United States Court of Appeals for the Federal Circuit

ASTRAZENECA LP
AND ASTRAZENECA AB,
Plaintiffs-Cross Appellants,

v.

APOTEX, INC.
AND APOTEX CORP.,
Defendants-Appellants.

2009-1381, -1424

Appeal from the United States District Court for the District of New Jersey in case no. 09-CV-1518, Judge Renee Marie Bumb.

Decided: November 1, 2010

DENISE L. LORING, Ropes & Gray LLP, of New York, New York, argued for plaintiffs-appellees. With her on the brief were CHRISTOPHER J. HARNETT, PABLO D. HENDLER and DEREK M. KATO.

RICHARD J. BASILE, St. Onge Steward Johnston & Reens LLC, of Stamford, Connecticut, argued for defendants-appellants. With him on the brief were DAVID W. ALDRICH and ROY D. GROSS. Of counsel on the brief was

SHASHANK UPADHYE, Intellectual Property Law Apotex, Inc., of Toronto, Ontario, Canada.

WILLIAM A. RAKOCZY, Rackoczy Molino Mazzochi Siwik LLP, of Chicago, Illinois, for amicus curiae Breath Limited. With him on the brief were DEANNE M. MAZZOCHI and AMY D. BRODY.

RICHARD T. RUZICH, Duane Morris LLP, of Chicago, Illinois, for amicus curiae Xttrium Laboratories, Inc. With him on the brief were JOSEPH M. BENNETT-PARIS, of Atlanta, Georgia; ANTHONY J. FITZPATRICK and CHRISTOPHER S. KROON, of Boston, Massachusetts; MATTHEW C. MOUSLEY, of Philadelphia, Pennsylvania; and KERRY B. MCTIGUE, of Washington, DC.

Before RADER, *Chief Judge*,* BRYSON and LINN, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LINN.

Opinion concurring-in-part and dissenting-in-part filed by *Circuit Judge* BRYSON.

LINN, *Circuit Judge*.

Apotex, Inc. and Apotex Corp. (collectively "Apotex") appeal from the grant by the United States District Court for the District of New Jersey of a preliminary injunction barring Apotex from launching a generic version of a budesonide drug made and distributed under the approval of the United States Food and Drug Administration ("FDA") by AstraZeneca LP and AstraZeneca AB (collectively "AstraZeneca") and covered under method

---

* Randall R. Rader assumed the position of Chief Judge on June 1, 2010.

and kit claims in AstraZeneca's U.S. Patents No. 6,598,603 ("the '603 Patent") and No. 6,899,099 ("the '099 Patent"). AstraZeneca cross-appeals the district court's ruling that the asserted kit claims in both patents are invalid. Because the district court did not abuse its discretion by granting the preliminary injunction and did not err in determining that the kit claims are invalid, this court affirms.

BACKGROUND

I. The Drug Approval Process

In part, this appeal concerns the procedures for obtaining permission to sell either a "new" or generic drug under the Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.). Under the Act, the FDA must approve all new drugs before such drugs may be distributed in interstate commerce. 21 U.S.C. § 355(a). To obtain approval for a new drug, an applicant may file a New Drug Application ("NDA") that includes examples of the proposed label for the drug and clinical data demonstrating that the drug is safe and effective for use. *Id.* § 355(b)(1)(A), (b)(1)(F). The NDA must contain the patent number and expiration date of any patent that claims either the drug or a method of using the drug if "a claim of patent infringement could reasonably be asserted." *Id.* § 355(b)(1). The FDA publishes the names of approved drugs and their associated patent information in the *Approved Drug Products with Therapeutic Equivalence Evaluations* list, commonly referred to as the "Orange Book."

An applicant seeking approval to market a generic version of a drug may file either an Abbreviated New Drug Application ("ANDA") or a "505(b)(2) application," which is also known as a "paper NDA." *Id.* § 355(b)(2), (j).

An ANDA allows an applicant to rely on the safety and efficacy information for the listed drug if the applicant can show that the generic drug is "bioequivalent" to the listed drug.

An ANDA has three requirements that are particularly relevant here. First, the applicant must 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," unless the FDA has approved a "suitability petition" requesting permission to file an ANDA that differs from the listed drug in one or more of these respects. *Id.* § 355(j)(2)(A)(iii), (j)(2)(C). Second, subject to changes required by FDA regulations or a successful suitability petition, the applicant must also show 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, for each patent listed in the Orange Book that claims either the listed drug or a use of the listed drug for which the applicant is requesting approval, an ANDA must include either one of four certifications or a "section viii statement."

If an applicant chooses to submit a certification, the applicant must certify "(I) that . . . patent information has not been filed, (II) that such patent has expired, (III) . . . 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." *Id.* § 355(j)(2)(A)(vii)(I)-(IV). These certifications are referred to as Paragraph I, II, III, and IV certifications, respectively.

Assuming all regulatory requirements are satisfied, the FDA may immediately make effective the approval of an ANDA that includes either a Paragraph I or II certification. *Id.* § 355(j)(5)(B)(i). By contrast, the filing of a

Paragraph III or IV certification may delay the effective date of an ANDA approval, and, in the case of a Paragraph IV certification, invite a patent infringement suit. *See* 35 U.S.C. § 271(e)(2), 21 U.S.C. § 355(j)(5)(B)(ii)-(iii).

If, however, an applicant is seeking approval for a method of use not claimed in a "method of use patent" associated with the listed drug, the applicant must submit a section viii statement declaring that the patent does not claim such a use. 21 U.S.C. § 355(j)(2)(A)(viii). The applicant 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."). Unlike a Paragraph III or IV certification, the filing of a section viii statement will not by itself delay approval of an ANDA.

Finally, in contrast to an ANDA, a paper NDA must include safety and effectiveness data. 21 U.S.C. § 355(b)(2). However, a paper NDA may rely on safety and effectiveness data not developed by the applicant. *Id.* As with an ANDA, a paper NDA requires the applicant to submit either a patent certification or a statement declaring that the patent does not claim the method of use for which the applicant is seeking approval. *Id.* § 355(b)(2)(A)-(B).

II. AstraZeneca's Budesonide Drug and Patents

In 2000, the FDA approved AstraZeneca's NDA for a budesonide inhalation suspension that AstraZeneca now markets under the name "PULMICORT RESPULES®." Each "respule" is a plastic vial containing a single dose of budesonide, an anti-inflammatory corticosteroid, sus-

pended in a sterile liquid. The drug is administered by squeezing the entire contents of a vial into a jet nebulizer and inhaling the resulting mist through a mask attached to the nebulizer.

The Orange Book entry for AstraZeneca's budesonide product includes the '099 Patent and its parent, the '603 Patent. Both patents are owned by AstraZeneca and have specifications that are nearly identical in all relevant respects. The patents explain that "[t]he invention provides a new method of treating respiratory diseases such as asthma that involves administering a budesonide composition with a nebulizer not more than once per day." '603 Patent col.1 ll.20-23; '099 Patent col.1 ll.26-29. "The invention also features a kit for treating respiratory diseases, the kit including a budesonide composition in a sealed container . . . and a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day." '603 Patent col.2 ll.1-6; '099 Patent col.2 ll.7-12. Both patents include method claims directed to administering a budesonide composition once daily and product claims directed to the described kit containing either a budesonide composition or suspension and a label indicating once-daily administration by nebulization.

