UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ASTRAZENECA LP and ASTRAZENECA AB, Plaintiffs, v. APOTEX, INC. and APOTEX CORP., Defendants.	Civil Action No. 09-1518 (RMB) **OPINION**

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BUMB, United States District Judge:[1]

I. Introduction

Plaintiffs AstraZeneca LP and AstraZeneca AB ("AstraZeneca" or "Plaintiffs") are pharmaceutical companies who develop new and innovative drugs and treatment methods. Defendants Apotex, Inc. and Apotex Corp. ("Apotex" or "Defendants") are pharmaceutical companies who manufacture generic versions of brand name drugs. At issue in this case is AstraZeneca's PULMICORT RESPULES, a once-daily inhaled corticosteroid used in the treatment of pediatric asthma. AstraZeneca holds two patents relating to PULMICORT RESPULES and seeks to enjoin Apotex from manufacturing and selling a generic version of this drug.

A. Asthma

Millions of Americans suffer from chronic respiratory diseases, such as asthma. Asthma alone affects approximately 22 million Americans. Asthma is particularly problematic for children. The Center for Disease Control estimates that 8.9% of all American children suffer from asthma.

Asthma is a chronic inflammatory disease of the airways. The symptoms of asthma include wheezing, breathlessness, coughing and chest tightness. These symptoms vary in severity from patient to patient and for individual patients. For example, the

[1] This Opinion has been redacted to omit references to confidential material.

"fall asthma epidemic," when some patients experience increased burden of symptoms and exacerbations in the fall season, is well known. Even patients with mild asthma may experience significant, and sometimes life-threatening, exacerbations.

B. Asthma Medications and Delivery Systems[2]

Asthma medications are designed in different formulations for use with different methods of administration and delivery systems. Examples of different formulations used in long-term asthma control include solutions, suspensions, dry powders, tablets or capsules. The formulation of the medication and delivery system used are often dictated by the characteristics of the particular active ingredient.

Depending on how the medication is formulated, asthma medications may be administered in different ways, including by inhalation, orally (ingested), rectally and parenterally (injected). The most common delivery system for inhaled products is a pressurized metered dose inhaler ("pMDI"), which includes formulations such as suspensions or solutions. pMDIs are referred to colloquially as "puffers." Another type of device for inhaled products is a dry-powder inhaler ("DPI"). DPIs typically are used by twisting the cap of the device to make available one dose of the dry powder medication. A nebulizer

[2] For a discussion of this topic see generally, the Declaration of Bradley Chipps, M.D., dated April 30, 2009 ("Chipps Decl."), at ¶¶ 18-56.

device vaporizes liquid medication into a mist that is inhaled through a face-mask or mouthpiece. The medication may be in the form of a suspension or a solution. A nebulizer permits the patient to receive the proper dose simply by breathing in a normal fashion. The face-mask is secured over the nose and mouth.

Prior to the availability of PULMICORT RESPULES®, discussed below, long-term asthma controller medications had significant disadvantages. Many of these medications required frequent dosing, at least twice per day, and sometimes more frequently. This frequent dosing led to problems with patients being able to adhere to the prescribed drug regimen, resulting in ineffective asthma control. Also, frequent dosing often increased the cost to patients. In addition, many of these medications failed to provide adequate asthma control, even when used properly.

C. AstraZeneca Patents

This case involves AstraZeneca's revolutionary invention of a once-daily inhaled corticosteroid under the trade name PULMICORT RESPULES®. AstraZeneca began selling PULMICORT RESPULES® in September 2000. PULMICORT RESPULES® became the first and only[3] once-daily inhaled corticosteroid approved by the FDA for children under the age of four on the market. As

[3] Other than any amount of a generic company's "at risk" launch product remaining in the sales channels described below.

discussed below, because children are an especially challenging patient population to diagnose and treat, PULMICORT RESPULES® was a long-desired treatment of pediatric asthma, and it has played a unique role in such treatment. PULMICORT RESPULES® is given to children twelve months to eight years of age. PULMICORT RESPULES® is used with a compressed air-driven jet nebulizer, a more appropriate method of administration for young patients.

AstraZeneca holds two patents related to PULMICORT RESPULES®: U.S. Patent No. 6,598,603 (the "'603 Patent") and U.S. Patent No. 6,899,099 (the "'099 Patent"). Both the '603 Patent and '099 Patent include two types of claims, "kits" and "methods" for administering the PULMICORT RESPULES® active ingredient, budesonide, a corticosteroid. Both types of claims are directed to administration of a budesonide composition or suspension using a nebulizer device in a continuing regimen at a frequency of not more than once per day. PULMICORT RESPULES® is often referred to as "budesonide inhalation suspension" or "BIS."

The label (approved by the Federal Drug Administration ("FDA")) for PULMICORT RESPULES® includes in the DOSAGE AND ADMINISTRATION section a table that shows recommended starting doses and highest doses of budesonide based on prior asthma therapy. The highest recommended doses of BIS are 0.5 mg total daily dose, 1.0 mg total daily dose, and 10 mg total daily dose for bronchodilator, inhaled corticosteroid, or oral

corticosteroid therapy, respectively. The BIS is supplied in single dose ampules of two strengths of BIS, .25 mg, .5 mg or 1.0 mg per 2ml. The label stipulates that the recommended starting dose may be administered as either the total daily dose once-daily or in divided doses twice daily.

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

The patient instruction sheet accompanying the PULMICORT RESPULES® instructs the patient to empty the contents of the ampule into the nebulizer cup. (See, e.g., Declaration of Thomas O. Garvey, III, M.D., at Ex. 4.)

D. Apotex's ANDA Application and FDA Approval

The generic drug approval process is governed by the Hatch-Waxman Act. Specifically, 21 U.S.C. § 355(j) established a procedure for the submission and review of Abbreviated New Drug Applications ("ANDA"). Pursuant to this procedure, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; rather, an ANDA relies on the FDA's prior determination that the reference

listed drug (RLD) is safe and effective. See generally FDA Response to Citizen Petition, dated November 18, 2008 ("FDA Response") (Reply Declaration of Bradley Chipps, at Ex. 19). The ANDA applicant must show, inter alia, that its generic drug is bioequivalent to the RLD and contains the same active ingredient, conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences). Id. at 4-5. It must also show that its generic drug product meets approval requirements concerning the chemistry, manufacturing, and controls for the drug product. Id. at 5.

Additionally, an ANDA applicant must file with the FDA a list of patents that claim the approved drug product or method of using the drug product and submit one of four specified certifications with respect to each patent. Id. at 7-8. However, if a patent is listed only for a method of use and an ANDA applicant seeks to omit the method of use covered by the listed patent, the ANDA applicant must submit a "section viii statement" (in lieu of the specified certifications) in which the applicant acknowledges that the relevant method of use patent has been listed but that the patent at issue does not claim a use for which the applicant seeks approval.[4] Id. at 9.

[4] Section 505(j)(2)(A)(viii) provides, "if with respect to the listed drug referred to in [section 505(j)(2)(A)(I)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a

In this case, Apotex filed ANDA No. 078-202 seeking FDA approval to manufacture and sell a generic version of PULMICORT RESPULES. (Apotex Opp. Brief, at 5). On March 30, 2009, Apotex's ANDA was approved by the FDA. (Id.).

II. Procedural History

Immediately following Apotex's ANDA approval, AstraZeneca filed a Complaint against Apotex asking this Court to render a declaratory judgment that Apotex's sale of its generic BIS would "infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '603 and '099 Patents." (Compl. ¶ 20). On April 6, 2009, AstraZeneca filed a motion for a temporary restraining order ("TRO") to enjoin Apotex from marketing its generic version of PULMICORT RESPULES®. In its motion, AstraZeneca contended that it established all elements necessary for the issuance of a TRO: "(1) the likelihood of the patentee's success on the merits; (2) irreparable harm if the injunction is not granted; (3) the balance of hardships between the parties; and (4) the public interest." Abott Labs. V. Andrx Pharms., Inc., 473 F.3d 1196, 1200-01 (Fed. Cir. 2007). For purposes of the TRO motion, AstraZeneca limited its discussion of its likelihood of success on the merits to Apotex's alleged

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statement that the method of use patent does not claim such a use."

direct infringement of the kit claims, choosing not to address the alleged indirect infringement of the method claims. (See Pl. Motion at 6, n. 5).

On April 16, 2009, the Court heard the argument of counsel on the issues presented in AstraZeneca's application for a TRO.[5] At the conclusion of the hearing, the Court issued a temporary restraining order preventing Apotex from immediately entering the market and requiring AstraZeneca to post a bond in the amount of $2,500,000. [Dkt. No. 45]. The Court scheduled a preliminary injunction hearing to commence April 27, 2009.

The Court also ordered the parties to submit supplemental memoranda addressing Apotex's argument that the kit claims are invalid under the holding of In re Ngai, 367 F. 3d 1336 (Fed. Cir. 2004). The Court did so because, as Apotex aptly argues, if the Ngai decision renders AstraZeneca's kit claims invalid, then AstraZeneca cannot make a showing of likelihood of success on such claims.

On April 27, 2009, the Court commenced the preliminary injunction hearing. At the beginning of the hearing, the Court questioned whether or not AstraZeneca had abandoned its claim of

[5] On April 6, 2009, the Court held a telephone conference to discuss AstraZeneca's filing. The Court did not render a ruling because the parties agreed that Apotex would not launch its generic product, AstraZeneca would post a bond in the amount of $1,000,000, and the Court would hold a hearing on the emergent application on April 16, 2009. The Court permitted Apotex to file its brief in opposition to the motion.

indirect infringement relating to the method claims. The Court recognized that if AstraZeneca intended to press its indirect infringement claims in the context of injunctive relief, then it would behoove the parties and the Court to hear all issues relating to infringement at the same time. Apotex objected to the Court affording AstraZeneca any opportunity to modify its basis for emergent relief, arguing that AstraZeneca should not have "two bites at the apple." Over Apotex's objection, the Court permitted AstraZeneca to amend its request for injunctive relief to include its claims based on indirect infringement. The Court did so because it wanted to address all the claims in one proceeding and it was not aware of any prohibition against allowing AstraZeneca to proceed with a previously preserved, but not briefed, argument. Moreover, the ten-day time period for the issuance of the temporary restraining order had not elapsed, and the Court found that there existed good cause for extending the TRO in light of the fact that the preliminary hearing was in progress. See Fed. R. Civ. P. 65(b)(2). Accordingly, both claims asserted by AstraZeneca – direct infringement of the kit claims and indirect infringement of the method of use claims - are discussed below.

III. Standard for Issuance of Preliminary Injunction

In determining whether to issue a preliminary injunction,

the Court should consider the following four factors: "(1) the likelihood of the patentee's success on the merits; (2) irreparable harm if the injunction is not granted; (3) the balance of hardships between the parties; and (4) the public interest." Abott Labs. v. Andrx Pharms., Inc., 473 F.3d 1196, 1200-01 (Fed. Cir. 2007) (citations omitted). "These factors, taken individually, are not dispositive; rather, the district court must weigh and measure each factor against the other factors and against the form and magnitude of the relief requested." Hybritech, Inc. v. Abbot Labs., 849 F.2d 1446, 1451 (Fed. Cir. 1988). However, as explained by the Federal Circuit, "case law and logic both require that a movant cannot be granted a preliminary injunction unless it establishes both of the first two factors, i.e., likelihood of success on the merits and irreparable harm." Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1350 (Fed. Cir. 2001) (emphasis included); Reebok Inter. Ltd. v. J. Baker, Inc., 32 F.3d 1552, 1556 (Fed Cir. 1994) (citing Hybritech, 849 F.2d at 1451, 1456). The Court will discuss each of the four factors in turn.

