IADC Committee Newsletter

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Kara Stubbs and Caroline Tinsley report on the Different Manufacturers Exception as a new argument challenging preemption under Mensing.

A New Argument against Preemption under *Mensing*: The Different Manufacturers Exception

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The Drug, Device and Biotechnology Committee serves as an educational and networking resource for in-house counsel employed by pharmaceutical, medical device and biotech manufacturers and the outside counsel who serve those companies. The Committee is active in sponsoring major CLE programs at the Annual and Midyear Meetings as well as internal committee programs. The Committee also publishes a monthly newsletter that addresses recent developments and normally contributes two or more articles to the *Defense Counsel Journal* annually. In the future, the Drug, Device and Biotechnology Committee will be focusing on increasing its use of technology to make it an even more valuable resource for its members. Learn more about the Committee at www.iadclaw.org. To contribute a newsletter article, contact:

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The backdrop for this discussion is *Krelic v. Mutual Pharmaceuticals Co.*, No. GD-08-024513, *slip op*. (Pa. C.P. Allegheny Co. April 11, 2013). You are probably asking yourself what relevance could a case from the Court of Common Pleas of Allegheny County have to my practice? We encourage you to read on and find out.

The case is typical of what one may encounter in cases against generic pharmaceutical manufacturers in the post – *Mensing* world. The plaintiffs make a claim for state tort failure-to-warn claims against the generic manufacturer. The generic manufacturer, who uses the warning label used by the manufacturer of the brand-name drug, seeks dismissal of the failure-to-warn claim on preemption grounds based on the June 23, 2011 ruling by the United States Supreme Court in *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011). What is novel about the case is the plaintiffs' argument that the Different Manufacturers Exception does not bar a generic manufacturer from including risks that are not disclosed in the brand-name label. While the plaintiff's argument did not ultimately persuade the judge to overrule the preemption motion, there are some lessons to be learned from the case in what the judge found to be persuasive.

In *Wyeth v. Levine*, the Supreme Court addressed the issue of whether a state law failure-to-warn tort claim may be brought against a brand-name manufacturer for failure to have changed the warning label placed on the drug after it had been approved by the FDA. In ruling against Wyeth, the Court found that it was not impossible for Wyeth to comply with both state and federal law obligations because of the "changes being effected" regulation, which permits a brand-name manufacturer to make certain changes to its label prior to receiving FDA approval. The Court stated in pertinent part:

> Among other things, this "changes being effected" (CBE) regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval. §§314.70(c)(6)(iii)(A),(C).
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> *Id.* at 568.

A different result was reached by the Court in *Mensing* based on its finding that the FDA's interpretation of legislation and regulations allow changes to generic labels, but only when a generic drug manufacturer changes its labels to match an updated brand-name label or to follow instruction from the FDA. Any change made independently by the generic manufacturer to enhance its warning label would violate federal legislation and FDA regulations. *Mensing* at 2575.

The plaintiffs in *Krelic* argue that *Mensing* does not bar a generic manufacturer from including risks that are not disclosed in the brand-name label. Plaintiffs rely on the fact that the *Mensing* Court only considered 21 U.S.C. § 355(j)(2)(A)(v), which requires the generic manufacturer to use the labels of the brand-name manufacturer and did not rely on or discuss the Different Manufacturers Exception. Plaintiffs argue that this exception allows a generic manufacturer to comply with state tort law governing a failure to warn by

strengthening its safety and efficacy labeling such that plaintiffs' claims should not be preempted. The exception states 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 by different manufacturers.** 21 U.S.C. §355(j)(2)(A)(v).

The death knell to this argument was plaintiffs' failure to articulate why the Different Manufacturers Exception would permit generic manufacturers to alter the labeling of brand-name drugs by adding contraindications, warnings, precautions, adverse reactions, and other information related to the active ingredients of both the brand-name and generic drug. The *Krelic* court explained 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. Thus, under the plaintiffs' construction of the Different Manufacturers Exception, the scheme under which generic drugs shall use the FDA-approved label of the brand-name manufacturer would be rendered almost meaningless. *Krelic* at 4.

Moreover, the Different Manufacturers Exception does not include any differences relating to the active ingredients:

> 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 505(i)(5)(F) of the act.** 21 C.F.R. §314.94(a)(8)(iv)(emphasis added). Slip op. at 5.

The *Krelic* Court found that a February 8, 2012 letter from Dr. Jane Woodcock, Director of FDA's Center for Drug Evaluation and Research, Docket No. FDA-2011-P-0702, provided further support for the limitations on the permitted changes. In summary, Dr. Woodcock explains that the Different Manufacturers Exception will allow deviations in labeling that relate to differences between the generic drug and the brand-name drug. However, the active ingredients of the

generic drug and the brand-name drug must be the same, therefore, the warnings as to the side effects and safety of the active ingredients must be the same.

The Court was also persuaded by PLIVA's brief before the Supreme Court in *Mensing* and its discussion of the Different Manufacturer's Exception, as follows:

> 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 or 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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> > 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.
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> *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).

In conclusion, the *Krelic* court held that "the exception does not permit different labeling as to safety and efficacy." Slip op. at 9. All claims raised in Plaintiffs' First Amended Complaint that require a showing of a failure to warn were, therefore, dismissed.

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