While AstraZeneca's patents are directed to once-daily treatment, the label that accompanies AstraZeneca's budesonide product indicates that the drug may be administered once or twice daily. The label states that the drug is available in three strengths—0.25 mg, 0.5 mg, and 1.0 mg per 2 mL vial—and provides a table of recommended starting doses based on a patient's history of therapy. The label repeatedly warns that patients should "titrate down" to the lowest effective dose of the medication to avoid any adverse effects from excessive use of the medication. For example, in its DOSAGE AND

ADMINISTRATION section, the label states that "[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved" and "[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose." The PRECAUTIONS section also warns that "suppression of HPA function may be associated . . . when the dose is not titrated to the lowest effective dose" and "[t]o minimize the systemic effects of orally inhaled corticosteroids . . . each patient should be titrated to his/her lowest effective dose." It is undisputed that the FDA requires all manufacturers of inhaled corticosteroids such as budesonide to include this downward titration language in the labels of their inhaled corticosteroid products.

III. Apotex's ANDA

Apotex submitted an ANDA seeking FDA approval to manufacture and sell a generic version of budesonide for twice-daily use, a use not claimed in either the '603 or '099 patents. The ANDA included a proposed label for the generic drug that, with certain exceptions, is identical to the label included with AstraZeneca's budesonide product. Specifically, in its label, Apotex replaced the "PULMICORT RESPULES®" brand name on AstraZeneca's product with the generic name "budesonide inhalation suspension." Apotex also submitted a section viii statement asserting that it was not seeking approval for the once-daily method of use claimed in the '603 and '099 patents and that its proposed generic label would contain no explicit mention of once-daily administration. However, the proposed label retained the FDA-mandated downward-titration language found in AstraZeneca's PULMICORT RESPULES® product label. Apotex further represented that the proposed label would indicate that the generic drug is available in only two strengths: 0.25

mg and 0.5 mg per 2 mL vial. The FDA approved Apotex's ANDA on March 30, 2009.

IV. Proceedings Before the District Court

On March 31, 2009, the day after Apotex's ANDA was approved, AstraZeneca initiated the declaratory judgment action underlying this appeal and moved for a preliminary injunction barring Apotex from distributing its generic budesonide drug. In that action, AstraZeneca argued that Apotex would directly infringe certain kit claims in both patents (claims 29 and 30 of the '603 Patent and claims 17, 18, 20, 21, and 24-27 of the '099 Patent) and would induce infringement of specified method claims in the '603 Patent (claims 1-3, 6-8, 11-18, and 21-28) by including the downward-titration statements in the proposed label. AstraZeneca asserted that the downward-titration statements effectively instructed consumers to use the drug once daily. Claims 1 and 29, respectively, are representative of the asserted method and kit claims in the '603 Patent:

> 1. A method of treating a patient suffering from a respiratory disease, the method comprising administering to the patient a nebulized dose of a budesonide composition in a continuing regimen at a frequency of not more than once per day.

'603 Patent col.10 ll.18-22.

> 29. A kit for treating respiratory diseases, the kit comprising (a) a budesonide composition in a sealed container, the composition containing 0.05 mg to 15 mg budesonide and a solvent, and (b) a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day.

Id. col.12 ll.3-8.

Claim 17 is representative of the asserted kit claims in the '099 Patent:

> 17. A kit for treating a respiratory disease, the kit comprising (a) a budesonide suspension in a sealed container, the suspension containing 0.05 mg to 15 mg budesonide and a solvent, and (b) a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day.

'099 Patent col.11 ll.9-14.

The court held a five-day hearing on AstraZeneca's request for a preliminary injunction. At the hearing, Apotex argued that U.S. Patent No. 5,192,528 ("the '528 Patent") anticipates all but three of the asserted method claims (claims 12, 14, and 16). Apotex also argued that a 1994 advertisement for AstraZeneca's PULMICORT RESPULES® drug in the British medical journal *Thorax* ("the *Thorax* advertisement") anticipates each of the asserted method claims. Apotex contended that the asserted kit claims of both patents were invalid because the claimed budesonide composition and suspension were known in the prior art and the recited label could not render a known product patentable.

Apotex further argued that it would not induce infringement of the asserted method claims. Apotex contended that the proposed label would not lead consumers to directly infringe the claims because the downward-titration statements included in the label did not instruct users to take the generic drug once daily. In support of this argument, Apotex pointed out that the FDA had previously issued a letter agreeing that the downward-

titration language did not "teach" once-daily usage and was not protected by the '603 and '099 patents. Apotex also contended that it lacked the requisite specific intent to induce infringement because it was the FDA that had required Apotex to include the downward-titration statements in the label. Moreover, because the generic drug allegedly has substantial noninfringing uses (e.g., twice-daily administration to treat asthma), Apotex argued that the district court could not infer that Apotex intended to induce infringement.

In the first of two opinions**,** the district court agreed that Apotex had shown a likelihood of success in its contention that all of the asserted kit claims were invalid, concluding that the "addition of the instruction does not functionally alter the known product so as to create a new patentable product." *AstraZeneca LP v. Apotex, Inc.* ("*Opinion*"), 623 F. Supp. 2d 579, 591 (D.N.J. 2009). With respect to the asserted method claims, the court determined that under its construction of the term "budesonide composition" Apotex had not shown the asserted method claims likely to be anticipated by the '528 Patent. *Id.* at 595. The court likewise was not convinced that the *Thorax* advertisement anticipated these claims, finding persuasive evidence that one of ordinary skill in the art at the time of the invention would not have understood the advertisement to instruct once-daily usage of AstraZeneca's PULMICORT RESPULES® drug. *Id.* at 596.

Regarding inducement, the district court concluded that the downward-titration language would lead many users to directly infringe the asserted method claims because titrating down from the recommended starting doses would necessarily lead to once-daily usage. *Id.* at 601-02. The court found that the proposed label provided evidence of Apotex's affirmative intent to induce infringement and that there was no evidence in the record

that Apotex had attempted to craft a noninfringing label. *Id.* at 605, 607.

The district court also found that AstraZeneca would suffer irreparable harm if the court did not issue a preliminary injunction, as the damage caused by layoffs and loss of consumer goodwill would be unquantifiable, and a confidential settlement agreement between AstraZeneca and Teva Pharmaceuticals ("Teva") made determining economic harm speculative. *Id.* at 611-14. The court found that the public interest did not favor either party. *Id.* at 614. Before deciding whether to issue the requested preliminary injunction, the court offered Apotex the opportunity to present additional evidence addressing whether Apotex had the necessary specific intent to induce infringement of the asserted method claims. Apotex accepted and presented testimony regarding Apotex's efforts to develop a non-infringing label. After considering this testimony, the court issued a supplemental opinion in which it concluded that AstraZeneca had shown that Apotex had the requisite specific intent to induce infringement. *AstraZeneca LP v. Apotex, Inc.* ("*Supplemental Opinion*"), 623 F. Supp. 2d 615 (D.N.J. 2009). The district court then issued its preliminary injunction. Apotex filed a timely appeal and AstraZeneca timely filed a cross-appeal. This court has jurisdiction under 28 U.S.C. § 1292(c)(1).

DISCUSSION

I. The Preliminary Injunction

This court reviews a decision to grant a preliminary injunction for abuse of discretion. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009) (citing *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001)). "An abuse of discretion may be established by showing that the court made a clear error

of judgment in weighing relevant factors or exercised its discretion based upon an error of law or clearly erroneous factual findings." *Amazon.com*, 239 F.3d at 1350 (quoting *Novo Nordisk of N. Am., Inc. v. Genetech, Inc.*, 77 F.3d 1364, 1367 (Fed. Cir. 1996)).

"A plaintiff seeking a preliminary injunction must establish that [it] is likely to succeed on the merits, that [it] is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in [its] favor, and that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 129 S. Ct. 365, 374 (2008); *see also Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1375 (Fed. Cir. 2009). Apotex appeals only the district court's findings that AstraZeneca is likely to succeed on the merits with respect to the asserted method claims and is likely to suffer irreparable harm in the absence of a preliminary injunction.