IV. Analysis

A. Likelihood of Success on the Merits

To obtain a preliminary injunction, "a patent holder must establish a likelihood of success on the merits both with respect

to validity of its patent and with respect to infringement of its patent." Hybritech, 849 F.2d at 1451. Thus, AstraZeneca must show that, "in light of the presumptions and burdens that will inhere at trial on the merits, (1) [AstraZeneca] will likely prove that [Apotex] infringes its ['603 Patent and/or '099] patent, and (2) [AstraZeneca's] infringement claim will likely withstand [Apotex's] challenges to the validity and enforceability of the [] patent[s]." Amazon, 239 F.3d at 1350 (citing Genentech, Inc., v. Novo Nordisk, A/S, 108 F.3d 1361, 1364 (Fed Cir. 1997)); Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1374 (Fed. Cir. 2006).

If Apotex "raises a substantial question concerning either infringement or validity, i.e., asserts an infringement or invalidity defense that the patentee cannot prove lacks substantial merit, the preliminary injunction should not issue." Amazon, 239 F.3d at 1350-31 (internal quotation omitted); see also Oakley, Inc. v. Sunglass Hut Intern., 316 F.3d 1331, 1340 (Fed. Cir. 2003) ("the injunction should not issue if the party opposing the injunction raises 'a substantial question concerning infringement or validity, meaning that it asserts a defense that [the party seeking the injunction] cannot prove lacks substantial merit'") (quoting Tate Access Floors, Inc. v. Interface Architectural Resources, Inc., 279 F.3d 1357, 1365 (Fed Cir. 2002)).

In the Complaint, AstraZeneca raises two different infringement claims.[6] First, AstraZeneca alleges that Apotex will directly infringe AstraZeneca's kit claims (claims 29 and 30 of the '603 Patent and claims 17, 18, 20, 21, 24-27 of the '099 Patent)[7] by marketing and selling (or intending to market and sell) a generic BIS with a label that instructs consumers to use the drug once-daily. Second, AstraZeneca alleges that Apotex will indirectly infringe AstraZeneca's method claims (Claims 1-3, 6-8, 11-18, 21-28 of the '603 Patent)[8] by inducing consumers to infringe AstraZeneca's patented method because Apotex's label instructs physicians to prescribe the generic BIS for once-daily use. Before embarking on the infringement analysis, however, the Court must first consider the validity of the underlying patented claims, as challenged by Apotex.

1. Validity

Under 35 U.S.C. § 282, "'a patent is presumed valid, and

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[6] As noted above, although AstraZeneca originally relied solely on its direct infringement claim in seeking a preliminary injunction, it has amended its pleadings to add its indirect infringement claim as a basis for its request for interim relief.

[7] Claim 29 of the '603 patent and claim 17 of the '099 patent are independent claims, meaning that they stand on their own without referring to any other claim. Claim 30 of the '603 patent and claims 18, 20, 21, 24-27 of the '099 patent are dependent claims that refer to other independent claims. (Chipps Decl. ¶ 91).

[8] Regarding the method claims in the '603 patent, claim 1 is an independent claim, and claims 2-3, 6-8, 11-18, and 21-28 are dependent claims. (Chipps Decl. ¶¶ 251, 262-67).

this presumption exists at every stage of the litigation.'" Sanofi-Synthelabo v. Apotex, 470 F.3d 1368, 1375 (Fed. Cir. 2006) (quoting Canon Computer Sys., Inc. v. Nu-Kote Int'l, Inc., 134 F.3d 1085, 1088 (Fed. Cir. 1998)). However, this presumption is not a substantive rule but a procedural device that serves to assign the burden of proof during litigation. D.L. Auld Co. v. Chroma Graphics Corp., 714 F.2d 1144, 1147 n. 2 (Fed. Cir. 1983). As § 282 makes clear, "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." Notwithstanding, "in resisting a preliminary injunction, [] one need not make out a case of actual invalidity. Vulnerability is the issue at the preliminary injunction stage, while validity is the issue at trial." Amazon, 239 F. 3d at 1359. In other words, "a showing of a substantial question of invalidity requires less proof than the clear and convincing evidence standard to show actual invalidity." Erico Int'l Corp. v. Vutec Corp., 516 F.3d 1350, 1356 (Fed. Cir. 2008) (citing Amazon, 239 F. 3d at 1358).

Apotex challenges the validity of both the kit claims and the method claims. The Court will address each argument separately.

a. Kit Claims

The Court first turns to the validity of AstraZeneca's kit claims (claims 29 and 30 of the '603 Patent and claims 17, 18,

20, 21, 24-27 of the '099 Patent). Apotex argues that AstraZeneca's kit claims are invalid because, under the holding of In re Ngai, 367 F.3d 1336 (Fed. Cir. 2004), AstraZeneca cannot create a new patentable product by simply adding a new method of use (i.e., once-daily administration) to a known product (i.e., a suspension containing 0.05 mg to 15 mg of budesonide). To the extent AstraZeneca is entitled to any patent for its invention, Apotex contends, such patent is limited to a method of use, which is enforceable only through method of use claims, not kit claims.[9]

In response, AstraZeneca contends that because a label (and, more particularly, a dosing instruction) is an essential and functional component of a drug product, the addition of such label (and dosing instruction) functionally changes the known product into a new product - a BIS product that can be safely and effectively administered once-daily. In other words, AstraZeneca argues, the once-daily labeling creates a new and unobvious product for which AstraZeneca is entitled to patent protection.

Patentability is governed by Section 101 of the Patent Act, which establishes categories of patentable subject matter:

> 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 therefore, subject to the conditions and requirements of this title.

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[9] The Court notes that Apotex does not concede the validity of AstraZeneca's method claims and will discuss this argument below.

35 U.S.C. § 101.

Machines, manufactures, and compositions of matter are generally grouped into product claims. Thus, products and processes are considered the two general categories of patents. See Caterpillar Inc. V. Detroit Diesel Corp., 961 F. Supp. 1249, 1252 (N.D. Ind. 1996), aff'd, 194 F. 3d 1336 (Fed. Cir. 1999). Traditionally, "printed matter" by itself did not fall within any of the statutory classes of patentable subject matter. However,

> [a]s an exception to the traditional rule, printed matter constituted an element of a patentable claim if the claim concerned a new and useful feature of physical structure or a new and useful relation between the printed matter and the physical structure.

1 Donald S. Chisum, Chisum on Patents § 1.02[4] (Supp. 2006) at 1-25. The doctrine of printed matter rule developed when printing was the primary means for recording and communicating information. Id. As technology advanced, new means of communication developed, such as electronic storage and communication, and the line between the rule and the exception became more difficult to draw. Id. A discussion of some relevant cases is helpful here.

In re Miller, 418 F. 2d 1392 (CCPA 1969), involved a measuring device that contained legends for fractioning recipes. If a person wanted to make only one-half of a recipe, he could simply select the "one-half recipe" measuring receptacle, follow

the recipe numbers literally and end up with one half the recipe. Thus, s/he could avoid the trouble of trying to calculate and measure one-half of each ingredient. The Court of Customs and Patent Appeals (CCPA) determined that this printed material was patentable because it functioned together with the known product to create a new product. Had the printed matter been removed, the product itself would be fundamentally different, just a measuring cup.

In 1983, the Court of Appeals for the Federal Circuit decided the case, In re Gulack, 703 F. 2d 1381 (Fed. Cir. 1983), which clarified the standard laid out in Miller: "[w]here the 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 1385. The claimed invention in Gulack comprised three basic elements: (1) a band, ring, or set of concentric rings; (2) a plurality of individual digits imprinted on the band or ring at regularly space intervals; and (3) an algorithm by which the digits were developed. Id. at 1382. The band could be placed on hats, jewelry or other articles of apparel. The court determined that, based on the physical and functional interrelations between the printed matter (the numbers) and the substrate (the band), there was a "functional relationship" between the two. As the court explained,

> [t]he appealed claims...require a particular sequence of digits to be displayed on the outside surface of the band. These digits are related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits - each digit residing in a unique position with respect to every other digit in an endless loop. Thus, the digits exploit the endless nature of the band.

Id. at 1386-87. The court held that this functional relationship between the information and the substrate was different than a prior patent, which consisted of printed information (various types of data to be committed to memory such as multiplication tables, historical dates and the like) on a hat band.[10] As to the new invention, the court found that the numbers did bear a new and unobvious functional relation to the band. The court found that if the printed matter (the digits on the band) were removed, the product itself would be fundamentally different - it would no longer be a mathematical device.

Over twenty years later, the Federal Circuit distinguished Gulack in its decision, In re Ngai, 367 F.3d 1336 (Fed. Cir. 2004). In Ngai, the patent application disclosed a new method for normalizing and amplifying RNA. The application was granted a method claim because it had presented a new and non-obvious method. However, the application also sought a kit claim comprising a known reagent and instructions detailing the new

[10] In the prior art invention, the information was positioned on the hat band so that the answer to an inquiry displayed on the outer surface of the band was visible from inside the hat through an aperture. Gulack, 703 F.2d at 1384, n. 5.

method. The Patent and Trademark Office rejected the applicant's kit claim in view of prior art showing a kit with different instructions and the same known reagent. In rejecting the kit claim, the PTO relied on the statement in Gulack that the "critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate." Id. at 1338 (quoting Gulack, 703 F.2d at 1386). The Federal Circuit agreed with the PTO that, unlike Gulack, "[h]ere, 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." Id. at 1339. Ultimately, the court held that,

> Ngai is entitled to patent his invention of a new RNA extraction method, and the claims covering that invention were properly allowed. He is not, however, entitled to patent a known product by simply attaching a set of instructions to that product.

Id.

The foregoing cases demonstrate one critical fact: the printed matter was what, in essence, created the new and unobvious product. In Miller, the legends turned a measuring cup into a "recipe cup." In Gulack, the numbers turned the band into a "mathematical device." In both cases, the printed matter did much more than simply offer instructions on use; the printed matter was "functionally related" to the substrate.

The question here, then, is whether the addition of a label

indicating once-daily dosing to the BIS creates a new product or recites how the product is to be used. In other words, is there a functional relationship between the printed matter (the once-daily instruction) and the substrate?[11] "Where the 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." Gulack, 703 F.2d at 1385.

AstraZeneca argues that because an FDA-approved drug product cannot exist without a label providing instructions for use, and a label cannot exist without a drug product, the two depend on each other and are, therefore, "functionally related," just like in Gulack. They assert that the end result is a new and useful patentable kit that did not exist in the prior art – "a nebulized budesonide product that can be safely and effectively administered once-daily." (Pl. Supp. Brief at 5).

Apotex argues that "the addition of the label does nothing to change the product other than to add a description of its use." (Apotex Supp. Reply Brief at 3) (emphasis included). It contends that there is no functional relationship between the instructions and the drug because "[b]oth with and without the instructions, the composition is the same, it works the same, and it can be used in the same ways." (Id. at 2-3). As they explain

[11] The parties disagree as to what the "substrate" is – the paper label or the drug product. This seems to be a distinction without much difference, as explained below.

it, "the drug can be made and used regardless of whether there is a label accompanying it." (Id. at 3).

