UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORP., Plaintiff, v. SANDOZ, INC., et al., Defendants.	Civil Action Nos. 12-CV-01617 13-CV-316 **MEMORANDUM OPINION AND ORDER**

This matter comes before the Court on a motion by Defendant, Sandoz Inc. ("Sandoz"), seeking summary judgment on the issue of non-infringement of U.S. Patent No. 7,999,007(ECF No. 123). Plaintiff, United Therapeutics Corporation ("UTC"), has timely opposed Defendant's motion; and the Court has considered these submissions together with the parties' oral argument, given on March 13, 2014. For the reasons stated below, the Court finds that there is sufficient evidence to support Plaintiff's claim of infringement, and denies Defendant's motion.

I.

In 1984, Congress adopted the *Drug Price Competition and Patent Term Restoration Act*, ("the Hatch-Waxman Act"), in an effort to strike a balance between two competing interests: "(1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). The Hatch-Waxman Act "provided brand name drug manufacturers with limited extensions of their

patent terms in order to restore a portion of the market exclusivity lost through the lengthy process of drug development and approval." *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325 (Fed. Cir. 2003). In addition, the Hatch-Waxman Act "provided generic drug manufacturers with a patent infringement exemption for experimentation in connection with an application for FDA approval of a generic drug," as well as "a shortened FDA approval process." *Id.*

Before introducing a new drug into interstate commerce, a pharmaceutical company must submit a New Drug Application ("NDA") to the FDA for approval. *See* 21 U.S.C. § 355(a). Among other things, a NDA must identify any patents for "which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1). Once an application is approved, the patent information is published in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the "Orange Book". *See Merck & Co., Inc. v. Hi-Tech Pharmacal, Inc.*, 482 F.3d 1317, 1319 (Fed. Cir. 2007).

Rather than submit its own set of extensive information, a potential generic drug manufacturer is thereafter permitted to file an abbreviated new drug application ("ANDA") for "the same drug that has been approved by the FDA" or for a drug that "is the bioequivalent of a drug that has been approved by the FDA." *Id.* at 1326. The ANDA allows the generic drug manufacturer to bypass the rigors of "proving the safety and efficacy of a drug that [is] already the object of an NDA." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1357 (Fed. Cir. 2003).

However simplified by the Hatch-Waxman Act, the ANDA approval process is still far from simple. As explained below, an applicant has many hoops to jump through in order to meet the requirements for FDA approval.

Generally, an applicant must first demonstrate that "the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug." 21 U.S.C. § 355(j)(2)(A)(iii), (j)(2)(C). Second, an applicant must demonstrate that "the labeling proposed for the new drug is the same as the labeling approved for the listed drug." *Id*. § 355(j)(2)(A)(v). Third, an applicant must make appropriate certifications to the FDA with respect to any patent previously listed in the Orange Book. 21 U.S.C. § 355(j)(2)(A)(vii). For each Orange Book patent that claims either the listed drug or a use of the listed drug for which the applicant is requesting approval, the applicant must certify either that the applicant is seeking approval for a method of use not claimed in a "method of use patent" associated with the listed drug (a "Section viii statement") or provide certification (I) that such patent information has not been filed, (II) that such patent has expired, (III) of the date on which such patent will expire, or (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] application is submitted (a "Paragraph IV certification"). *See* 21 U.S.C. § 355(j)(2)(A)(vii)-(viii).

An applicant choosing to submit a Section viii statement, declaring that its patent does not claim an infringing use, must also remove or "carve out" any mention of the patented method of use from the proposed label for the generic drug. *See* 21 C.F.R. § 314.92(a)(1); *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359, 1361 (Fed. Cir. 2010) ("Along with the section viii statement, the generic manufacturer must submit

a proposed label to the FDA that does not contain the patented method of using the listed drug.").

II.

UTC is the lawful owner of three patents—United States Patent Nos. 5,153,222 ("the ’222 Patent"); 6,765,117 ("the ’117 Patent"); and 7,999,007 ("the ’007 Patent")—which are listed in the Orange Book in connection with treprostinil sodium injection. UTC markets and sells treprostinil sodium injection under the registered trademark REMODULIN® for use in the treatment of pulmonary arterial hypertension, a rare life-threatening disease which narrows the arteries of the lungs and slowly deprives the body of oxygen. The present action arises out of Defendant’s efforts to produce a generic version of REMODULIN® (hereafter "generic Remodulin") before expiration of, *inter alia*, the ‘007 patent.