A. Likelihood of Success on the Merits

For a patentee to establish that it is likely to succeed on the merits, it "must demonstrate that it will likely prove infringement of one or more claims of the patents-in-suit, and that at least one of those same allegedly infringed claims will also likely withstand the validity challenges presented by the accused infringer." *Amazon.com*, 239 F.3d at 1351. When reviewing the grant of a preliminary injunction, this court "views the matter in light of the burdens and presumptions that will inhere at trial." *Titan Tire Corp.*, 566 F.3d at 1376 (citation omitted). A preliminary injunction should not issue if an alleged infringer raises a substantial question regarding either infringement or validity, i.e., the alleged infringer asserts an infringement or invalidity defense that the patentee has not shown lacks substantial merit. *Genen-*

tech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1364 (Fed. Cir. 1997).

Apotex contends that AstraZeneca has failed on both validity and infringement. Regarding validity, Apotex repeats its argument that the '528 Patent and the *Thorax* advertisement anticipate the asserted method claims. With respect to infringement, Apotex renews its contention that the distribution of its generic version of AstraZeneca's budesonide product would not induce infringement because such distribution fails to show that Apotex possessed the requisite specific intent to infringe. These contentions are addressed in turn.

i. The '528 Patent

The '528 Patent, entitled "Corticosteroid Inhalation Treatment Method," issued in 1993, several years before the filing of the application that matured into the '603 Patent. The '528 Patent discloses a method for treating lung conditions such as asthma by administering a suspension of budesonide "entrapped" within a liposome (i.e., a spherical vesicle) once daily. Col.7 ll.57-63, col.8 ll.4-11.

Before addressing validity, the district court construed the term "budesonide composition" in the asserted method claims. The court concluded that the term means "budesonide dispersed in a solvent in the form of a solution or suspension" and excludes "the involvement of liposomes as described in the '528 Patent." *Opinion* at 595. In support of this construction, the district court noted that the '603 Patent consistently describes the compositions used in the claimed method as either suspensions or solutions of budesonide dispersed in a solvent. *Id.* The court also cited the testimony of Dr. Robert O. Williams III, an expert witness presented by AstraZeneca. Dr. Williams testified that the '603 Patent discloses a "depot effect" associated with budesonide that enables the

drug to be effective when administered only once per day. Prelim. Inj. Hr'g Tr. 16-17, May 4, 2009. Dr. Williams explained that the '603 Patent teaches dispersing budesonide in a solvent as either a solution (i.e., budesonide dissolved in the solvent) or as a suspension (i.e., budesonide particles floating in the solvent). *Id.* at 16-19. According to Dr. Williams, dispersing budesonide in the solvent in either form places the budesonide in direct contact with the solvent, which allows the budesonide to be absorbed by lung cells where the drug binds with fatty acids and is rendered inactive. *Id.* at 16-18. This inactive budesonide acts as a "depot" or reservoir of budesonide that replaces free budesonide as the free budesonide is used. *Id.* at 16-17. He explained that, unlike the liposome-entrapped budesonide disclosed in the '528 Patent, "the budesonide is provided . . . in . . . immediate contact with the solvent[] such that . . . the budesonide molecules . . . are available to be absorbed by the airway cells . . . and act as a depot effect." *Id.* at 26-27. Dr. Williams testified that the '603 Patent "tells one of skill in the art that it's important to provide budesonide immediately in contact with the solvent either dissolved as a solution or suspended in a suspension" and later opined that providing budesonide in direct contact with the solvent was critical to the depot effect. *Id.* at 17-18. Based on the testimony of Dr. Williams, the court found that the "'depot effect' is at the heart of AstraZeneca's revolutionary method and it could not occur if the liposomes involved in the '528 Patent were present." *Opinion* at 595. Accordingly, the district court concluded that the '528 Patent does not anticipate the asserted method claims because the patent does not disclose the claimed "budesonide composition." *Id.*

On appeal, Apotex points out that the '603 Patent discloses budesonide formulations that include liposomes:

"[T]herapeutic suspensions can also contain one or more excipients. Excipients are well known in the art and include . . . *liposomes* . . . . Solutions or suspensions can be encapsulated in *liposomes* or biodegradable microspheres." '603 Patent col.3 ll.32-39 (emphases added). Apotex argues that the district court improperly relied on expert testimony to arrive at a construction of "budesonide composition" that excludes these formulations, violating this court's warnings that claims should generally not be interpreted in a manner that excludes embodiments disclosed in the specification.

In response, AstraZeneca argues that the district court correctly construed the "budesonide composition" term based on the intrinsic evidence and expert testimony in the record. AstraZeneca contends that the district court's reliance on the testimony of Dr. Williams was entirely proper, as his testimony simply explained the meaning of the term "budesonide composition" in the context of the '603 Patent.

There is no serious dispute that the '528 Patent would anticipate the majority of the asserted method claims if the term "budesonide composition" is interpreted to include the liposome embodiments disclosed in the '528 Patent and would not anticipate the method claims if the district court's construction was correct. Thus, the question before us is whether the district court correctly construed the term to exclude these embodiments. This court reviews the district court's claim construction de novo. *Cybor Corp. v. Fas Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc).

This court agrees with AstraZeneca and concludes that the district court was correct in its claim construction. A claim term is generally given its "ordinary and customary meaning," that is, "the meaning that the term

would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc). "[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313. "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Id.* at 1316. The specification need not reveal such a definition explicitly. *See Bell Atl. Network Servs., Inc. v. Covad Commc'ns Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) ("[A] claim term may be clearly redefined without an explicit statement of redefinition."). "[W]hen a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term 'by implication.'" *Id.* at 1271 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

Here, the specification of the '603 Patent supports the conclusion that one of ordinary skill in the art would have understood the term "budesonide composition" to mean "budesonide dispersed in a solvent in the form of a solution or suspension" as construed by the district court. The specification consistently describes the budesonide compositions in that way. The SUMMARY OF THE INVENTION states that "the invention features a method of treating a patient suffering from a respiratory disease in which a composition, e.g., a suspension, of budesonide is administered by nebulization," '603 Patent col.1 ll.29-31, and explains a few sentences later that "[t]he drug can be provided as an aqueous suspension in which the budesonide is suspended in a solvent," *id.* col.1 ll.37-39.

The SUMMARY OF THE INVENTION notes that "the invention also features a kit . . . including a budesonide composition in a sealed container, the composition including 0.05 mg to 15 mg budesonide and a solvent." *Id.* col.2 ll.1-6. Similarly, the DETAILED DESCRIPTION states that "[t]he drug can be delivered in a solvent, e.g., in the form of a solution or a suspension." *Id.* col.3 ll.22-23. The DETAILED DESCRIPTION goes on to note that nebulizable budesonide is packaged in vials containing "micronized budesonide suspended in a volume, e.g., 2 ml, of solvent." *Id.* col.4 ll.12-14. The EXAMPLES section describes two clinical studies performed to determine the safety and efficacy of administering budesonide once daily. The patent discloses that in each study "[b]udesonide was administered once per day as a nebulized suspension." *Id.* col.4 ll.65-67, col.7 ll.57-60.

As noted above, the specification does mention liposome formulations in two places. *Id.* col.3 ll.32-39 ("[T]herapeutic suspensions can also contain one or more excipients. Excipients are well known in the art and include . . . *liposomes* . . . . Solutions or suspensions can be encapsulated in *liposomes* or biodegradable microspheres." (emphases added)). Contrary to Apotex's contention, however, the district court's construction does not exclude either of these formulations. The district court's construction excludes "the involvement of liposomes as described in the '528 Patent." Neither of the liposome formulations discussed in the specification use liposomes in the manner described in the '528 Patent. The '528 Patent describes entrapping budesonide in a liposome. Such entrapment separates the budesonide from the surrounding solvent. By contrast, the reference in the specification to placing liposomes in a suspension as an excipient indicates a formulation where budesonide and liposomes are in the same suspension, with the liposomes

independent of and apart from the budesonide, which remains in contact with the solvent. The statement that "[s]olutions or suspensions can be encapsulated in liposomes or biodegradable microspheres" indicates that *budesonide either dissolved or floating in a solvent* may be placed *within* a liposome, not that the term "budesonide composition" includes budesonide separated from a solvent by a liposome as described in the '528 Patent.