The Court is persuaded that the addition of the instructions does not functionally alter the known product so as to create a new patentable product. Rather, the instructions simply explain how to use the known product. This type of relationship does not qualify as a functional one and, therefore, it does not create a new patentable product. See In re Schreiber, 128 F. 3d 1473, 1477 (Fed. Cir. 1997) ("[i]t is well settled that the recitation of a new intended use for an old product does not make a claim to that old product patentable"); see also, In re Spada, 911 F. 2d 705, 708 (Fed. Cir. 1990) ("[t]he discovery of new property or use of a previously known composition, even when that property and use are unobvious from prior art, cannot impart patentability to claims to the known composition"); see also, In re Haller, 161 F.2d 280 (CCPA 1947) ("[i]f there is no novelty in an article or composition, then a patent cannot be properly granted on the article or composition, regardless of the use for which it is intended").

Gulack's requirement that the printed matter be functionally related to its substrate ensures that patentable weight is only given to printed matter that actually contributes to the creation of the product itself, not to printed matter that simply provides a description of how to use a product. Ngai made this

distinction clear and confirmed that, when considering a product claim, adding a set of instructions for using that product does not add any patentable weight to the claim. As the court held:

> This case ... is dissimilar from Gulack. There the printed matter and the circularity of the band were interrelated, so as to produce a new product useful for 'educational and recreational mathematical' purposes. Here, addition of a new set of instructions into a known kit does not interrelate with the kit in the same way as the numbers interrelated with the band. In Gulack, the printed matter would not achieve its educational purposes without the band, and the band without the printed matter would similarly be unable to produce the desired result... As the Gulack court pointed out, '[w]here the 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.'... If we were to adopt [the applicant's] position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product. This was not envisioned by Gulack.

367 F. 3d at 1338-39.

The cases dictate that the focus must be on the relationship between the printed matter and the substrate. If there is a new functional relationship between the two, the resulting product is entitled to patentable weight. As mentioned, the parties disagree as to what the "substrate" actually is in this case. Apotex contends that the substrate is the paper on which the label is printed and AstraZeneca contends that the substrate is the BIS product itself. Whether the substrate is the paper or the drug, under either definition, the relevant relationship is still not a functional one. That is, there is no functional

relationship (significant to the overall product) between the once-daily dosing instruction (the printed matter) and the paper label, nor is there a functional relationship between the once-daily dosing instruction and the drug product – with or without the instructions or the paper they are printed on, the drug product remains the same.

AstraZeneca urges this Court to forge new ground and hold that because the FDA requires that a drug product contain a label, the question of patentability must be examined within the confines of those legally imposed restrictions. It is a tempting argument. However, there is no place in patent law to consider the impact that regulations might have on the marketability of a product. Indeed, such a holding could easily produce a slippery slope. Presumably, AstraZeneca's strategy in obtaining patents for the kit claims was to arm itself with easier to prove claims of direct infringement rather than having to prove indirect infringement of the method of use claims. This, however, is not a valid reason to permit the kit claims to go forward. As one court explained, although

> it is desirable that patent protection should extend to the article here involved and not merely to the process of using it, since the process claim might be directly infringed by the ultimate users and not by those who make and sell the composition for use as an insecticide. However, the allowance of claims must be based on statutory provisions and not upon the type of protection considered desirable.

In re Haller, 161 F.2d at 282.

Based on the above reasoning, the Court finds that the kit claims (Claims 29 and 30 of the '603 Patent and Claims 17, 18, 20, 21 and 24-27 of the '099 Patent) are invalid. Therefore, Apotex has met its burden.

b. Method Claims

The Court next turns to the validity of AstraZeneca's method claims (Claims 1-3, 6-8, 11-18, 21-28 of the '603 Patent). Apotex argues that AstraZeneca's method claims are invalid because they were 1) anticipated by the prior art and 2) obvious in light of the prior art. The Court will discuss each challenge in turn.

(1) Anticipation

To qualify for patent protection, an innovation must fulfill the novelty requirement as set forth in 35 U.S.C. § 102. Consistent with this novelty requirement, "patent law has long required that an innovation not be anticipated by the prior art in the field." Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 149-50 (1989). "A patent is invalid for anticipation when the same device or method, having all of the elements contained in the claim limitations, is described in a single prior art reference." Crown Operations Int'l, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375 (Fed. Cir. 2002); see also Hazani v. United States ITC, 126 F. 3d 1473, 1379 (Fed. Cir.

2003) (prior art renders a patented invention "anticipated-and-thus invalid-if it discloses every feature of the claimed invention, either explicitly or inherently") (internal quotation omitted); Lindemann Maschinenfabrik v. American Hoist and Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984) ("anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim"); Studiengesellschaft Kohle v. Dart Industries, 726 F.2d 724, 726 (Fed. Cir. 1984) ("[i]t is hornbook law that anticipation must be found in a single reference, device, or process").

In this case, Claim 1 of the '603 Patent, the only independent method claim at issue, recites:

> A method of treating a patient suffering from a respiratory disease, the method comprising administering to a 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. 10:18-22). Thus, Claim 1 contains the following four elements or limitations:

- method of treating a patient with respiratory disease
- nebulized administration
- budesonide composition
- not more than once per day

The remaining method claims are all dependant on claim 1, meaning that they include all of the limitations of Claim 1 as well as

additional limitations.[12]

Apotex points to three specific prior art references which it argues anticipate AstraZeneca's method claims.

(i) U.S. Patent No. 5,192,528

U.S. Patent No. 5,192,528 (Radhakrishnan) (the "'528 Patent") relates to a "Corticosteroid Inhalation Treatment Method" and was issued on March 9, 1993, more than one year before the '603 Patent. The ABSTRACT of the '528 Patent describes the invention as a "method for delivering a therapeutic dosage of corticosteroid drug to the lungs, for treating a lung condition or disease." ('528 Patent). Specifically, the method involves aerosolizing "[a]n aqueous suspension of sized liposomes containing the drug in liposome-entrapped form..." (Id.). In simpler terms, the '528 Patent describes a method for the

[12] Claim 2 depends from Claim 1 and further recites: "wherein the frequency is once and only once per day." (Chipps Decl. ¶ 262). Claim 6 depends from Claim 1 and further recites: "wherein the respiratory disease is selected from the group consisting and inflammatory airway disease... ." (Id. ¶ 263). Claim 7 depends from Claim 6 and recites: "wherein the respiratory disease is asthma." (Id.). Claims 12, 14 and 16 depend from Claim 1 and recite: "wherein the patient is" "one day to fifteen years old", "one month to eight years old" and "six months to five years old," respectively. (Id. ¶ 264). Claims 18, 22 and 24 depend from Claim 1 and recite various ranges of budesonide, i.e., "0.05 mg to 15 mg," "0.1 mg to 2.0 mg" and "0.25 mg to 1.0 mg," respectively. (Id. ¶ 265). Claim 26 depends from Claim 1 and further recites: "wherein the budesonide composition is a suspension." (Id. ¶ 266). Claims 3, 8, 11, 13, 15, 17, 21, 23, 25, 27 and 28 depend directly or indirectly from Claim 1 and/or other of the asserted method claims and each further recites: "wherein budesonide is the only active ingredient in the budesonide composition." (Id. ¶ 267).

delivery of corticosteroids using liposomes.

As explained by AstraZeneca's expert, Robert O. Williams III, PhD., liposomes are spherical vesicles composed of a bilayer membrane. (Tr. May 4, 2009 (Williams) at 21). The membrane consists of molecules, such as phospholipids and sterols, that generally have both hydrophilic (water-loving) and hydrophobic (water-hating) portions. (Id. at 22). These molecules align themselves to form the membranes in which the hydrophilic portions face outward and the hydrophobic portions face inward in an aqueous environment. (Id. at 22-23). Liposomes have been used for the delivery of drugs, particularly lipophilic, or water-insoluble, drugs. Lipophilic drugs are generally incorporated within the liposomal membranes so that they may be more readily delivered in a medium to the target site of action.

Apotex contends that the '528 patent discloses each and every feature of claim 1 of AstraZeneca's '603 patent as follows:

- a "means for treating a variety of lung diseases and conditions, such as bronchial asthma" ('528 Patent, Col. 1, ln. 38-40)
- a composition containing a corticosteroid which may include budesonide (Id. at Col. 7, ln. 59-61; Col. 4, ln. 13)
- "the aerosol particles are formed by a pneumatic nebulizer" (Id. at Col. 3, ln. 42-43; Col. 6, ln 61-Col. 7, ln. 5)
- "the effective daily dose can be administered readily as a single dose" (Id. at Col. 8, ln. 7-11; Col. 9, ln. 7-8)

(See Def. Supp. Br. [Dkt. No. 80] at 4). AstraZeneca argues that the '528 patent does not anticipate the AstraZeneca '603 patent because it does not disclose "administration by nebulization of a budesonide composition or suspension as those terms are used and defined in the AZ patents." (Pl. Post-Hearing Br. at 7). Specifically, AstraZeneca contends, the '528 Patent neither discloses nor suggests a budesonide composition in which the budesonide is dispersed in a solvent.

Thus, the issue here is one of claim construction - the parties dispute the meaning of AstraZeneca's claim term "budesonide composition" and whether that claim term includes the composition containing budesonide described in the '528 Patent. To resolve this dispute, the Court must determine how a person of ordinary skill in the art would understand the claim term. Pfizer, 429 F.3d at 1372-73 ("'[t]he inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to being claim interpretation") (quoting Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1454-56 (Fed. Cir. 1998)).

During the hearing, Dr. Williams testified that a person of ordinary skill in the art would understand "budesonide composition" to mean "budesonide dispersed [directly] in a solvent in the form of a solution or suspension." (Tr. May 4, 2009, at 13). Thus, unlike the composition in the '528 patent

which involves liposomes, the term “budesonide composition”, as defined by Dr. Williams in the context of the ‘603 patent, does not involve liposomes. The distinction between the budesonide composition of AstraZeneca’s ‘603 patent and the liposome suspension of the ‘528 Patent is critical. As Dr. Williams explained, in the method taught by the ‘603 Patent, “the budesonide is provided in immediate contact with the solvent, such that when the budesonide molecules begin to dissolve from these particles, they are available to be absorbed by the airway cells and be conjugated and act as a depot effect.” (Id. at 26-27). This “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. Thus, the ‘528 Patent actually teaches away from the ‘603 Patent.

Notwithstanding the opposing methods taught by the ‘603 and ‘528 patents, Apotex still argues that the budesonide composition of the ‘603 patent embodies the composition containing budesonide of the ‘528 patent. In support of their position, they point to Column 3 of the ‘603 patent, which states that “[s]olutions or suspensions can be encapsulated in liposomes or biodegradable microspheres.” (‘603 Patent, Col. 3, ln. 38-39). However, as Dr. Williams explained, one mention of the liposome delivery method does not overcome the larger lesson the patent is trying to teach – i.e., the use of a budesonide composition where the

budesonide is dispersed directly in a solvent. (Tr. May 4, 2009 (Williams) at 47) ("I think that even though it's mentioned in column three as solutions or suspensions can be encapsulated in liposomes' biodegradable microspheres, it's one sentence out of the whole patent and I don't' think that this patent in the context of what's being taught really addresses the complexity of administering budesonide either in a liposome or frankly in a biodegradable microsphere. So even though it mentions it, I don't really think it teaches it.").

