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Hatch-Waxman Developments: Artificial Infringement by Artificial Drugs

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The Hatch-Waxman Act seeks to balance the competing interests of encouraging the development of pioneering drugs while enabling low-cost, generic versions of these drugs to efficiently enter the market when the patents on the drugs expire. To this end, patent infringement was defined in 35 U.S.C. § 271(e)(2) to include the act of submitting an ANDA to the FDA with the intent to market a drug that is protected by product or use patents before their expiration. This is an artificial act of infringement that gives pioneer drug makers the chance to litigate their patents before the generic drug is actually marketed. In such cases, infringement is based on how the generic drug is described in the ANDA and the approved uses on the label, not whether or not the generic drug as it is manufactured actually embodies any of the claims in the patent.

Pioneer drug patents are listed in the FDA's Orange Book. To avoid being sued under § 271(e)(2), a generic drug maker scours its ANDA specification and label to remove any statements that fall within the scope of the patents in the Orange Book. This can be a tricky process. Under FDA labeling rules, with limited exception, the language on a generic drug's label must be identical to the language on the pioneer drug's label. FDA rules are not so clear, however, when it comes to generic drug specifications. In particular, the chemistry, manufacturing and controls (CMC) section of a generic drug's ANDA does not need to be the same as the CMC section of the pioneer drug. This means that a generic drug on the market may not have all of the patented features of the pioneer drug. But what if FDA requires these features to be identified in the ANDA as a matter of policy, and also allows the generic drug to be manufactured without such a feature solely for the purpose of avoiding infringement?

The court addressed such a question in *Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc.*, 2013 WL 5356823 (Fed. Cir. Sept. 26, 2013). In *Sunovion*, the Court of Appeal for the Federal Circuit affirmed that, under 35 USC § 271(e)(2), an ANDA specification – here, the purity level of the active ingredient – that comes within the scope of a valid patent will infringe as a matter of law even if the generic drug product lawfully placed on the market would not otherwise infringe the patent. This ruling is significant because it means that FDA policies are, in some cases, forcing generic drug applicants to describe artificial features in ANDAs that give rise to artificial acts of infringement under Hatch-Waxman.

Understanding the *Sunovion* Decision

Sunovion Pharmaceuticals, Inc., (Sunovion) owns the '673 patent which claims a single-enantiomer compound eszopiclone, the active ingredient of the sleep medication Lunesta®. The '673 patent claims a compound that is "essentially free" of its levorotatory (R) isomer. The court in *Sunovion* construed "essentially free" to mean no more than 0.25% of the R-isomer. In contrast, the FDA approval of Lunesta® requires that each tablet contain no more than 0.3% of the R isomer.

Drug manufacturer Dr. Reddy's Laboratories (Reddy's) submitted a Paragraph IV-certified ANDA to the FDA seeking approval to sell a generic version of eszopiclone. Reddy's ANDA requested approval to market generic eszopiclone with not less than 0.3% and not more than 1.0% of the R-isomer. Rejecting this request, the FDA required Reddy's to limit the R-isomer to not more than 0.3%, the same level it required in Lunesta®. Nevertheless, Reddy's revised ANDA sought approval for an R-isomer impurity of no more than 0.6%. Importantly, since an impurity of not more than 0.6% includes tablets with not more than 0.25% impurity, this second ANDA described a compound which fell within the scope of Sunovion's patent.

Despite the ANDA's description of an infringing drug, the district court found no infringement because Reddy's promised to manufacture eszopiclone with an impurity of at least 0.3%. Overruling this decision, the court of appeals found that Reddy's infringed the '673 patent because "what a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement." Reddy's had argued that, if it ever strayed into the impurity range claimed in the patent, Sunovion could assert its patent at that time. The court rejected this argument as not comporting with the Hatch-Waxman goal of addressing infringement early in the ANDA process rather than deferring it indefinitely. Instead, the court found that Reddy's promise to make the drug with an impurity exceeding 0.25% was irrelevant because, under the Hatch-Waxman framework, an ANDA describing a drug that falls within the scope of the pioneer drug is an act of infringement as a matter of law.

Sunovion makes it clear that infringement under § 271(e)(2) turns on the language of an ANDA's specification. However, an ANDA's specification does not dictate how a drug must be manufactured. Manufacturing requirements are found in the CMC section of an ANDA which indicates the "identity, strength, quality, and purity" of the drug. Unlike the specifications in an ANDA, the CMC section of an ANDA may deviate from the CMC of the original NDA as long as there is bioequivalence between the generic and pioneer drug, and the CMC controls are sufficient.

So, could a generic drug maker such as Reddy's avoid liability for patent infringement as in *Sunovion* by specifying a "no less than" limit in its ANDA that matches what it actually intends to make, e.g., tablets with an impurity of 0.3-0.6% rather than an impurity of 0-0.6%? In view of an FDA response to a citizen's petition from Pzifer, the answer is no.

FDA Adds Some Clarity

Pfizer asked the FDA to refuse to approve any ANDA referencing Lyrica (pregabalin) that contains an isomeric impurity specification based on a "no less than" minimum level. In granting the request, the FDA noted that it has issued guidance on isomeric impurity minimum levels based on ICH guidelines. Under these guidelines, if an enantiomeric impurity is quantifiable, the same rigorous standards apply that would apply to other impurities, so a "no less than" impurity level is unacceptable. Although the FDA has previously accepted a range of impurity levels for certain drugs (e.g., gabapentin and oxaliplatin), it has reconsidered this policy and decided against it. The FDA's rationale for this is that, since impurities provide some risk and no benefit, "the exposure to risk is high compared to the benefit (if any), resulting in a substantially negative risk/benefit ratio." It further explained that, per 21 C.F.R. 314.127(a)(1) and FD&C Act § 505G)(4)(A), an ANDA must include controls that ensure a drug's identity, strength, quality and purity, and a minimum level of impurity is inconsistent with these provisions. The FDA clarified that it "do[es] not object to applicants having internal limits for patent purposes," but a "less than limit that is included as a specification in the ANDA is not appropriate" and any such internal impurity limit "will have no FDA regulatory significance."

So where does this leave generic drug manufactures who seek to use acceptance criteria to avoid patent infringement? On the one hand, the FDA does not object to this tactic in principle. But on the other hand, the FDA forbids an ANDA from stating a minimal impurity level even if that is how the drug will actually be manufactured and sold. Such a policy forces generic drug makers to infringe a pioneer drug patent under § 271(e)(2) even though there is an acceptable way to manufacture the generic drug that does not otherwise infringe the pioneer drug patent.