The specification and the claims are not the only sources that a court may consider when determining the meaning of a claim term. A court may look to "those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean," which, in addition to the claims and the rest of the specification, may include "the prosecution history[] and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Phillips*, 415 F.3d at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Id.* at 1317 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995)).

Here, the record includes the testimony of AstraZeneca's expert, Dr. Williams. This court generally views expert testimony "as less reliable than the patent and its prosecution history in determining how to read claim terms." *Id.* at 1318. However, expert testimony can be useful "for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, [or] to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art . . . ." *Id.* at

1318. In this case, the district court properly relied on the testimony of Dr. Williams to understand how the claimed invention works and construed the disputed term in a manner consistent with that understanding. As described above, Dr. Williams explained that the '603 Patent discloses that the depot effect permits budesonide to be effective when administered once daily and opined that for the depot effect to occur budesonide must be in direct contact with the solvent. He also testified that one of skill in the art would have understood the '603 Patent to disclose budesonide in immediate contact with the solvent as either a solution or suspension. This would exclude the liposome-entrapped embodiments disclosed in the '528 Patent. Although Apotex takes issue with the district court's reliance on Dr. Williams's testimony, Apotex does not seriously dispute his explanation of how the claimed invention works and provided no testimony to the contrary at the preliminary injunction hearing. This court sees no error in relying on uncontested expert testimony to explain how the invention described in the intrinsic record functions. *See Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1356 (Fed. Cir. 2001) ("[A] district court can not be faulted for relying on the only expert explanation of the technology that was presented.").

Considered together, the intrinsic evidence and expert testimony support the conclusion that a person skilled in the art would have understood the term "budesonide composition" to mean "budesonide dispersed in a solvent in the form of a solution or suspension" and excludes "the involvement of liposomes as described in the '528 Patent."[1] Accordingly, this court concludes that, based on the

[1] The dissent notes that after discussing the depot effect, the '603 Patent states that "[t]his proposed mechanism of action is exemplary; the invention is not limited by any particular mechanism of action," '603

evidence of record at this point, the district court correctly construed this term, and thus correctly found that the asserted method claims are likely to withstand the validity challenge posed by the '528 Patent.

ii. The *Thorax* Advertisement

As discussed above, a British medical journal published the *Thorax* advertisement in 1994, more than one year before the filing of the application that issued as the '603 Patent. The advertisement touts AstraZeneca's PULMICORT RESPULES® drug as "[a] high-dose nebulised steroid that's low on side effects" and notes that the drug can be used to treat bronchial asthma in children. The advertisement indicates that the drug was available in 2 mL single dose vials, each vial containing either 0.25 mg/mL or 0.5 mg/mL of budesonide. The advertisement includes the following statement regarding dosing:

Patent col.3 ll.11-12, and concludes that the testimony of Dr. Williams regarding the necessity of the depot effect is therefore contrary to the specification. But no other "mechanism of action" is disclosed in the patent, and the undisputed testimony of Dr. Williams—the only expert testimony provided to the court on this issue—is that after reading the '603 Patent a person of skill in the art would have understood that the claimed invention simply would not work without the depot effect. Therefore this court sees no error in the district court's construction, as the evidence of record leaves no doubt that the claimed invention would be inoperable if the claims are construed in the manner suggested by Apotex. *See Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1376 (Fed. Cir. 2002), *vacated and remanded on other grounds*, 537 U.S. 802 (2002) ("[A] construction that renders the claimed invention inoperable should be viewed with extreme skepticism." (citation omitted)).

> Initially . . . the recommended dose in adults . . . is usually 1-2 mg twice daily. . . . Children . . . 0.5-1 mg twice daily. The maintenance dose should be the lowest dose which keeps the patient symptom-free. Recommended doses are Adults . . . 0.5-1 mg twice daily. Children . . . 0.25-0.5 mg twice daily.

When the advertisement was published, AstraZeneca's budesonide product was not approved for any use in the United States and was approved for only twice-daily use in Europe.

Because it is undisputed that the asserted method claims cover the use of budesonide solution, the only question before the district court was whether the advertisement disclosed administering that solution "in a continuing regimen at a frequency of not more than once per day" as recited in the claims. The district court found that the advertisement does not anticipate the asserted method claims, finding persuasive the explanation of AstraZeneca's expert, Dr. Bradley Chipps, that the advertisement does not explicitly or inherently disclose once-daily dosing because the advertisement was published "before we had any information or historical perspective that once a day therapy worked for anyone." *Opinion* at 596. The district court reached that conclusion with the understanding of Dr. Chipps, who also testified that, if made today, the statement "[t]he maintenance dose should be the lowest dose which keeps the patient symptom-free" would be equivalent to the downward-titration language included in the proposed label that AstraZeneca claimed would induce infringement of the asserted method claims. Prelim. Inj. Hr'g Tr. 186, May 4, 2009.

On appeal, Apotex asserts that if the language in the *Thorax* advertisement would today suggest to those in the art the possibility of administering the drug once daily, it

would also have suggested this possibility when the advertisement was published, regardless of whether anyone had proven that the drug could be effective when administered once per day. Apotex argues that in concluding otherwise the district court improperly imposed a temporal limitation on the anticipation inquiry, violating the oft-repeated axiom "that which would literally infringe if later in time anticipates if earlier." AstraZeneca responds that because the drug was only approved for twice-daily use and was not known to be safe or effective when administered once daily, there is nothing to show that one of skill in the art at the time the patent application was filed would have understood the advertisement to disclose once-daily dosing. AstraZeneca thus argues that the *Thorax* advertisement was not enabling and for that reason cannot be considered anticipatory. In any event, AstraZeneca argues that the reference simply does not disclose once-daily dosing.

Anticipation is a question of fact, *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008) (citation omitted), that must be established at trial by clear and convincing evidence, *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001). This court reviews for clear error the district court's determination that AstraZeneca has demonstrated that the asserted method claims will likely survive the validity challenge posed by the *Thorax* advertisement. *See Amazon.com*, 239 F.3d at 1350.

While the question is close, this court agrees with AstraZeneca that the district court correctly determined that AstraZeneca has demonstrated that the asserted method claims will likely withstand the validity challenge presented by the *Thorax* advertisement. In the context of anticipation, the question is not whether a prior art reference "suggests" the claimed subject matter as posited

by Apotex. Rather, "the dispositive question regarding anticipation [is] whether one skilled in the art would reasonably understand or infer from a [prior art reference]" that every claim element is disclosed in that reference. *In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991). And although a reference must be enabling to be anticipatory, *see Sanofi-Synthelabo*, 550 F.3d at 1082, unlike enablement under § 112, a reference need not, as AstraZeneca suggests, demonstrate utility or efficacy to be enabling in the context of § 102, *see In re Gleave*, 560 F.3d 1331, 1335-36 (Fed. Cir. 2009) ("[A] reference need disclose no independent use or utility to anticipate a claim under § 102."); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). As explained in *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005), the reason for this distinction "is that [§] 112 'provides that the specification must enable one skilled in the art to 'use' the invention whereas [§] 102 makes no such requirement as to an anticipatory disclosure.'" *Id.* (quoting *In re Hafner*, 410 F.2d 1403, 1405 (CCPA 1969)).