Finally, the language of the patent itself makes clear that the term "budesonide composition" means "budesonide dispersed in a solvent in the form of a solution or a suspension." Throughout the patent specification, the compositions used in the inventive method are consistently described as being either a suspension or solution of budesonide in a solvent. The SUMMARY OF THE INVENTION describes the budesonide composition as "including 0.05 mg to 15 mg budesonide and a solvent." ('603 Patent, Col. 2, ln. 3-4). The DETAILED DESCRIPTION section also describes the budesonide composition as "budesonide suspended in a solvent" and explains that the budesonide "can be delivered dispersed in a solvent, e.g., in the form of a solution or a suspension." (Id. at Col. 2, ln. 51; Col. 3, ln. 22-23). The patent goes on to define the "solvent" into which the budesonide is dispersed as "an appropriate physiological solution", containing the inactive

ingredients, for example, "physiological saline or a buffered solution containing [defined inactive ingredients]." (Id. at Col. 3, ln. 22-25). Moreover, all of the clinical studies described in the EXAMPLES section involved a budesonide composition consisting of budesonide suspended in a solvent. (Id. at Col. 4, ln. 30-col. 10, ln. 7). The EXAMPLES section also describes the solvent as the water and other inactive ingredients in which the budesonide is suspended. (Id. at Col. 5, ln. 3-7; see also Tr., May 4, 2009, at 29 (Williams)).

In sum, the Court agrees with Dr. Williams that the term budesonide composition does not contemplate the involvement of liposomes as described in the '528 Patent; rather, it means "budesonide dispersed in a solvent in the form of a solution or a suspension." Accordingly, the '528 Patent does not anticipate the '603 Patent as it does not disclose each and every element of the claim.[13]

(ii) U. S. Patent No. 5,049,389

Apotex also relies upon United States Patent No. 5,049,389 ("the '389 Patent"), entitled "Novel Liposome Composition for The Treatment Of Interstitial Lung Diseases," to support its invalidity argument. The '389 Patent, issued on September 17,

[13] Because the '528 Patent does not disclose each and every element of claim 1 of the '603 Patent, there is no need to analyze the remaining dependent claims of the '603 Patent, as they all recite the same "budesonide composition" element.

1991, refers to the same liposomes containing steroidal components as the ‘528 Patent and their use for delayed release of corticosteroids to the lungs to treat a respiratory disease, interstitial lung disease. The ‘389 Patent also lists one of the same inventors listed on the ‘528 Patent. The application for the ‘389 Patent was filed on the same day as the application for the ‘528 Patent and both are assigned on their face to Liposome Technology, Inc.. The Court notes that the ‘389 Patent includes virtually all of the disclosures of the ‘528 Patent, which the Court has already found did not anticipate the AstraZeneca method.

Significantly, the ‘389 Patent was before the United States Patent and Trademark Office during prosecution of the AstraZeneca patents. (See ‘603 Patent, References Cited). Given the tremendous overlap between the ‘389 Patent and the ‘582 Patent, as well as the Court’s rejection of the ‘582 Patent as anticipating prior art, Apotex has not overcome the presumption that the patent examiner properly considered the ‘389 Patent as prior art and found that it did not anticipate the innovative AstraZeneca method. See, e.g., American Hoist & Derrick Co. V. Sowa & Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir. 1984), cert. denied, 469 U.S. 821 (1984) (“examiners ... are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty

it is to issue only valid patents").

(iii) The Gleich Patent

Apotex also argues that the '603 Patent was anticipated by U.S. Patent No. 5,837,713 (the "Gleich Patent"), which relates to the "Treatment of Eosinophil-Associated Pathologies By Administration of Topical Anesthetics and Gencocorticoids." (Gleich Patent, attached as Ex. N to Gross Decl.). The Gleich Patent is directed to a method of treating certain respiratory diseases, e.g., bronchial asthma, by "co-administering ... a topical anesthetic and [] a glucocorticoid... ." (Id. at Col. 4, ln. 34-36).

First, the Gleich Patent was before the United States Patent and Trademark Office during prosecution of the AstraZeneca '603 Patent. (See '603 Patent, References Cited). Second, and more importantly, the Gleich Patent would likely not even be considered prior art because it involves a co-administration of two different therapies, whereas the '603 Patent involves the administration of only one therapy - i.e., orally inhaled corticosteroids. This difference is significant. Indeed, as Dr. Chipps stated in his declaration, "Gleich teaches away from the AstraZeneca invention because it refers only to treatment with both a glucocorticoid and an anesthetic." (Chipps Reply Decl. at ¶ 175). Nowhere does Gleich disclose that a nebulized budesonide composition may be used effectively in a once-daily dosing

regimen to treat respiratory diseases. Thus, the Court rejects Apotex's anticipation argument based on the Gleich Patent.

(iv) Other Publications

Finally, Apotex argues that other publications disclosed or suggested AstraZeneca's innovative method. However, neither the Ilangovan or Carlsen study (attached as Exs. J and K to Gross Decl.) refers to once-daily dosing. Moreover, the Ilangovan study was before the Patent Examiner during prosecution of the AstraZeneca patents. (See '603 Patent, References Cited).

Similarly, despite Apotex's argument to the contrary, the 1994 European advertisement for AstraZeneca's PULMICORT RESPULES that was printed in the Thorax journal (attached as Ex. I to Gross Decl.) does not refer to once-daily dosing. Although 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." (Tr. May 4, 2009 (Chipps) at 162). The Court finds this answer persuasive.

(2) Obviousness

Apotex also argues that the method of the '603 Patent is invalid because it was obvious in light of the prior art. Under 35 U.S.C. § 103,

> [a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Thus, even where a patent overcomes an invalidity challenge based on anticipation, it may still be invalidated if the differences between the invention and the prior art are so small that the invention would have been obvious to one of ordinary skill in the art. In assessing the obviousness of a patented invention, the Court should consider (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) the objective evidence of secondary considerations. Loctite Corp. V. Ultraseal Ltd., 781 F.2d 861, 875 (Fed. Cir. 1985), overruled by Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059 (Fed. Cir. 1998); see also Crown Operations, 289 F.3d at 1375 (listing the same four factors).

With the exception of the ‘528 Patent, none of the prior art references cited by Apotex discusses a once-daily treatment for respiratory disease. As for the ‘528 Patent, although it mentions once-daily use, the method involved there actually teaches away from the method involved in the ‘603 Patent, as explained above. Thus, it cannot be said that the ‘603 Patent was obvious in light of the ‘528 Patent because the two teach

different methods. Singh v. Brake, 317 F.3d 1334, 1346 (Fed. Cir. 2003) (prior art that teaches away is relevant in determining whether or not a claimed invention would have been obvious) (citing W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1550 (Fed. Cir. 1983)). Moreover, as Dr. Williams testified, a person skilled in the art could not predict the performance of one delivery device (the budesonide composition) based on the performance of a different delivery device (the drug entrapped liposome). (Tr. May 4, 2009 at 44 (Williams)).

In addition, AstraZeneca has presented testimony regarding secondary considerations that shows the once-daily administration of BIS was not obvious to one skilled in the trade. Most significantly, the inventor of the method of the '603 Patent, Bertil Andersson, confirmed that there were many skeptics even within AstraZeneca itself. (Tr. May 5, 2009, at 52 (Andersson)). In fact, Andersson testified that he was not permitted to go forward with the once-daily clinical trial unless those trials also included a study of a twice-daily administration of BIS.[14] (Id. at 54-55 (Andersson); see also Declaration of Kathleen O'Connor Ververeli, M.D., at ¶¶ 18-20).

Moreover, AstraZeneca has introduced evidence that shows

[14] Interestingly, Apotex did not cross-examine Andersson when he testified at the hearing. Presumably, if Apotex felt it had a compelling invalidity argument, it would have confronted Andersson with such evidence.

there was a long-felt need for a once-daily dosing pediatric asthma controller medication. Dr. Vellturo testified as to the tremendous commercial success of PULMICORT RESPULES®. (Tr. May 5, 2009, at 5-6 (Vellturo)). Teva Pharmaceuticals USA, a generic company, recently acquiesced in the validity of the PULMICORT RESPULES® patent (see infra). Dr. Chipps testified that there was a long-felt demand within the medical community for something new and that there has been much praise in the industry for PULMICORT RESPULES®. (Tr. May 4, 2009, at 158-59 (Chipps)).

Given the above, this Court cannot find that AstraZeneca's once-daily method was either anticipated by the prior art or obvious in light of the prior art. Accordingly, the Court holds that the method claims of the '603 patent are valid.

2. Infringement

Because the Court has found that the kit claims are invalid, it need not engage in an analysis of direct infringement associated with the kit claims. However, because the Court has found that the method claims are valid, the Court will proceed with an analysis of indirect infringement associated with the method claims.

35 U.S.C. § 271(b) provides that "whoever actively induces infringement of a patent shall be liable as an infringer." AstraZeneca alleges that Apotex will induce infringement of AstraZeneca's patented method claims (Claims 1-3, 6-8, 11-18, 21-

28 of the ‘603 Patent) because the FDA approved label for Apotex BIS product (the “Apotex Label”) instructs physicians to prescribe Apotex’s generic BIS for once-daily use by patients. “‘In order to succeed on a claim of inducement, the patentee must show, first that there has been direct infringement,’ and ‘second, that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another’s infringement.’” Symantec Corp. v. Computer Assoc. Int’l, Inc., 522 F.3d 1279, 1292 (Fed. Cir. 2008) (quoting MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp., 420 F.3d 1369, 1378 (Fed. Cir. 2005)). The Court will examine each part separately.

a) Direct Infringement by Consumers

The infringement analysis also involves two parts: “first claim construction and second a comparison of the properly construed claims to the accused product [or method].” Pfizer, Inc. V. Teva Pharms. USA, Inc., 429 F.3d 1364, 1372 (Fed. Cir. 2005). In order to prove infringement, the plaintiff must show that the accused product or method includes every limitation of an asserted claim of a patent. Baxter Healthcare Corp. V. Spectramed, Inc., 49 F.3d 1575, 1582 (Fed. Cir. 1995).

As set forth above, Claim 1 of the ‘603 Patent contains the following limitations:

- method of treating a patient with respiratory disease
- nebulized administration

- budesonide composition
- not more than once per day

Having resolved the only dispute concerning the construction of these claims (i.e., the meaning of "budesonide composition"), supra, the Court will proceed to a comparison of these claim limitations to the Apotex Label. As the Apotex Label makes clear, the first three limitations are present in Apotex's generic BIS. Specifically, the Apotex Label states that the generic BIS is "indicated for the maintenance treatment of asthma" (Apotex Label at 6), designed for "inhalation via jet nebulizer" (Id. at 1), and "contains the active ingredient, budesonide (micronized), and [various] inactive ingredients..." (Id. at 1). Thus, the only limitation that the parties dispute is whether the Apotex product also involves once daily administration.

To be clear, in AstraZeneca's claim of inducement to infringe, the alleged infringer is not Apotex, but the consumer/patient who ultimately uses the generic BIS product in an infringing manner, i.e., once daily. Thus, in this section, the Court seeks to determine whether there is (or would be) direct infringement by the consumers who use Apotex's generic BIS according to the instructions on the Apotex Label.[15]

[15] The Court notes that the actual chain of instruction involves physicians – the drug label instructs physicians who then instruct patients as to how to take the BIS.

The Apotex Label is virtually identical to the PULMICORT RESPULES® label. (See generally Apotex Label, attached as Ex. 2 to Accetta Declaration [Dkt. No. 33-3]). However, the trade name "PULMICORT RESPULES®" is replaced with Apotex's generic name, "budesonide" or "budesonide inhalation suspension." (Id.). Additionally, all explicit references to once-daily dosing have been removed from the Apotex Label.