The ‘007 patent, entitled "Buffer solutions having selective bactericidal activity against gram negative bacteria and methods of using same" covers pharmaceutical preparations in which treprostinil or treprostinil sodium is diluted with a high pH glycine buffer, and the methods of using those preparations in order to facilitate safer intravenous use of REMODULIN® for patients with pulmonary arterial hypertension.[1] Plaintiff’s Statement of Material Facts at 6 (ECF 152). A revised drug label for REMODULIN® provides that the drug "must be diluted with either Sterile Water for Injection, or 0.9%

[1] The patent explains that the patented method of use and pharmaceutical preparation is associated with a decreased incidence of blood stream infections in patients administering REMODULIN® intravenously for the treatment of pulmonary arterial hypertension.

Sodium Chloride Injection, or Flolan Sterile Diluent for Injection[2]" prior to intravenous infusion. *Id.*

The claims of the '007 patent can be summarized as follows. Claim 1 is representative of Plaintiff's asserted method claims. Claim 1 states:

> A method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium, the method comprising supplying the active agent with a buffer comprising glycine and having a pH of greater than 10 with low buffer capacity.

('007 patent, claim 1).

Claim 23, which is representative of Plaintiff's pharmaceutical preparation claims, is directed to pharmaceutical compositions consisting of treprostinil or treprostinil sodium in a solution comprising glycine and sodium hydroxide and having a pH greater than 10. ('007 patent, claims 22-23). Notably, each of UTC's asserted claims requires the presence of a buffer containing glycine and having a pH greater than 10 (hereafter a "glycine 10 buffer"). ('007 patent, claims 1-5, 7-17, 19-21, 23).

On December 2, 2011, Defendant Sandoz, Inc. ("Sandoz") filed ANDA No. 203649 with the FDA, seeking approval to market and sell a generic form of UTC's patented REMODULIN® in 10mg/mL dosage form. On March 14, 2012, UTC filed the first of two lawsuits against Sandoz for patent infringement based upon the submission of

[2] Flolan® is a third party competitive product marketed by GlaxoSmithKline and used for treating pulmonary hypertension. The "Sterile Diluent for Flolan," or "Flolan diluent" is a solution which physicians or patients may use to dilute Flolan prior to intravenous infusion.

ANDA No. 203649. *See United Therapeutics Corporation. v. Sandoz, Inc., et al.*, Civil No. 12-1617.

On December 7, 2012, Sandoz filed an amendment to ANDA No. 203649 seeking approval from the FDA to market and sell generic REMODULIN® in three additional dosage concentrations. On January 16, 2013, UTC filed a second lawsuit against Sandoz for patent infringement based upon Defendant's Amended ANDA. *See United Therapeutics Corporation. v. Sandoz, Inc., et al.*, 13-316 ("13-316").

In Counts 5 and 6 of Plaintiff's operative complaints, UTC alleges that ANDA No. 203649 infringes the '007 patent under 35 U.S.C. § 271(a), (b) and (e). Civil No. 12-1617, ECF No. 1, ¶¶ 69-84; Civil No. 13-316, ECF No. 1, ¶¶ 77-92. UTC contends that Sandoz infringes and induces infringement of asserted method Claims 1-5, 7-17, and 19-21 because Sandoz's generic Remodulin label encourages doctors to practice the claims of the '007 patent. UTC further contends that Sandoz similarly infringes Claim 23 of the '007 patent, directed to the pharmaceutical preparation of REMODULIN®.

Normally, the label associated with the generic version of a drug must be exactly the same as the label associated with the drug approved in the original New Drug Application. 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). But, a Section viii statement allows a generic manufacturer to avoid infringement by carving out patented use from its proposed label information, thus allowing it to avoid infringement under Paragraph IV. 21 U.S.C. § 355(j)(2)(A)(viii).

In its initial application to the FDA, Sandoz proposed a label for generic Remodulin that copied the instructions contained in the label for UTC's patented

REMODULIN®. The label explicitly instructs physicians and end-users to dilute the product with "Sterile Water for Injection, 0.9% Sodium Chloride Injection or Flolan Sterile Diluent for Injection" prior to intravenous infusion. Plaintiff's Statement of Material Facts at 10. Because neither sterile water nor 0.9% Sodium Chloride is a glycine 10 buffer, using either to dilute generic Remodulin would not implicate the asserted claims of the '007 patent. Conversely, the Flolan diluent is a glycine 10 buffer. Pl.'s SMF at 11-12. Therefore, its use would directly implicate UTC's asserted claims.