Apotex's argument that the *Thorax* advertisement is anticipatory because the advertisement and the proposed label are essentially the same ignores a key difference between the advertisement and the proposed label. As discussed in greater detail in the next section, depending on a patient's previous therapy, the proposed label recommends initially administering 0.25 mg of budesonide twice daily. The district court concluded that the proposed label would induce infringement because, absent instructions to the contrary, titrating down to the lowest effective dose from the recommended starting dose of 0.25 mg of budesonide twice daily would necessarily lead some users to take 0.25 mg of budesonide once daily as a maintenance dose, as there would be no way to properly ad-

minister less than 0.25 mg of the drug. By contrast, the *Thorax* advertisement explicitly discloses that such maintenance doses should be administered twice daily. Immediately after the advertisement warns that "[t]he maintenance dose should be the lowest dose which keeps the patient symptom-free," the advertisement sets out recommended doses for adults and children: 0.5-1 mg twice daily for adults, and 0.25-0.5 mg twice daily for children. The most natural reading of this passage is that the recommended doses are recommended *maintenance* doses, which the advertisement explicitly states should be administered *twice daily*. Thus, although Dr. Chipps testified that the statement "[t]he maintenance dose should be the lowest dose which keeps the patient symptom-free" would, if made today, be equivalent to the downward-titration language included in the proposed label, the advertisement—unlike the proposed label—clearly states how often a maintenance dose should be given: twice per day.

Dr. Chipps confirmed that one of ordinary skill in the art would have understood the advertisement to disclose administering budesonide twice-daily, not once per day as argued by Apotex. He testified that "there's nothing in [the *Thorax* advertisement] that talks about or alludes to once a day dosage," and noted that the advertisement instructs that the recommended starting and maintenance doses are to be administered twice daily. Prelim. Inj. Hr'g Tr. 144, May 4, 2009. Dr. Chipps opined that when the *Thorax* advertisement was published in 1994 a physician reading the dosing recommendations set forth in the advertisement would not have understood the dosing recommendations to teach once-daily dosing. *Id.* at 144. He explained that until AstraZeneca conducted clinical studies on its budesonide product in 1997 there was no evidence that administering budesonide once-daily

would be safe and effective. Indeed, he noted that prior to 1997, the lowest dose of budesonide known to be effective was 0.25 mg taken twice a day. *Id.* at 147-48. Apotex presented no testimony or evidence to the contrary.

After considering the reference and appreciating how that reference would have been understood by persons of ordinary skill in the art at that time, this court is not left with a definite and firm conviction that the district court clearly erred by concluding that at trial Apotex will likely not be able to demonstrate by clear and convincing evidence that the *Thorax* advertisement anticipates the asserted method claims.[2] Accordingly, the district court's determination is affirmed.

iii. Inducement

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "[I]nducement requires that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in

[2] By rearranging the language of the *Thorax* advertisement, the dissent makes it appear that the advertisement and the proposed label both recommend administering a starting dose of 0.25 to 0.5 mg twice daily followed by eventual reduction to the lowest effective dose. But the facts do not support that suggestion. The *Thorax* advertisement actually specifies higher levels of initial recommended twice daily dosing and then goes on to state that "[t]he maintenance dose should be the lowest dose which keeps the patient symptom-free. Recommended doses are: . . . 0.25-0.5 mg twice daily." The *Thorax* advertisement thus recommends reducing a higher dose to the twice daily dose of 0.25-0.5 mg, not first administering 0.25-0.5 mg twice daily and then reducing the dosage to either once daily or twice daily doses as suggested by the dissent.

relevant part) (citation omitted) (internal quotation marks omitted). "Infringement is a question of fact reviewed for clear error." *Golden Blount, Inc. v. Robert H. Peterson, Co.*, 438 F.3d 1354, 1361 (Fed. Cir. 2006) (citation omitted). "A factual finding is clearly erroneous when, despite some supporting evidence, the reviewing court is left with the definite and firm conviction that a mistake has been made." *Id.* at 1361 (citation omitted).

Before the district court, AstraZeneca contended that Apotex's proposed label would induce consumers to infringe the asserted method claims because the label implicitly instructed users to administer the generic drug once daily. As in AstraZeneca's PULMICORT RESPULES® drug label, the DOSAGE AND ADMINISTRATION section of the proposed generic label explains that "[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved." The section also includes the following table of recommended starting doses and highest recommended doses, which differs from AstraZeneca's label in the removal of all mention of once-daily dosing:

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

In the paragraph following the table, the label again warns that "[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose."

The district court agreed with AstraZeneca that the proposed label would cause some users to infringe the asserted method claims. The proposed label indicates that the generic drug will be available in only two strengths: 0.25 mg and 0.5 mg per 2 mL vial. The court noted that, once opened, each vial of the generic drug must immediately be administered in its entirety because dividing the contents of a vial for use at different times would compromise the drug's sterility. *Opinion* at 600 n.17. Because the recommended starting dose for patients in the first two rows of the dosing table is "0.5 mg

total daily dose administered twice daily in divided doses" (i.e., 0.25 mg administered twice a day), the court reasoned that the first step in titrating down from this dose would have to be 0.25 mg once daily, as there was no way of decreasing the amount of each dose below 0.25 mg. *Id.* at 602. Accordingly, the court concluded that, for patients whose previous treatments fell within the first two rows of the dosage table, the downward-titration language would necessarily lead patients to use a 0.25 mg vial of the drug once-daily.

The district court found that a letter issued by the FDA supported this conclusion. In 2008, AstraZeneca filed a citizen petition with the FDA concerning an ANDA submitted by IVAX Pharmaceuticals, Inc. ("IVAX") that is virtually identical to the ANDA submitted by Apotex. In the petition, AstraZeneca asked the FDA to determine that labeling for a generic budesonide inhalation suspension must include once-daily dosing language. AstraZeneca also questioned the propriety of including downward-titration language in a proposed label for a generic budesonide inhalation suspension. In response, the FDA issued a letter explaining that the labeling for a generic budesonide inhalation suspension could omit references to once-daily dosing "[b]ecause the weight of the evidence is stronger in support of efficacy for twice-daily dosing as opposed to once-daily dosing . . . omission of once-daily dosing in the generic BIS labeling would not render the generic drug less safe or effective than PULMICORT RESPULES®." Letter from the FDA to AstraZeneca 16 (Nov. 18, 2008). The letter also stated that the FDA found it appropriate to include the downward-titration language in proposed labeling for generic budesonide inhalation suspensions because the FDA believed that the language did not "teach" once-daily dosing:

> Titration to the lowest effective dose may involve, for example, a twice-daily regimen, once-daily dosing, or even alternate day dosing . . . . The labeling does not state the lowest effective dose is 0.25 mg once daily. As such, contrary to your assertion, the downward titration statement does not "teach" once-daily dosing.
>
> . . . .
>
> . . . . The downward titration statement does not specify or instruct that the dosing frequency must be once daily and need not be carved out as protected by the 6,598,603 and 6,899,099 patents.

Id. at 18. The district court concluded that the letter supported the court's finding of direct infringement because the letter explicitly stated (and therefore put Apotex on notice) that downward titration may involve once-daily dosing. *Opinion* at 601.

Regarding specific intent to induce infringement, the district court found that AstraZeneca had submitted evidence of Apotex's affirmative intent that consumers use the generic drug in an infringing manner: Apotex's inclusion of the downward-titration language in the proposed label. *Id.* at 605. The court also noted that Apotex had presented no evidence that the company had attempted to draft a non-infringing label. *Id.* at 606-07. Because the question of Apotex's efforts to draft a non-infringing label had arisen late in the proceedings, the court offered Apotex the opportunity to continue the hearing and present evidence on this issue.