As set forth in the Apotex Label, Apotex's generic BIS will be supplied in single dose vials of two strengths: 0.25 mg/2 ml or 0.5 mg/2 ml.[16] (Id.). The "DOSAGE AND ADMINISTRATION" section of the Apotex Label sets forth a chart showing the recommended starting doses and highest recommended doses for three different groups of patients (depending on their previous therapy):

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

(Id. at 16). This section of the label also states that "[o]nce

[16] PULMICORT RESPULES® is supplied in these strengths as well as 1.0 mg/2 ml.

the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose" and "[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved." (Id. at 15, 16). Similarly, the "PRECAUTIONS" section of the Apotex Label states that "suppression of HPA function may be associated when ... the dose is not titrated to the lowest effective dose" and "[t]o minimize the systematic effects of orally inhaled corticosteroids, including budesonide inhalation suspension, each patient should be titrated to his/her lowest effective dose." (Id. at 8).

AstraZeneca contends that although Apotex has removed all explicit references to once-daily dosing in its label, the Apotex Label still implicitly instructs once-daily dosing because it includes instructions to "downward titration" and "taper[] to the lowest effective dose." To illustrate this argument, AstraZeneca highlights the dosing indications for the top two rows of patient groups – i.e., patients who previously used was bronchodilators alone and patients who previously used inhaled corticosteroids. For both categories of patients, the "recommended starting dose" is "0.5 mg administered twice daily in divided doses[,]" which means 0.25 mg twice daily. If a patient (whose asthma is controlled by that starting dose) is then titrated-down as the label provides, the only dosing option is 0.25 mg once-daily.

There is no other option because the Apotex generic BIS will only be available in vials of 0.5 mg and 0.25 mg.[17]

The only category of patients for whom titrating down from the recommended starting dose would still indicate a twice-daily regimen is the third row of patients – that is, patients whose previous therapy was oral corticosteroids. For these patients, the recommended starting dose is 1 mg administered twice daily (e.g., 0.5 mg in the morning and 0.5 mg in the evening). Titrating down from 0.5 mg twice daily would not necessarily instruct a once-daily dosing of 0.5 mg, but could indicate a variety of twice-daily options as a first step: 0.5 mg in the morning and 0.25 mg in the evening; 0.25 mg in the morning and 0.5 mg in the evening; or 0.25 mg in the morning and 0.25 mg in the evening. Thus, the downward titration provision does not pose the same immediate problem in this group of patients as it does in the first two groups of patients. Indeed, were the downward titration language limited to this third category of

[17] A physician following the instructions on Apotex's label would know that the entire 0.25 mg vial should be administered at once, and not divided in half for administration two times daily. This is because both PULMICORT RESPULES® and Apotex's generic BIS are "sterile suspension[s]" and dividing the contents of a single vial for use at two separate times would compromise the sterility. Thus, Apotex's label states that "[a]ny opened vial must be used promptly" and that patients are to "[p]lace the open end of the vial into the nebulizer cup and slowly squeeze out all of the contents." (Id. at 17, 20).

patients, perhaps there would be no infringement,[18] but the Apotex label clearly states that "[i]n all patients it is desirable to titrate down to the lowest effective dose." (Apotex label at 15) (emphasis added).[19]

As further evidence of infringement, AstraZeneca points to a letter issued by the FDA on November 18, 2008 (the "FDA Letter") in response to a citizen petition submitted on behalf of AstraZeneca.[20] (See FDA Letter, attached as Ex. B to Simon Reply Decl., at 18). The first issue the FDA considered was "whether generic BIS, when labeled to exclude protected [once-daily dosing] information currently in the PULMICORT RESPULES labeling, would be rendered less safe or effective than PULMICORT RESPULES for all remaining, nonprotected conditions of use." (Id. at 14). The FDA concluded that it would not. In reaching this conclusion, the FDA pointed to its earlier determination in

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[18] The Court recognizes that although the first step of downward titration for this category of patients might not entail the infringing use, it is possible that the second or third steps in the downward titration process might reach the infringing use.

[19] As discussed below in the section regarding intent, it is perplexing that Apotex included this problematic downward-titration language in its label when it did not necessarily need to do so to obtain FDA approval.

[20] The citizen petition, filed on June 9, 2006, addressed a label that another generic company had submitted to the FDA for approval and which was identical in virtually all respects to the Apotex label. The label was one proposed by another generic company, IVAX Pharmaceuticals, Inc., a company that ultimately settled its litigation with AstraZeneca. See discussion infra.

connection with AstraZeneca's new drug application ("NDA") for PULMICORT RESPULES® that, in terms of efficacy, "the weight of evidence by all measures is stronger for twice daily dosing" than for once-daily dosing. (Id. at 15). Based on this determination, the FDA found that omission of the once-daily dosing references on the generic BIS label would not render the generic product less efficacious than PULMICORT RESPULES®. Additionally, the FDA stated that because the type and incidence rate of adverse events for 0.25 mg once-daily dose does not differ significantly from the 0.5 mg and 1.0 mg total daily dose, there would be no safety risk if once-daily dosing references were eliminated from the label. (Id. at 16). Thus, the FDA concluded that the generic company could omit explicit references to once-daily dosing from its label without sacrificing efficacy or safety.

The second issue the FDA addressed in its letter was whether or not the generic company's proposed label should include the downward titration statement. The FDA concluded that it was "appropriate" for the generic company to retain the downward titration language on its label because such language would help minimize the risks of side effects associated with exposure to corticosteroids such as budesonide. (Id. at 17). The FDA also concluded that the downward titration language did not "teach" once-daily dosing because it could lead to a variety of dosing

regimes, not just once-daily administration:

> The titration statement is relevant for the twice-daily dosing schedule that would be retained in the generic BIS product labeling. Titration to the lowest effective dose may involve, for example, a twice-daily regimen, once-daily dosing, or even alternate day dosing, as determined appropriate by a prescribing physician. The labeling does not state that 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.

(FDA Letter at 18).

AstraZeneca claims that the FDA's conclusion that "[t]itration to the lowest effective dose may involve ... once-daily dosing" shows that there will be infringement by consumers. Apotex, however, interprets the FDA's conclusion differently. According to Apotex, the FDA's conclusion shows that there are other non-infringing titrations available (such as twice-daily dosing and alternate-day dosing) and, thus, the titration statement does not "teach" the infringing use.

As an initial matter, the Court must note that the FDA does not have the authority to make legal findings concerning patent infringement. Thus, the FDA's opinion as to whether or not the titration statement will cause infringement is only relevant as persuasive authority. Beyond that, the Court must recall that the issue to be addressed under this part of the infringement analysis is whether there will be infringement by consumers, not whether the label will "teach" the infringing use - that issue concerns the element of intent, discussed infra. Focusing on the

issue at hand, the Court finds that the FDA's statement that titration down "may involve ... once-daily dosing" supports AstraZeneca's argument that there will be infringement. While it may be true that there are other non-infringing titrations available, the existence of such non-infringing uses does not eliminate the existence of infringing uses.

Moreover, in light of the expert testimony during the hearing, the FDA's opinion that the titration statement can lead to non-infringing uses is only accurate for some patients. Experts for both AstraZeneca (Bradley E. Chipps, M.D. and Thomas Q. Garvey III, M.D.) and Apotex (Donald Accetta, M.D., MPH) testified that downward titration should be done "incrementally," by diminishing the total daily dose one step at a time. (See, e.g., Tr., May 1, 2009, at 65 (Accetta)) ("you wouldn't just go from the highest dose to the lowest dose, but you'd probably do it in gradual [incremental] steps..."). This can be accomplished by either decreasing the amount of each dose and maintaining the frequency, or decreasing the frequency and maintaining the amount of each dose. (Id. at 65-66 (Accetta)). However, for patients in the first two categories of the dosage chart (whose previous therapy was bronchodilators alone or inhaled corticosteroids), the first step in titrating down from the recommended starting dose (0.25 mg twice-daily) would necessarily be to take 0.25 mg once-daily because there is no way of decreasing the amount of

each dose below 0.25 mg. Thus, for these patients, the first step of downward titration would be the infringing once-daily dosing. The non-infringing titration (alternate-day dosing) could only happen as a second step, if at all.

In addition to the downward titration language, the Apotex label contains other information that could reasonably lead to once-daily dosing. In the dosage table of the label, the recommended starting doses all specify "twice daily" yet, for unknown reasons, the adjacent highest recommended doses are silent as to dosing frequency. This juxtaposition could indicate to prescribing physicians that the highest recommended dose need not be twice daily.[21]

Thus, for the foregoing reasons, the Court finds that the consumers using Apotex's generic BIS according to the indications on the label will infringe the AstraZeneca patented method of use.

b) Specific Intent

The Court turns now to the second part of the inducement to infringe claim – specific intent. The parties dispute what is

[21] AstraZeneca also argues that because the first sentence of the CLINICAL TRIALS section of Apotex's label refers to "[t]hree double-blind, placebo-controlled ... U.S. clinical trials" but reports data for only two of the trials, the prescribing physician would have to refer to the PULMICORT RESPULES® label if s/he wanted to read the results from the third study. This argument, while perhaps correct, was not supported by any evidence of such practice by physicians.

necessary to prove "specific intent." As the Federal Circuit recently clarified,

> the specific intent necessary to induce infringement "requires more than just intent to cause the acts that produce direct infringement. ... [T]he inducer must have an affirmative intent to cause direct infringement." [] Thus, "inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." Id.

Symantec Corp., 522 F.3d at 1292 (quoting DSU Med. Corp. v. JMS Co., 471 F.3d 1293, 1306 (Fed. Cir. 2006)) (emphasis added); see also Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1469 (Fed. Cir. 1990) ("Proof of actual intent to cause the acts which constitute the infringement is a necessary prerequisite to finding active inducement"); Rodime PLC v. Seagate Tech., Inc., 174 F.3d 1294, 1306 (Fed. Cir. 1999) ("[i]nducement requires proof that the accused infringer knowingly aided and abetted another's direct infringement of the patent"), cert. denied, 528 U.S. 1115 (2000). Although this is a difficult standard to meet, "direct evidence [of intent] is not required; rather, circumstantial evidence may suffice." Water Techs. Corp. v. Calco, Ltd., 850 F.2d 660, 668 (Fed. Cir. 1988), cert. denied, 488 U.S. 968 (1988).

In this case, because Apotex's generic drug has not launched, AstraZeneca cannot point to any of Apotex's marketing or promotional activities to demonstrate specific intent to

induce infringement.[22] Indeed, Apotex introduced the testimony of the marketing director of Apotex Corp. (the United States company), Ellen Gettenberg, who testified that Apotex does not market, sell, or promote its products directly to consumers or patients but, rather, to national and regional wholesalers, warehousing chains, mail-order organizations, distributors and retailers. She further testified that Apotex does not devote any resources to the practice of "detailing," that is, providing promotion or educational materials to health care providers.

However, the lack of Apotex's promotional and marketing activities does not necessarily mean that Apotex lacks the specific intent to infringe. Intent may be shown in a variety of ways including in the product instruction itself. See, e.g., Chiuminatta Concrete Concepts, Inc. v. Cardinal Industries, Inc., 145 F. 3d 1303,1312 (Fed. Cir. 1998)(advertisements encouraging use during the time of the claimed process); Superior Merchandise Co., Inc. v. M.G.I. Wholesale, Inc., 2000 WL 322779, *13 (E.D. La. 2000) ("inducement of infringing activities is said to embrace 'a wide variety of sales-related activities, including advertising, solicitation, and product instruction"); VLT Corp.