Recognizing the infringement potential posed by including the Flolan diluent in its generic label, Sandoz subsequently submitted a proposed amendment to ANDA No. 203649, in which it revised its proposed label to delete all references to dilution with the sterile diluent for Flolan. (Exhibit E, April 25, 2013 Amendment to Sandoz's ANDA No. 203649 and Amended Label No. 203649 at Sandoz-Trep 0048791, 93). Therein, Sandoz also submitted a Section viii statement, stating that the '007 patent does not claim uses for the treprostinil sodium ANDA products for which Sandoz is seeking FDA approval, namely use of treprostinil sodium diluted with sterile water or 0.9% sodium chloride for intravenous administration. (Exhibit E, April 25, 2013 Amendment to ANDA No. 203649 at Sandoz-Trep 0048806; see also Id., Patent Certification at Sandoz-Trep 0048842- 43).

Following this carve-out, Sandoz's amended label instructs physicians and end users that its treprostinil sodium products can either be administered as supplied for subcutaneous infusion or diluted "with Sterile Water" or "0.9% Sodium Chloride" for intravenous infusion. (Exhibit E, April 25, 2013 Amended Label in ANDA No. 203649 at Sandoz-Trep 0048791). Presently, Sandoz's amended label does not instruct users that its

treprostinil sodium products can or should be diluted with the sterile diluent for Flolan. (Id. at Sandoz-Trep 0048791, 93).

III.

Summary judgment is appropriate under Fed. R. Civ. P. 56(c) when the moving party demonstrates that there is no genuine issue of material fact and the evidence establishes the moving party's entitlement to judgment as a matter of law. *Celotex Corp. v. Catrett*, 477 U.S. 317, 322-23 (1986). A factual dispute is genuine if a reasonable jury could return a verdict for the non-movant, and it is material if, under the substantive law, it would affect the outcome of the suit. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). The Court may grant summary judgment "only when no reasonable jury could return a verdict for the nonmoving party." *Monon Corp. v. Stoughton Trailers, Inc.*, 239 F.3d 1253, 1257 (Fed. Cir. 2001).

In considering a motion for summary judgment, the Court must "view the evidence in a light most favorable to the party opposing the motion with doubts resolved in the favor of the opponent." *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309, 1315 (Fed. Cir. 1998); *see also Marino*, 358 F.3d at 247 (*quoting Anderson*, 477 U.S. at 255) ("In considering a motion for summary judgment, a district court may not make credibility determinations or engage in any weighing of the evidence; instead, the non-moving party's evidence 'is to be believed and all justifiable inferences are to be drawn in his favor.'"). Evidence in support of summary judgment "is viewed through the prism of the evidentiary standard of proof that would pertain at a trial on the merits."

TriMed, Inc. v. Stryker Corp., 608 F.3d 1333, 1339-40 (Fed. Cir. 2010) (internal quotations omitted).

IV.

Sandoz asserts that its label does not infringe or induce infringement of the high pH glycine buffers because its label initially recommends subcutaneous infusion in which a buffer is not used, and secondly it recommends aseptic techniques when preparing/administering treprostinil (wiping hands with alcohol as opposed to using the FLOLAN® diluent. (T. 37, 1-17). UTC on the other hand, argues that Sandoz is inducing infringement through its instructions because its label uses words and phrases that implicitly instruct to use the FLOLAN® diluent.

According to the statute, "whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. §271(b). As such, the inducement is "a question of affirmative intent." (T. 42, 1-2). Usually, such intent is shown through circumstantial evidence (T. 43, 12-13). UTC argues that Sandoz's label implicitly instructs to use the sterile diluent for FLOLAN®. That is, the label indicates that the intravenous route of a treprostinil injection is associated with those bloodstream infections and that sepsis may be fatal. Accordingly, that language alerts a practitioner to research those bloodstream infections for precautionary measures. (T. 47, 15-18). In fact, the Sandoz label refers to a CDC survey about such infections. (T. 48, 19-2); and the CDC survey easily leads practitioners to review the medical research concerning the CDC survey. One such article found in the research is written by Dr. Rich who recommends using the FLOLAN® diluent to prevent bloodstream infections (T. 52, 3-19). Hence, the label circuitously

leads the practitioners to infringe the '007 patent. This argument by UTC presents a fact question as to whether Sandoz is implicitly inducing infringement through deliberate indifference. *See*, Fed. Judicial Ctr., Patent Law and Practice 185 (7th ed. 2011). In light of the UTC argument, Sandoz's carve out theory does not warrant judgment as a matter of law. Therefore, summary judgment is denied.

ORDER

For the reasons set forth above;

IT IS on this 15th day of April, 2014;

ORDERED that the motion for summary judgment by Sandoz, Inc. ("Sandoz") on the issue of non-infringement of U.S. Patent No. 7,999,007(ECF No. 123) is denied.

s/Peter G. Sheridan
PETER G. SHERIDAN, U.S.D.J.