Apotex accepted the court's offer and presented Bernice Tau, the Director of Regulatory Affairs at Apotex, to

testify at the hearing. Tau testified that, in addition to removing all explicit references to once-daily dosing, at the advice of counsel, Apotex had also inserted the phrase "by administration twice-daily" in sections of the proposed label that Apotex included with its ANDA. Prelim. Inj. Hr'g Tr. 19, 21-22, May 20, 2009. She explained that the FDA responded by instructing Apotex to delete this phrase and sending Apotex a template containing the language Apotex was to include in the proposed label. *Id.* at 22-23.

Tau stated that Apotex never intended to instruct or encourage either physicians or patients to use its generic drug once-daily. *Id.* at 32. She also testified that it never occurred to Apotex that the downward-titration statements in the proposed label would suggest once-daily use of Apotex's generic version of the drug. *Id.* at 27. She explained that she became aware that the language was problematic after Apotex obtained approval of its ANDA, when Apotex's counsel notified her that AstraZeneca was objecting to use of the language. *Id.* at 27, 37. She stated that after learning of the issue, she made two calls to the FDA to address AstraZeneca's concerns and proposed the following three amendments to the label: (1) adding the words "twice daily" to the downward-titration language; (2) adding language stating the drug is not approved for less than twice-daily use; and (3) removing the downward-titration language *Id.* at 27-31. She testified that she did so despite believing, based on her experience with the FDA, that the FDA would not allow Apotex to alter the label. *Id.* at 27-28. She stated that during these calls the FDA informed her of the letter it issued in response to AstraZeneca's petition. *Id.* at 37-38. As she expected, the FDA did not permit Apotex to make any of the suggested changes. She explained that Apotex did not submit a formal labeling amendment because, based on her conver-

sations with the FDA, she believed doing so would have been futile. *Id.* at 33-34.

Tau acknowledged that she knew that FDA decisions could be appealed, but stated that she was not familiar with the process, as she had never had to appeal an FDA decision regarding an ANDA. *Id.* at 37, 40. Tau also admitted that had Apotex wanted to seek approval to distribute a different strength of the generic drug, Apotex could have submitted a suitability petition, but she explained that she thought this was unnecessary because Apotex's ANDA satisfied all of the applicable requirements. *Id.* at 11-12, 52-53.

Based on the evidence presented on the hearing, the district court found that Apotex "was aware of and certainly concerned about the potential infringement problem posed by its label," but nevertheless decided to proceed with the label. *Opinion* at 618. The district court noted that Apotex had other options at its disposal that it chose not to pursue. The court pointed out that Apotex could have formally appealed the FDA's decision. *Id.* The court also noted that Apotex could have filed a suitability petition or a paper NDA that sought approval to produce the generic drug at a strength of 0.125 mg per 2 mL. At that strength, AstraZeneca conceded that the downward-titration language would not teach an infringing use. *Id.* at 619 & n.3. The court found that this conduct showed that Apotex had the requisite specific intent to induce infringement and granted AstraZeneca's request for a preliminary injunction. *Id.* at 618-19.

Apotex, joined by two amici, mounts multiple challenges to the district court's finding that Apotex had the necessary specific intent to induce infringement. Apotex first contends that the district court inferred specific intent to induce infringement from Apotex's planned

distribution of the generic drug. Apotex argues that drawing such an inference is improper where the product in question has substantial non-infringing uses. AstraZeneca responds that the district court based its specific intent finding not on an improper inference but rather on the circumstances surrounding Apotex's decision to proceed with its planned distribution of the generic drug and the affirmative evidence of intent provided by the proposed label.

This court agrees with AstraZeneca. Apotex is correct that "where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the [alleged inducer] has actual knowledge that some users of its product may be infringing the patent." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003). However, "liability for active inducement may be found 'where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement.'" *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1341 (Fed. Cir. 2008) (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.* ("*Grokster*"), 545 U.S. 913, 935 (2005)). As the Supreme Court explained in *Grokster* in the context of infringement under the copyright laws, "[e]vidence of active steps . . . taken to encourage direct infringement, such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe." 545 U.S. at 936 (internal quotation marks and citations omitted).

The district court correctly concluded that such evidence exists here. As an initial matter, the district court suggested that there was insufficient evidence to establish that any noninfringing use of the generic drug was substantial, calling into question the applicability of the

"substantial non-infringing use" doctrine in this case. *Opinion* at 605 n.25. Be that as it may, the district court found that Apotex had the requisite specific intent to induce infringement because Apotex included instructions in its proposed label that will cause at least some users to infringe the asserted method claims. *Id.* at 605. The district court also found that, despite being aware of the infringement problem presented by the proposed label, Apotex nonetheless proceeded with its plans to distribute its generic drug product. *Supplemental Opinion* at 618. This conduct, not merely the planned distribution of the generic drug, formed the basis of the district court's specific intent finding. *See id.* at 618-19. To the extent that Apotex contends that such circumstantial evidence cannot support a finding of specific intent, this court has explicitly stated otherwise. *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988) ("While proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice." (citation omitted)).

Apotex next contends that the proposed label is not evidence of specific intent because warnings on drug labels do not influence how a drug is used. Apotex further argues that even if labels did affect how drugs are used, the district court erroneously determined that the downward-titration language would lead the generic drug to be used in an infringing manner. Apotex asserts that the label does not instruct users to titrate down from a specific starting dose; instead, the label contains a general recommendation that is applicable to any dosing regimen.

This court disagrees. In the context of specific intent, it is irrelevant that some users may ignore the warnings in the proposed label. The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of Apotex's affirmative intent to induce infringement. *See*

Vita-Mix Corp. v. Basic Holding, Inc., 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009) ("The question is not . . . whether a user following the instructions may end up using the device in an infringing way. Rather, it is whether [the] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent."). Even if Apotex were correct that the downward-titration language may be applied to other dosing regimens, the language is still applicable to the recommended starting doses and, as correctly determined by the district court, would inevitably lead some consumers to practice the claimed method.

Apotex and the amici also argue that the proposed label alone is not sufficient evidence of specific intent because the FDA required Apotex to include the downward-titration language in the label and stated that the language does not teach the patented method. Apotex asserts that it agrees with the FDA and has never believed that the downward-titration language teaches the claimed once-daily method of administration. In response, AstraZeneca contends that Apotex's compliance with FDA requirements and agreement with the FDA's opinion regarding the downward-titration is immaterial. AstraZeneca argues that if Apotex could not create a noninfringing label, Apotex should have waited for the '603 Patent to expire before attempting to market its generic drug.

This court again agrees with AstraZeneca. As explained above, the district court's specific intent finding was not based solely on the proposed label, but also on Apotex's decision to proceed with its plan to distribute the drug despite being aware that the label presented infringement problems. Apotex and the amici make much of the Hobson's choice they contend that Apotex faced: either comply with FDA requirements and risk a patent

infringement suit or remove the downward-titration language and ensure that the ANDA would not be approved. This court sees no such dilemma. Apotex was free to submit a Paragraph III certification and wait until the patents expired before distributing its generic drug or file a Paragraph IV certification and challenge infringement and validity of the asserted claims. Or, as observed by the district court, Apotex could have formally appealed the FDA's denial of Apotex's proposed labeling amendments or filed either a suitability petition or a paper NDA seeking approval for a 0.125 mg per 2 mL strength of the drug.

Apotex's reliance on the FDA's statements that the downward-titration language does not "teach" once-daily dosing and is not protected by the '603 and '099 patents is misplaced. As acknowledged by both the parties and the district court, the FDA is not the arbiter of patent infringement issues. *See* Applications for FDA Approval To Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, Fed. Reg. 36,676, 36,683 (June 18, 2003) ("[W]e lack expertise in patent matters. An administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside both our expertise and our authority.").