[22] The Court had questioned the parties whether expedited discovery could occur in this case. The Court has the discretion to consolidate the injunction hearing with the trial of the merits. See Rule 65(a)(2). Because the parties dispute whether discovery could be concluded on an expedited basis, the Court did not order discovery and renders its decision herein based on the record presented thus far.

v. Unitrode Corp., 130 F. Supp. 2d 178, 200 (D. Mass. 2001) ("'[i]n fact, it is a textbook violation of § 271(b) where ... a defendant selling products capable of either innocent or infringing use provides through labels, advertising or other sales methods instructions and directions as to the infringing use'"); Saes Getters S.P.A. v. Ergenics Inc., 17 U.S.P.Q. 2d 1581, 1586 n.9 (D.N.J. 1990), aff'd, 914 F. 2d 270 (Fed Cir. 1990) (sales of an ingredient for use in a process claimed in a process patent do not ipso facto constitute infringement, however, instructions provided to users to use the ingredients in accordance with the claimed process constitute infringement); Rexnord Inc. v. Laitram Corp., 6 U.S.P.Q. 2d 1817, 1842 (E.D. Wisc. 1988)("[l]iability under [section 271(b)] can be established where a party takes active steps to induce infringement through advertising or by providing instructions"). Thus, the language of Apotex's label is relevant to the issue of intent.[23]

AstraZeneca argues that the Court should infer Apotex's specific intent to infringe based on three facts: first, the language of the label itself encourages infringement; second,

[23] If Apotex's label explicitly instructed that the generic BIS was to be administered once-daily, there can be no doubt that such instruction would show the requisite intent to infringe. Although Apotex's label is not so explicit, the foregoing statement illustrates the point that an examination of the Apotex label is quite relevant to the issue of intent to induce infringement.

Apotex was aware that the titration language would cause infringement, as confirmed by its undisputed knowledge of the FDA Letter; and third, Apotex did not even try to find alternative non-infringing language for its label. Apotex asserts a variety of counter-arguments as to why they have no specific intent. Because many of the parties' arguments overlap and blend together, the Court will address them all together.

As discussed at length above, the Court has found that the Apotex Label contains language that will cause infringement - most significantly, the statements concerning downward titration. The question now is whether the Court can infer from this language that Apotex specifically intended to cause infringement. Apotex first argues that there is no evidence of culpable conduct by the company; the culprit, if any, is an inanimate object, the label. This is a stretch, to say the least. As discussed, Apotex undertook the drafting of the label, and decisions were made by the company as to what language to include or omit.

Second, Apotex argues that, contrary to AstraZeneca's characterization, its label does not actually "instruct" the infringing once-daily dosing. It points to the FDA's conclusion that "the downward titration statement does not 'teach' once-daily dosing." (FDA Letter at 18). However, as the Court has stated, the FDA is not the arbiter of legal issues such as infringement. While the Court may consider the FDA's opinion, it

is not bound by the FDA's conclusion that Apotex's label does not "teach" once-daily dosing. Indeed, in this case, the Court disagrees with the FDA's conclusion. During the hearing, Dr. Chipps testified that the downward titration language "[i]s telling us that we need to titrate to the lowest effective dose that maintains asthma control. And one of those doses is .25 milligrams once a day which is shown to be safe and effective in the clinical trials... ." (Tr., May 4, 2009, at 183-184 (Chipps)) (emphasis added). It "[t]eaches that downward titration to .25 milligrams is a safe and effective dose." (Id.) (emphasis added). Thus, the Court finds that the Apotex Label does indeed teach that once-daily dosing is permissible.

Apotex also contends that its label does not "instruct" dosage, but merely "recommends" or "suggests" dosage. The Court finds this argument to be nothing more than semantics. Even Apotex's own expert, Dr. Accetta, testified that the issue might be a semantic one: "I wrestled with this thought, is it an instruction versus a teaching versus a recommendation, ... are those just semantic differences or are they real differences." See (Tr., May 1, 2009, at 83 (Accetta)). Regardless of how the language is characterized, this Court finds that the language in Apotex's label encourages once-daily use for at least some patients.

Next, Apotex argues that its label is not actually causing

the infringement because doctors will prescribe the drug however they please regardless of what the label provides. For example, Dr. Accetta testified that no matter what the label instructed, he would prescribe BIS twice-daily as he saw fit. This testimony misses the point. If the label explicitly instructed a once-daily administration, i.e., clearly an infringing use, Dr. Accetta's refusal to follow such instruction would not absolve Apotex. Apotex's label would still infringe. Yet, Apotex appears to gloss over this point.

As to AstraZeneca's assertion that Apotex was aware of the potential for infringing use because of the FDA's conclusion, Apotex argues that knowledge of a potential infringing use is insufficient to prove specific intent. Apotex is correct - "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." Warner-Lamber Co. v. Apotex Corp., 316 F.3d 1348, 1364(Fed. Cir. 2003) (citing Manville Sales Corp. v. Paramount Sys., Inc., 817 F.2d 544, 554 (Fed. Cir. 1990)).

Finally, Apotex asserts that because its generic BIS has a non-infringing use, Apotex does not have the specific intent to induce infringement. They argue that because physicians will prescribe the generic BIS to many of their patients for twice-daily administration (a non-infringing use), there can be no inference of Apotex's intent to induce infringement. "[W]here a

product has substantial non-infringing uses, intent to induce infringement cannot be inferred even when the defendant 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).[24]

This could be a very persuasive argument. However, it ignores the fact that AstraZeneca has presented evidence of Apotex's "affirmative intent" through its drafting of an instruction that induces infringement.[25] As the Supreme Court recently made clear,

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[24] The Court notes that the facts in Warner-Lambert were distinguishable from this case in that the patented use was not on the generic label, nor FDA-approved, and there was evidence that 97.9% of the prescriptions would be non-infringing.

[25] Moreover, it ignores the fact that Apotex has failed to present any evidence of how "substantial" the alleged non-infringing use would actually be. Apotex's expert witness, Dr. Accetta, testified anecdotally that he prescribes twice-daily dosing, but he offered no specific percentages as to his own prescribing practices nor any information whatsoever as to the general prescribing practices. (Tr., May 1, 2009, at 55-56 (Accetta)).

AstraZeneca's expert, Dr. Chipps, testified that in his experience, 60% of primary care physicians prescribed PULMICORT RESPULES® for once-daily dosing and 30% of physicians in a tertiary referral practice did so, which presumably leaves 40% and 70% respectively that write prescriptions for twice-daily administration. (Tr., May 4, 2009, at 136 (Chipps)). However, these percentages are not necessarily reliable indicators of non-infringing use because physicians may write prescription for twice-daily dosing but simultaneously instruct once-daily dosing. (See e.g., Tr., May 5, 2009, at 23 (Vellturo)). Indeed, Dr. Accetta seemed to suggest that he writes prescriptions for twice-daily dosing but instructs patients to titrate down to once-daily dosing to help them "stretch" their medications, for economic reasons. (Tr., May 1, 2009, at 47 (Accetta)).

> [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, and a showing that infringement was encouraged overcomes the law's reluctance to find liability when a defendant merely sells a commercial product suitable for some lawful use.

Metro-Goldwyn-Mayer Studios Inc., v. Grokster, Ltd., 545 U.S. 913, 936 (2005) (quoting Oak Indus., Inc. v. Zenith Elec. Corp., 697 F. Supp. 988, 992 (N.D. Ill. 1988)) (other citations omitted) (emphasis added).[26]

Apotex has argued that its inclusion of the titration language should not be considered evidence of affirmative intent to induce infringement because this language was required by the FDA, as set forth in the FDA's class labeling requirements.[27]

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[26] The Court notes that the Patent Act's exemption from liability for those who distribute a staple article of commerce (under §271(c)) does not extend to those who induce patent infringement (under § 271(b)). Grokster, 545 U.S. at 935 n. 10. The concept is relevant to inducement to infringe only insofar as it relates to the issue of specific intent.

[27] During the hearing, Dr. Garvey explained the function of class labeling as follows:

> Q: And can you tell me what class labeling is?
>
> A: Well, class labeling is usually developed to offer a group of similar or identical drugs and class labeling then must be included in each drug's label. Usually related to safety.
>
> Q: So it's a requirement from the FDA?
>
> A: Yes.

(Tr., May 1, 2009, at 22 (Garvey)).

(See Class Labeling for Intranasal and Orally Inhaled Corticosteroid Containing Drug Products ("FDA Class Labeling"), Ex. 17 to Chipps Decl. or Hearing Ex. DH10). The FDA Class Labeling includes the following statement: "[t]o minimize the systemic effects of orally inhaled corticosteroids, including [sic] each patient should be titrated to his/her lowest effective dose." (FDA Class Labeling at 2). AstraZeneca's own expert witness, Dr. Garvey, testified that anyone who wanted to sell an orally inhaled corticosteroid product would have to include this statement on the product label. (Tr., May 1, 2009, at 28 (Garvey)). Similarly, another one of AstraZeneca's expert witnesses, Dr. Chipps, testified in his declaration that inclusion of this statement on Apotex's generic BIS label "is consistent with the FDA's previous decision requiring all labels for ICSs, such as budesonide, to instruct that '[t]o minimize the systemic effect of orally inhaled corticosteroids, each patient should be titrated to his/her lowest effective dose.'" (Chipps. Decl. at ¶ 109 (quoting FDA Class Labeling)).

Thus, Apotex claims that it had no choice but to include the downward titration language in its label. In other words, Apotex argues that it is caught between a rock and a hard place: either it includes the titration language, thereby complying with the FDA requirements but infringing on AstraZeneca's patent, or it excludes the titration language, thereby avoiding infringement of

AstraZeneca's patent but failing to comply with the FDA requirements. Given this impossible choice, Apotex argues that it would be improper to impute intent based on the inclusion of the titration language.

AstraZeneca counters that, despite the requirements of the FDA Class Labeling, Apotex could have attempted to develop a label with alternative language that would not induce infringement. Indeed, there is no evidence that Apotex filed a "suitability petition" with the FDA to modify the downward titration statement or otherwise alter its label.[28]

The Court understands that Apotex was in a difficult position, trying to comply with both the FDA requirements and patent law. However, that is not to say that there was no possible resolution and the record to date suggests that there might have been. While there is evidence that the FDA generally requires inclusion of the downward titration language, Apotex has not presented any evidence as to whether it attempted (or could have attempted) to work out some type of non-infringing instruction that would still comply with the FDA requirement or whether that was even a possibility that the FDA would consider.

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[28] 21 U.S.C. 355 §§(j)(2)(C) provides, "[i]f a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application."

Perhaps there were (and still are) ways to draft an appropriate label that would both comply with the FDA requirements and yet respect AstraZeneca's patent. For example, the Court notes that in the FDA Letter, the FDA stated that, "the weight of evidence is stronger in support of efficacy for twice-daily dosing as opposed to once-daily dosing (and safety has been demonstrated for both once-daily and twice-daily dosing)..." (FDA Letter at 16). The FDA Letter further stated that ".25 mg of PULMICORT RESPULES® administered [twice daily] was numerically superior to 0.5 mg administered as a single daily dose" and that "data favor[ed] a [twice-daily] schedule for dosing PULMICORT RESPULES® over the same nominal dose administered once-daily." (Id. at 15). In light of these conclusions concerning the safety and efficacy of twice-daily administration, perhaps Apotex did not actually need to include the downward titration language after all. Perhaps they could have proposed a label in which the downward titration statement applied only to patients in the third row (i.e., those whose previous therapy had been oral corticosteroids). Or perhaps they could have proposed a label that explicitly stated, "this drug is intended for twice-daily administration" or even "this drug is not intended for once-daily administration."

