/business/fda-proposes-letting-generic-drug-companies-alter-labels.html (last visited Jan. 9, 2014).

43 Alexander Gaffney, Experts: FDA's Generic Drug Labeling Rule Likely Illegal, Regulatory Affairs Professionals Society (Nov. 15, 2013), *available at* https://www.raps.org/focus-online/news/news-article-view/article/4317.aspx (last visited Jan. 9, 2014).

44 *Id.*

45 Hyman, Phelps & McNamara, P.C., *supra* note 41; *see also* Thomas, *supra* note 42.

46 Harry Jackson, *FDA needs to allow generic drug manufacturers to post warning labels on prescription drugs, says Public Citizen*, St. Louis Post-Dispatch, June 24, 2013, *available at* http://www.stltoday.com/lifestyles/health-med-fit/fda-needs-to-allow-generic-drug-manufacturers-to-post-warning/article_9d7dfd0a-b1fd-5234-9c56-e2265787a2ed.html (last visited Jan. 9, 2014).

47 Katie Thomas, *F.D.A. Rule Could Open Generic Makers to Suits*, N.Y. Times, July 3, 2013, *available at* http://www.nytimes.com/2013/07/04/business/fda-rule-could-open-generic-drug-makers-to-suits.html?_r=0 (last visited Jan. 9, 2014).

them another avenue for recovery, commentators wonder if it will "keep patients from harm in the first place."[48] However, it would likely undermine a significant amount of the savings currently enjoyed by consumers due to the success of the current regime under the Hatch-Waxman Amendments.

More fundamentally, it is unlikely FDA has legal authority to propose these changes. FDA says that the FDCA and the Public Health Service Act provide it with the authority to regulate drug labeling.[49] For example, FDA points to FDCA section 502, which "allows it to consider a drug misbranded if it bears inadequate directions for use or insufficient warnings."[50] Similarly, FDA points to FDCA section 701, which allows it to "regulate CBE supplements and their use."[51] However, one commentator points out that "[t]he 'sameness' requirement that underlies preemption is in the statute, and is unique to generic drugs."[52] As such, FDA may be precluded by the statute from making such rules.[53] Ultimately, these proposed rules could upset the "delicate balance of rights and responsibilities of the brand and generic industry."[54] If nothing else, they will "change the entire regulatory and liability landscape for generic drug manufacturers."[55]

VI. Conclusion

The decision in *Krelic* is not surprising in light of the Hatch-Waxman Amendments, FDA's labeling regulations, and the Supreme Court's decision in *Mensing*. But what cases like *Krelic* have done is open up a dialogue between the public and FDA on the differences in a branded drug company's duty to warn and a generic drug manufacturer's duty. FDA has proposed new rules that would change the current balance and possibly open generic drug manufacturers up to more liability under state tort statutes. But does FDA have the authority to make these proposed rule changes? Will these changes actually provide the clarity that so many consumers seek? Will these changes improve public safety? Or will they merely result in more confusion, increased costs, and more litigation?

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48 Hyman, Phelps & McNamara, P.C., *supra* note 41.

49 Gaffney, *supra* note 43.

50 *Id.*

51 *Id.*

52 *Id.*

53 *Id.*

54 *Id.*

55 Hyman, Phelps & McNamara, P.C., *supra* note 41.