In light of the evidence presented to the district court, this court is not left with a definite and firm conviction that a mistake has been made. Thus, this court affirms the district court's finding that AstraZeneca will likely prove induced infringement at trial.

B. Irreparable Harm

The district court found that AstraZeneca would suffer three types of irreparable harm if the court did not grant the requested preliminary injunction. First, the court determined that a confidential settlement agreement between AstraZeneca and Teva would make calculating the economic harm from a premature launch of Apotex's generic budesonide impossible. Second, the court concluded that AstraZeneca would incur unquantifiable damage to its reputation and goodwill if Apotex were allowed to launch its generic drug and was subsequently forced to remove the drug from the market. Third, the court found that the damage caused by layoffs stemming from entry of the generic drug into the market would also be significant and unquantifiable. Apotex challenges each of these findings, and each finding is considered in turn.

i. The Settlement Agreement

On November 18, 2008, Teva received FDA approval to distribute a generic version of AstraZeneca's budesonide drug and immediately began its distribution. Later that day, AstraZeneca initiated a patent infringement suit in the district court against Teva and successfully moved the court for a temporary restraining order enjoining Teva from selling the generic drug. AstraZeneca and Teva subsequently entered into a settlement agreement that granted Teva an exclusive license to sell its generic drug beginning December 15, 2009, with Teva agreeing to pay AstraZeneca a significant royalty. The agreement also included a "step down" provision that reduced the amount Teva was obligated to pay AstraZeneca if unlicensed drug manufacturers launched generic versions of the drug and certain conditions were met. In addition, Teva agreed to pay AstraZeneca a specified amount for

damages caused by Teva's unauthorized launch of its generic drug.

The district court observed that under the settlement agreement AstraZeneca would continue to have market exclusivity until December 15, 2009, and that after that date AstraZeneca and Teva would share the market. Based on expert testimony, the court concluded that to reliably calculate the economic harm AstraZeneca would suffer after December 15, 2009, the court would need data reflecting a market including only AstraZeneca and Teva. Because Apotex's planned launch would prevent a market with only AstraZeneca and Teva from ever occurring, the district court determined that it would be "complete speculation to put a number on what this market would have been worth to AstraZeneca." *Opinion* at 611. The court dismissed Apotex's argument that "the parties expectations when they entered into the licensing agreement" would be sufficient to calculate damages, explaining that "there is a distinction between what the parties expect and what actually would have occurred" and concluding that it would be impossible to calculate with reasonable certainty the economic damage that AstraZeneca would suffer under the settlement agreement if Apotex began distributing its generic drug. *Id.*

Apotex argues on appeal that testimony during the hearing established that during the settlement negotiations AstraZeneca and Teva had estimated the required market data. Because this information would be subject to discovery, Apotex contends that that district court clearly erred when the court concluded that the damages AstraZeneca would suffer would be incalculable.

In response, AstraZeneca suggests that the data generated during the settlement negotiations was influenced by the relative bargaining power of the parties and is not

an accurate reflection of a market with only AstraZeneca and Teva. AstraZeneca argues that without the benefit of actual data from such a market, any damages calculation would be based on speculation.

This court agrees with AstraZeneca. Both AstraZeneca and Apotex rely on the testimony of Richard Fante, the president of AstraZeneca. Fante admitted that AstraZeneca and Teva did forecast certain market data during the settlement negotiation, but characterized the negotiation as a "gun-to-head moment" and explained that the companies relied mostly on "the experience we'd had as executives" when generating the forecast. Prelim. Inj. Hr'g Tr. 63-64, Apr. 30, 2009. Given the lack of reliable data regarding a market with only AstraZeneca and Teva, this court is not left with a definite and firm conviction that the district court erred by concluding that the damages AstraZeneca would incur under the settlement agreement would be incalculable.

ii. Goodwill

The district court found that if Apotex began distributing its generic drug and was subsequently forced to remove the drug from the market, the resulting confusion among physicians and patients, as well as price changes, would cause unquantifiable harm to AstraZeneca's goodwill. Apotex asserts that this finding is speculative, as certain provisions of the settlement agreement would mitigate, if not eliminate, any adverse effects of Apotex launching and then removing its generic drug from the market. Although this court agrees with Apotex that there has not been a particularly strong showing regarding this finding, after reviewing the record, this court concludes that the district court did not clearly err by determining that AstraZeneca will suffer incalculable harm to its goodwill.

iii. Layoffs

Based on the testimony of Fante, the district court concluded that AstraZeneca would have to lay off some of its employees if Apotex launched its generic drug and the resulting noneconomic loss would be significant and unquantifiable. *Opinion* at 612. The parties' dispute regarding this finding largely concerns whether Fante testified that he would have to lay off employees if Apotex launched its generic drug or merely testified that layoffs *might* occur in that situation. Apotex points out that when asked whether Apotex's entry would force him to lay off employees at AstraZeneca's manufacturing facility, Fante responded, "It could." Prelim. Inj. Hr'g Tr. 100, Apr. 30, 2009. However, as noted by AstraZeneca, Fante later clarified that if Apotex and Teva were both in the market that "in that scenario we would have to have a layoff [in the manufacturing facility]." *Id.* Moreover, when asked what effect Apotex's launch would have on AstraZeneca employees, Fante explained that "[u]ndoubtedly . . . I would have to have a further reduction in the size of the U.S. workforce." *Id.* at 47. Similarly, when asked whether this reduction would occur if Apotex launched its product after December 15, he stated, "Absolutely." *Id.* Given this undisputed testimony, this court discerns no clear error in the district court's finding. This court has reviewed the other arguments raised by Apotex concerning this finding and conclude that they too lack merit.

* * * *

Because Apotex has not demonstrated that that any of the district court's findings regarding irreparable harm are clearly erroneous, this court sees no reason to disturb the district court's determination that AstraZeneca would suffer irreparable harm.

II. The Kit Claims

The asserted kit claims recite two elements: (1) a budesonide composition or suspension in a sealed container containing 0.05 mg to 15 mg budesonide and a solvent, and (2) a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day. *See, e g.*, '603 Patent col.12 ll.3-8; '099 Patent col.11 ll.9-14. The district court concluded that the kit claims are invalid, finding the claimed budesonide composition and suspension were known in the prior art and that the instructions in the claimed label are non-statutory subject matter and therefore not entitled to patentable weight. *Opinion* at 589-92. Regarding the instructions in the label, the district court explained that under Federal Circuit precedent "[w]here . . . printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." *Id.* at 590 (citation omitted). This court noted that here the parties disputed what constitutes the substrate, with Apotex contending that the label is the substrate and AstraZeneca asserting that the substrate is the drug. *Id.* at 592. After considering our precedent, the district court concluded that this dispute was immaterial because regardless of how the substrate was defined, "the instructions simply explain how to use the known product. This type of relationship does not qualify as a functional one . . . ." *Id.* at 591.

AstraZeneca argues that a drug label and its associated drug are "inextricably interrelated," as a drug cannot be approved unless and until the FDA approves its label. AstraZeneca notes that FDA regulations require the label for a drug to include information needed for proper use of the drug and argues that without the label a physician would be unable to safely and effectively treat patients. In light of this, AstraZeneca contends that a drug label is

essential to physicians when prescribing a drug and, therefore, is functionally related to the drug.

Apotex counters that, for the purposes of determining whether the claimed label is entitled to patentable weight, the relationship between the drug and the label is irrelevant. According to Apotex, the proper inquiry is whether there is a functional relationship between the printed matter and its substrate, i.e., the object the printed matter is printed on. Apotex contends that here the printed matter is the instruction for once-daily use and the substrate is the paper label. Citing *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004), Apotex argues that the instructions are not functionally related to the label on which they are printed because they do not function together in any way.