However, there is no evidence in the record as to whether any of these types of questions were asked or even contemplated

by Apotex. Similarly, there is no evidence in the record as to whether the FDA may have entertained any alternative label proposals. Indeed, based on the record before this Court, it appears that Apotex drafted its label by simply deleting the explicit references to once-daily dosing without even attempting to come up with alternative non-infringing language.[29] If that is the case, then an inference of intent would be proper. Because there is no evidence to the contrary, the Court cannot find, based on the record before it, that it would be improper to infer intent from Apotex's inclusion of the downward titration language.

The Court is well aware that the issue of alternative labeling arose late in the hearing. In fact, the issue of a suitability petition did not arise until the cross-examination of Ms. Gettenberg, Apotex's last witness, and was not raised in any briefs until the post-hearing brief by AstraZeneca. But, as the Court has stated, these questions raised above (concerning Apotex's attempt to find alternative non-infringing language for its label and the FDA's willingness to consider alternative proposals) go to the heart of Apotex's intent and, yet, they

[29] Moreover, as AstraZeneca points out, it is curious that the column entitled "Highest Recommended Dose" does not refer to a "twice daily" total dose, but simply a "daily dose", a fact that might convey an intent to induce infringement. However, the Court recognizes that perhaps Apotex was simply following AstraZeneca's label as required by the FDA.

remain unanswered.

Because the Court must rule on the preliminary injunction within no more than 20 days (absent Apotex's consent[30]), however, there is not enough time to explore these issues. Given the current record, this Court is inclined to find a likelihood of specific intent on the part of Apotex, which, in combination with the Court's other findings, would require the issuance of a preliminary injunction. However, in the event Apotex wishes to continue the proceeding so that the Court may be more fully informed on these particular issues, it may consent to an extension of the temporary restraining order currently in place until such time as the Court can resolve these issues. Absent Apotex's consent communicated to the Court by the close of business today, May 14, 2009, a preliminary injunction will issue.

B. Irreparable Injury

"Irreparable harm is presumed when a clear showing of patent validity and infringement has been made." Amazon.com, 239 F.3d at 1350; see also Bell & Howell Document Mgt. Prods. Co. v. Altek Sys., 132 F.3d 701, 708 (Fed Cir. 1997) ("'[i]n matters involving patent rights, irreparable harm has been presumed when a clear

[30] See Fed. R. Civ. P. 65(b)(2) (allowing Court to extend TRO beyond 20 days if "the adverse party consents to a longer extension").

showing has been made of patent validity and infringement'") (quoting H.H. Robertson v. United Steel Deck, Inc., 820 F.2d 384, 390 (Fed. Cir. 1987), overruled on other grounds by Markman v. Westview Instruments, Inc., 52 F.3d 967, 977 (Fed. Cir. 1995)); Oakley, Inc. v. Sunglass Hut Intern., 316 F.3d 1331, 1345 (Fed. Cir. 2003) (affirming district court's application of the presumption of irreparable harm where patentee made "a sufficiently strong showing of likelihood of success on the merits").

Here, the Court has found that AstraZeneca has made a showing of likelihood of success on the merits; however, as discussed above, there are some significant weaknesses in its showing. Consequently, the Court finds that the presumption of irreparable harm should not apply. Nonetheless, the Court will proceed to an analysis of the testimony presented by both sides during the hearing to determine whether there is truly a risk of irreparable harm.

AstraZeneca argues that if Apotex is not enjoined from launching its generic BIS, AstraZeneca will suffer irreparable, unquantifiable harm in the form of irreversible market share, permanent price erosion, incalculable damages under the Teva license, loss of capitalization, adverse impact on employees, reduction of research and development funds, loss of goodwill and consumer confusion.

Apotex argues that all of the losses AstraZeneca claims it will suffer are actually quantifiable and compensable with money damages. Indeed, Apotex contends, AstraZeneca recently calculated values for these losses when it entered into a settlement agreement and licensing agreement with Teva Pharmaceuticals USA ("Teva"), another generic company that is now scheduled to enter the generic BIS market this December.

1. Irreversible Loss of Market Share

AstraZeneca contends that if Apotex is permitted to launch, it will suffer an irreversible loss of market share which will begin immediately. Dr. Vellturo explained that the introduction of Apotex's BIS will likely result in an 80% loss of market share in the first month and a 90% loss by the end of three months. (Vellturo Decl. ¶ 22; see also Fante Decl. ¶¶ 23-27). As sales of PULMICORT RESPULES drop, AstraZeneca claims that it will be unable to maintain its current level of promotional activity, which will allow for other branded competitors, such as Flovent and Singulair, to likewise take sales away from PULMICORT RESPULES.[31] (Vellturo Decl. ¶ 23). AstraZeneca contends that

[31] According to Richard Fante, the President of AstraZeneca, PULMICORT RESPULES®'s main competitors are Flovent HFA® 44 mcg, a corticosteroid administered via metered-dose inhaler approved for children ages four to eleven, and Singulair®, an oral leukotriene receptor antagonist approved for children 12 months and older. Intal® (cromolyn sodium) was also approved for treatment of asthma in children as young as two, but currently has a very small share of the market for pediatric asthma. In 2008 PULMICORT RESPULES® had approximately 24% of prescriptions and

once patients are being treated effectively with a competitor's product, it would be difficult, if not impossible, for AstraZeneca to ever recover lost sales to that universe of patients.

The Court disagrees that these damages are irreparable. Although significant, any damages AstraZeneca might suffer as a result of loss of market share or profits are calculable and compensable.

2. Permanent Price Erosion

AstraZeneca also contends that it will suffer from permanent price erosion if Apotex enters the market and is later forced to exit. This occurs for two reasons. [redacted]

48% of sales among its main competitors (Flovent HFA® 44 mcg, Singulair®, and Intal®). Singulair® had approximately 63% of prescriptions and 42% of sales of these pediatric asthma medications, while Flovent HFA® 44 mcg had approximately 12% of prescriptions and almost 7% of sales.

[redacted]

Moreover, if Apotex joins the market, AstraZeneca would lose its current advantageous formulary position. Some background is helpful in understanding this effect. AstraZeneca does not sell PULMICORT RESPULES® directly to patients, but rather to wholesalers and pharmacies. Consumers typically purchase drugs at pharmacies, and pay either the total cost of the drug or, if they are covered by insurance, only a portion of the total price, referred to as a co-pay. The pharmacy then bills the remaining amount back to the consumers' health insurance plans, which may be administered by either a private or government insurer. Such health insurance plans are known as third-party payers ("TPP"). Health insurance plans reimburse the pharmacy for the price of the drug and a dispensing fee. Approximately 90% of prescriptions are covered by TPPs, with close to 50% of prescriptions covered by Medicaid or Medicare.

Each TPP maintains a formulary that ranks pharmaceutical drugs by tiers. Tier 1 has the lowest co-pay, followed by Tier 2, and so on. These tiers enjoy relatively high patient demand. Tier 1 consists primarily of generic drugs, while Tier 2 consists of preferred branded drugs. Tier 3 pharmaceuticals are typically branded products that have a generic alternative; they

are assigned a higher co-pay and face reduced patient demand. Sometimes there is another tier that is non-reimbursed where the patient is required to pay 100% of the cost. Pharmaceutical companies such as AstraZeneca must negotiate prices with these TPPs to be placed on the preferred, or second, tier. AstraZeneca negotiates separately with over one hundred TPPs. TPPs wield considerable leverage in negotiating with pharmaceutical companies.

At present, PULMICORT RESPULES® has no generic or other equivalent product (other than Teva's leftover generic product remaining from its "at risk" launch described below) and enjoys a position in the second formulary tier (with average co-pays of $15) in approximately [redacted] of TPP formularies. [redacted]

[redacted]

However, AstraZeneca argues that if a generic BIS product is launched by Apotex, TPPs will most likely drop PULMICORT RESPULES® to a lower tier or potentially to non-reimbursed status. Although AstraZeneca could offer significant rebates in exchange for maintaining a favorable formulary tier, the generic BIS product would still be placed on the more advantageous Tier 1.

Against this backdrop, AstraZeneca asserts, is that fact that many states require substitution of branded products with

generics whenever possible. In addition, the difference in patient copays for different formulary tiers encourages generic use. Some Medicare plans and HMOs have also chosen not to cover branded medications when generic equivalents are available. Finally, pharmacists have financial incentives to dispense generics, as they usually earn higher margins on generic sales than on branded drug sales.

Thus, AstraZeneca argues, if Apotex were to launch and then subsequently have to leave the market, it would be would be virtually impossible for AstraZeneca to recover its pre-generic entry formulary status for all private and government insurers. This is because, if AstraZeneca were to lower its prices during the period Apotex's generic was on the market, once Apotex left the market, AstraZeneca would likely be unable to re-negotiate successfully with over one hundred TPPs to bring rebates and incentives back to the pre-Apotex launch levels. Furthermore, it would likely take a few months for PULMICORT RESPULES®'s formulary status to be negotiated with TPPs. AstraZeneca's ability to place PULMICORT RESPULES® on Tier 2 would also depend on whether other brands are on Tier 2 at the time of renegotiation.

Extrapolating from other "at risk" launches it has experienced, AstraZeneca predicts that if Apotex launches its generic 0.25 mg and 0.5 mg copy of PULMICORT RESPULES®,

approximately 80% of PULMICORT RESPULES® net sales will be converted to the generic within one month, and the conversion is expected to increase in subsequent months. This high and rapid erosion of the net sales of PULMICORT RESPULES® would result from health plans' decisions to include the generic in Tier 1, while PULMICORT RESPULES® would likely be moved to Tier 3. These formulary decisions would be driven by PULMICORT RESPULES®'s extensive coverage by insurance plans (approximately 90%) and government payment for the drug (close to 50%).

[redacted] Thus, AstraZeneca argues, any premature loss of formulary position due to Apotex's launch would be permanent. This can never be recaptured, AstraZeneca argues.

Apotex argues that any damage caused by a loss of favorable formulary position is clearly calculable because the ultimate damage suffered would be a loss of sales. By AstraZeneca's own calculations, the loss of approximately 90% of monthly PULMICORT RESPULES® net sales to the generic during the first six months of the entry into the market by Apotex would be calculated as

approximately [redacted] million in net sales per month. And if Apotex launched the 0.25 mg and 0.5 mg copies with a six month supply, AstraZeneca would lose approximately $290 million in net sales. (See Fante Decl.). The longer the generic product remained on the market, of course, the greater the loss of sales to AstraZeneca would be, but Apotex argues that these losses are all calculable.

AstraZeneca does not take issue with the fact that many of its losses are calculable and, thus, compensable via money damages. Indeed, AstraZeneca's witnesses, Richard Fante and Dr. Christopher Vellturo, both testified that although it would be difficult to predict damages, the damages would be calculable in part.

This Court agrees that these damages from loss of formulary positions are reasonably calculable. A loss of tier status will translate into sales losses that should be quantifiable. Moreover, this particular loss would be short-lived, as Teva's scheduled entry into the market will cause AstraZeneca to lose its formulary position in any event. Thus, it seems these damages are reasonably calculable and compensable.

3. Incalculable Damages regarding Teva's Premature Entry

AstraZeneca also argues that the irreparable harm it faces is further complicated by its agreement with Teva. On November 25, 2008, AstraZeneca settled its patent infringement litigation

with Teva. The parties entered into a license agreement in which AstraZeneca agreed to allow Teva to commence sales of its generic BIS under an exclusive license from AstraZeneca beginning on December 15, 2009.[32] Per the terms of the licensing agreement, AstraZeneca is to receive a significant royalty on the sales of Teva's generic product. If any additional at-risk generic products enter the market place, there is a step down provision in terms of the amount of royalties paid to AstraZeneca. In addition, Teva agreed to pay AstraZeneca a certain sum for damages resulting from the unauthorized launch of its generic product. Thus, without the entry of Apotex, the Teva licensing agreement contemplates a market exclusivity period for AstraZeneca until December 15, 2009. After that time, Teva is permitted to sell its generic product and AstraZeneca will receive a substantial royalty.