There is no dispute that the budesonide suspension recited in the claims is known in the prior art. The question before us is whether the district court correctly determined that the recitation in the claims of a label instructing not more than once-a-day dosing is of no patentable consequence. This court reviews de novo the district court's determination that the asserted claims recite non-statutory subject matter. *See In re Comiskey*, 554 F.3d 967, 975 (Fed. Cir. 2009) (explaining that "whether the asserted claims . . . are invalid for failure to claim statutory subject matter under 35 U.S.C. § 101[] is a question of law which we review without deference." (quoting *AT&T Corp. v. Excel Commc'ns, Inc.*, 172 F.3d 1352, 1355 (Fed. Cir. 1999))).

The categories of patentable subject matter are set forth in 35 U.S.C. § 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement

> thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

This court has generally found printed matter to fall outside the scope of § 101. *See In re Chatfield*, 545 F.2d 152, 157 (CCPA 1976) ("Some inventions, however meritorious, do not constitute patentable subject matter, e.g., printed matter . . . ." (citation omitted)). However, as observed by the district court, this court has long recognized an exception to this general rule: If there is a "functional relationship" between the printed matter and its substrate, the printed matter may serve to distinguish the invention from the prior art. *See In re Miller*, 418 F.2d 1392, 1396 (CCPA 1969); *In re Gulack*, 703 F.2d 1381, 1385-87 (Fed. Cir. 1983).

This court considered the printed matter exception in *Ngai*, a case similar to the one now before us. In *Ngai*, the Board affirmed the rejection of a claim reciting a kit comprising instructions to amplify ribonucleic acids. The Board found that the only difference between the claimed kit and the prior art was the content of the claimed instructions. Concluding that this content was not functionally related to the kit, the Board found that the claim was anticipated by the prior art. This court affirmed, rejecting the argument that the addition of new printed matter to a known product makes the product patentable. This court reasoned that "the printed matter in no way depends on the kit, and the kit does not depend on the printed matter. All that the printed matter does is teach a new use for an existing product." *Ngai*, 367 F.3d at 1339.

This court agrees with Apotex that as in *Ngai* the claimed instructions here are not entitled to patentable weight. The instructions in no way function with the drug to create a new, unobvious product. Removing the in-

structions from the claimed kit does not change the ability of the drug to treat respiratory diseases. Although AstraZeneca is correct that FDA regulations require a label containing information needed for the safe and effective use of any drug, this is a requirement for FDA approval, not patentability.

This court also agrees with the district court that the dispute over whether the "substrate" is the label or the drug is immaterial, for in both cases the instructions do nothing more than explain how to use the known drug. Our decision in *Ngai* foreclosed the argument that simply adding new instructions to a known product creates the functional relationship necessary to distinguish the product from the prior art. As explained in *Ngai*, if this court concluded otherwise "anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product." 367 F.3d at 1339. Neither the Patent Act nor our precedent countenances such an outcome. The district court's determination that the kit claims are invalid is affirmed.

CONCLUSION

For the foregoing reasons, this court concludes that the district court did not abuse its discretion by granting the preliminary injunction and did not err in determining that the kit claims are invalid.

AFFIRMED

United States Court of Appeals for the Federal Circuit

ASTRAZENECA LP
AND ASTRAZENECA AB,
Plaintiffs-Cross Appellants,

v.

APOTEX, INC.
AND APOTEX CORP.,
Defendants-Appellants.

2009-1381, -1424

Appeal from the United States District Court for the District of New Jersey in case No. 09-CV-1518, Judge Renee Marie Bumb.

BRYSON, *Circuit Judge*, concurring in part and dissenting in part.

I concur in the portion of the court's opinion sustaining the district court's ruling that the "kit" claims of AstraZeneca's '603 and '099 patents are invalid. Because I believe Apotex has raised a substantial question of invalidity as to the other claims of the '603 patent, *see Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1359 (Fed. Cir. 2001), I would reverse the district court's grant of a preliminary injunction.

Apotex has asserted that two prior art references anticipate the claims in dispute, the '528 patent and the *Thorax* advertisement.

1. The district court's ruling that the '528 patent does not anticipate the '603 claims was predicated on an unduly narrow claim construction of the term "budesonide composition" in the '603 claims. The court's construction required the budesonide to be "dispersed in a solvent in the form of a solution or a suspension," and it excluded "the involvement of liposomes as described in the '528 [reference.]" The claims of the '603 patent, however, are broader than that.

Claim 1, the only independent method claim of the '603 patent, recites the administration of a "nebulized dose of a budesonide composition in a continuing regimen at a frequency of not more than once per day." Even assuming that the reference to a "nebulized" dose requires dispersion in a solvent, nothing in the patent mandates a particular manner in which the budesonide and the solvent are to be combined.

More specifically, contrary to the testimony of AstraZeneca's expert Dr. Williams, the '603 patent does not require that the budesonide of the "budesonide composition" be directly suspended or dissolved in a solvent, free from encapsulation or entrapment within liposomes. In fact, the language of the patent undercuts Dr. Williams's rationale for that interpretation. While Dr. Williams assumed that use of the "depot effect," with which liposome involvement may interfere, is a critical aspect of the invention of the '603 patent, the specification explicitly disavows any need for the depot effect to occur. Thus, after describing the depot effect, the specification states: "This proposed mechanism of action is exemplary; the

invention is not limited by any particular mechanism of action." '603 patent, col. 3, ll. 12-13. That language indicates that the patentees did not consider the depot effect to be essential to the effectiveness of once-daily-or-less dosing, as Dr. Williams claimed. Because the patented method of treatment encompasses mechanisms of action other than the depot effect, the term "budesonide composition" need not consist of budesonide directly dispersed in solvent, and it need not exclude the involvement of liposomes as described in the '528 reference. The '528 reference therefore appears to anticipate (or render obvious) the asserted claims under the proper construction of the term "budesonide composition."

2. With respect to the 1994 advertisement for Pulmicort Respules® in the journal *Thorax*, AstraZeneca concedes that the advertisement discloses every limitation of the asserted method claims except for the frequency of drug administration: "not more than once per day." On that issue, the district court stated:

> [a]lthough the Thorax advertisement states that "[t]he maintenance dose should be the lowest dose which keeps the patient symptom-free[,]" Dr. Chipps testified that this statement does not instruct once-daily dosing because the ad was published "back in 1994 . . . before we had any information or historical perspective that once a day therapy worked for anybody." The Court finds this answer persuasive.

AstraZeneca LP v. Apotex, Inc., 623 F. Supp. 2d 579, 596 (D.N.J. 2009). The district court concluded that at the time of its publication the *Thorax* advertisement did not enable once-daily dosing, because a person of skill in the art in 1994 would not have believed that once-daily ad-

ministration of Pulmicort Respules® would be effective. As the majority acknowledges, however, a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

The *Thorax* advertisement contains a list of recommended dosing regimens as low as "0.25-0.5 mg twice daily"; it also suggests that "the maintenance dosage should be the lowest dosage which keeps the patient symptom-free." The Apotex label similarly recommends dosages of 0.25 mg to 0.5 mg administered twice daily and states that "[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose." The district court concluded that Apotex's label induced infringement by suggesting the administration of the drug once a day. There is no reason to treat the similar recitation in the *Thorax* advertisement differently. The district court's rationale for distinguishing between the Apotex label and the *Thorax* advertisement—that in 1994 the scientific community had yet to confirm that once-daily dosing was effective in large patient populations—does not undermine the effect of the advertisement in suggesting a reduction in dosage for particular patients, which would necessarily be achieved either by reducing the amount administered on each occasion or the frequency of administration.

Because Apotex has presented a substantial question concerning the validity of the '603 patent's method claims, I would vacate the preliminary injunction.