[redacted]

[32] The agreement also provided that any product already shipped by Teva could remain in the market.

[redacted]

The Court finds that the picture painted by Apotex is too simplistic. According to the terms of the licensing agreement, AstraZeneca was to receive market exclusivity until December 15, 2009. Post-December 15, it was to be an AstraZeneca-Teva-only market. Apotex's financial expert witness, Christopher Spadea, testified that the actual price levels and distribution of sales could all be calculated retrospectively. While Mr. Spadea is correct, the problem is that the other variables - the prices and distribution of sales had the AstraZeneca-Teva-only market played

out as contemplated by the license agreement - will never be known. As Dr. Vellturo testified, without the benefit of history of such an AstraZeneca-Teva-only market, it would be complete speculation to put a number on what this market would have been worth to AstraZeneca. This would make quantifying the damage in a reliable way impossible.

Additionally, as discussed above, the entry of one or more generic companies can result in price erosion among the generic companies. Trying to calculate the difference between what actually happens to the price when Apotex enters and what would have happened to the price had Apotex not entered would involve significant guesswork. Apotex argues that these amounts are still calculable based on the parties expectations when they entered into the licensing agreement, yet there is a distinction between what the parties might expect and what actually would have occurred.

[redacted]

In sum, the Court agrees with AstraZeneca that an

unauthorized launch by Apotex would result in unquantifiable damages under the Teva license.

4. Loss of Capitalization

AstraZeneca also contends that it will suffer other harms for which there can be no measure of damages. To illustrate its point, the company points to another "at risk" launch of generic BIS it recently faced.

On November 18, 2008, Ivax Pharmaceuticals, Inc., a wholly owned subsidiary of Teva, launched its generic BIS. This Court issued a temporary restraining order the very next day. However, even considering the speed with which the company acted, AstraZeneca claims that it suffered significant financial and reputational harm. According to Mr. Fante's analysis, the market capitalization of AstraZeneca fell $7.4 billion dollars (a 12% decline) between the market close on November 18 (the date of the launch) and the market close on November 19 (the day of the TRO, which issued after the close of business). (See Hearing Ex. P10). During this same period, the Dow Jones Industrial Average fell only 5%. (Id.). Mr. Fante testified that the extra 7% loss AstraZeneca suffered was attributable to Teva's at-risk launch. (Tr., April 30, 2009 at 39 (Fante)). Even though PULMICORT RESPULES only constitutes approximately three percent of AstraZeneca's global revenues, Mr. Fante explained that there was a disproportionate decline in capitalization because

AstraZeneca's investors are generally "defensive" investors who dislike risky investments. (Id. at 40). Upon seeing the Teva launch, Mr. Fante continued, these investors no longer wished to hold AstraZeneca stock.

Although Apotex argues that it is naive on the part of AstraZeneca to believe that the Teva launch was solely responsible for the decline in the company's stock, it is certainly reasonable based on the evidence at this stage to conclude that the Teva launch at least contributed to the decline of the company's capitalization. Nonetheless, as Apotex correctly argues, this type of loss, even assuming the generic launch was the sole contributing factor to the decline, is calculable and reparable.

5. Adverse Impact on Employees

AstraZeneca also points to the personnel losses it will likely suffer if Apotex is permitted to launch. Mr. Fante testified that the Teva launch resulted in the loss of jobs for 230 AstraZeneca sales employees. (Tr., April 30, 2009, at 44 (Fante)). According to Mr. Fante, this was the first time in AstraZeneca's history that it was forced to lay off its employees. (Id.). With the launch of the Teva product in December 2009, AstraZeneca does not anticipate that it will need to lay off any additional employees. If Apotex were to launch its product, however, Mr. Fante testified that he is certain that

additional sales employees would have to be terminated, perhaps all the remaining 230 employees who currently promote PULMICORT RESPULES. (Id. at 87-88 (Fante)). He also testified that there would have to be a reduction in work force at the Westboro plant, where PULMICORT RESPULES are manufactured, perhaps as high as 90% of the 150 employees who manufacture PULMICORT RESPULES. (Id. at 48, 100-01 (Fante)).

In response, Apotex argues that personnel layoffs are commonplace in the business industry and, in the end, do not impact the company's overall economic position. What Apotex fails to appreciate, however, is the non-economic loss the company suffers due to the layoffs. Indeed, as Mr. Fante testified, "the biggest single impact when you have layoffs for a company that hasn't had substantial layoffs in its history is that it unsettles the workforce and distracts the workforce. So instead of worrying about discovering and developing new medicine, the employees are worried about whether or not they're going to lose their job and that leads to a loss in productivity that I can't put a dollar figure behind..." (Id. at 48 (Fante)).

The Court agrees with AstraZeneca that the damage caused by a loss in personnel and the impact this would have on the company are indeed significant and unquantifiable.

6. Reduction in Research and Development Funds

AstraZeneca asserts that the reduced profits it will suffer

if Apotex launches will force AstraZeneca to decrease the amount of funds it invests in research and development (R&D). Mr. Fante testified that the budget for AstraZeneca's R&D is dependant on its profits; specifically, he stated that AstraZeneca typically invests approximately 15-20% of its net sales in R&D. (Tr., April 30, 2009 at 52 (Fante)). Because the R&D budget is based on profits, AstraZeneca claims that a reduction in profits will necessarily lead to a reduction in R&D. Although the less promising projects would likely be cut in this instance, Mr. Fante explained that this is not a desirable result because sometimes the less promising projects turn out to be very successful, as was the case with Prilosec. (Id. at 53).

However, Mr. Fante testified that PULMICORT RESPULES only contributes approximately three percent of AstraZeneca's global business and ten percent of AstraZeneca's U.S. business. (Tr., April 30, 2009, at 40 (Fante)). In his declaration, Mr. Fante stated that if AstraZeneca lost all revenue from PULMICORT RESPULES, at most, the reduction in R&D would be $150 million. The Court agrees with Apotex's expert, Mr. Spadea, that this loss in profit would be unlikely to alter AstraZeneca's R&D budget in any significant way. AstraZeneca's publicly filed financial documents show that they have historically spent approximately 14-19% of their total annual revenue on R&D. (Tr., April 30, 2009, at 172-73 (Spadea)). Using AstraZeneca's 2008 financials,

Mr. Spadea calculated the percentage of revenue that would be spent on R&D if AstraZeneca received zero revenue from PULMICORT RESPULES but did not reduce its R&D budget – the result was 16.86 percent, which is right in line with what AstraZeneca generally spends on R&D. The Court finds this analysis persuasive.

7. Loss of Goodwill and Consumer Confusion

AstraZeneca claims that an unauthorized launch by Apotex (followed by a subsequent exit) would result in intangible and unquantifiable damage to AstraZeneca's reputation and goodwill. For example, they assert that doctors who would have prescrived Apotex's BIS may blame AstraZeneca for the sudden unavailability of Apotex's generic BIS once Apotex is forced to leave the market. Similarly, they contend that a sudden decrease in the price of PULMICORT RESPULES to compete with Apotex's BIS may cause customers to believe that the original price for the drug had been set at an unfairly high level.

Moreover, AstraZeneca argues it would be impossible to evaluate and quantify the damage caused by consumer confusion resulting from an improper launch by Apotex, as such was the case with the Teva "at risk" launch. This problem is particularly evident in states that require substitution of branded products with generics. In these states, pharmacies might not be able to fill prescriptions for PULMICORT RESPULES® because they might not have a generic supply, yet they would not be able to distribute

PULMICORT RESPULES® either because the state Medicaid electronic database would reflect that there is an approved generic substitute. As such, patients might have to seek out another pharmacy that carries a generic product or go without treatment.

Additionally, AstraZeneca contends that the appearance and then disappearance of Apotex's BIS will result in confusion and frustration for patients and physicians, which could lead to ill will towards AstraZeneca. Mr. Fante testified that after the unauthorized Teva launch, consumers were confused by the sudden availability of the generic drug. (Tr., April 30, 2009, at 49-50 (Fante)). They were concerned because it looked different than what they were used to and they did not want to give their babies the wrong drug. (Id.).

The Court agrees that an unauthorized launch by Apotex would have some intangible effects on AstraZeneca's goodwill. The confusion among consumers and physicians due to the "yo-yo" effect (when a generic comes on and off the market quickly) as well as price changes would likely impact AstraZeneca's reputation. This, in turn, would impact AstraZeneca's sales of other products. [redacted]

[redacted]

Nonetheless, the Court finds that AstraZeneca has demonstrated that there will be some reputational harm as a result of Apotex's launch. This harm is not quantifiable.

Based on the all the evidence presented, the Court finds that AstraZeneca has demonstrated evidence of some irreparable harm in the form of incalculable damages under the Teva license, adverse impact on employees, and loss of goodwill.[33]

C. Balancing the Hardships Between the Parties

In balancing the hardships to the parties, the Court finds that this factor clearly tips in favor of AstraZeneca. If this Court does not issue the preliminary injunction, thereby allowing Apotex to market its generic drug, the launch of a generic would have a dramatic impact on AstraZeneca's licensing agreement with Teva. Such launch would also force AstraZeneca to alter its

[33] The Court also notes that there is no evidence in the record of Apotex's current financial status and whether it would even be able to satisfy a large money judgment if its launch were later deemed improper and it were forced to pay damages to AstraZeneca. In fact, AstraZeneca fairly suggests that, in light of the other patent litigation Apotex is currently involved in, Apotex has a significant exposure to liability and might find itself struggling to pay multiple damages awards. Of course, without any evidence of Apotex's finances, this is mere speculation.

conduct with respect to its marketing of PULMICORT RESPULES®. Moreover, if a subsequent trial on the merits proved infringement, thereby requiring Apotex to pull its generic from the market, AstraZeneca would undoubtedly have a difficult time restoring its pre-generic launch market position. However, if this Court issues the preliminary injunction, thereby preventing Apotex from launching its generic drug, the only hardship Apotex faces is a loss of profits pending the outcome of a trial on the merits. In other words, in this Court's view, it would be much more difficult for AstraZeneca to put the genie back in the bottle. Accordingly, this factor weighs strongly in favor of Plaintiffs.

D. Public Interest

As the Court found earlier in its decision concerning the TRO application, the public interest factor does not favor one side over the other in this case. Both AstraZeneca and Apotex have advanced convincing arguments as to why the public interest is aligned with their positions. As an innovator company, AstraZeneca provides a significant service to the public by creating new pharmaceutical products and uses for pharmaceutical products. AstraZeneca's ability to patent its inventions and enforce those patents is critical to its viability. On the other hand, Apotex, too, provides a significant service to the public by offering generic drugs at a lower cost. Apotex's ability to

create and sell generic versions of brand drugs is critical to its viability. Thus, as both sides have made clear, the public interest lies on both sides of this case. Accordingly, this factor does not tip in favor of either side.

V. CONCLUSION

For the reasons set forth above, Apotex shall advise the Court by the close of business today whether it wishes to extend the TRO hearing pursuant to Fed. R. Civ. P. 65(b)(2) so that the Court may resolve the issues relevant to specific intent. Absent Apotex's consent to such extension, a preliminary injunction shall issue. An appropriate order shall issue this date.

Date: May 14, 2009

s/Renée Marie Bumb
RENÉE MARIE BUMB
United States District Judge