IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA LP, et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 08-453-GMS
	)	
MYLAN PHARMACEUTICALS INC.,	)	
	)	
Defendant.	)	
	)	

MEMORANDUM

I. INTRODUCTION

In this patent infringement action, plaintiffs AstraZeneca LP, Aktiebolaget Draco, KBI Inc., and KBI-E Inc. (collectively, "AstraZeneca" or "the plaintiffs") allege that a pharmaceutical product proposed by defendant Mylan Pharmaceuticals Inc. ("Mylan" or "the defendant") infringes the asserted claims of the patent-in-suit. (D.I. 1.) The court held a three-day bench trial in this matter on May 18 through May 20, 2010. (D.I. 369-375.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity and enforceability of the patent-in-suit and whether the defendant's proposed product infringes the patent-in-suit. (D.I. 378 & 383.)

Pursuant to Fed. R. Civ. P. 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that the defendant's proposed product does not infringe the asserted claims of U.S. Patent No. 5,643,602 (the "'602 Patent" or the "patent-in-suit"). These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. AstraZeneca LP is a limited partnership organized and existing under the laws of the State of Delaware with its principal place of business in Delaware.

2. Aktiebolaget Draco is a corporation organized and existing under the laws of Sweden and has its principal place of business in Lund, Sweden.

3. KBI Inc. is a Delaware corporation having its principal place of business in New Jersey.

4. KBI-E Inc. is a Delaware corporation having its principal place of business in Delaware.

5. Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of West Virginia and does business in the State of Delaware.

B. The Patent-In-Suit

6. On July 1, 1997, U.S. Patent No. 5,643,602 titled "Oral Composition for the Treatment of Inflammatory Bowel Disease" was issued by the United States Patent and Trademark Office ("PTO"), listing Jan Ulmius as the inventor.

7. The application for the '602 Patent was filed on May 9, 1994 as U.S. Application No. 08/240,078. The '602 Patent claims priority to SE Application No. 8903914, which was filed on November 22, 1989.

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 107, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also removed paragraphs relating to the '340 Patent, the Barr litigation, and claims that are no longer being asserted against Mylan, since those matters were settled prior to trial. The court also made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the pretrial order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion section of this opinion, preceded by the phrase "the court finds."

8. The '602 Patent is set to expire on July 1, 2014.

9. In November 1989, Jan Ulmius transferred his rights in the invention to AB Draco. AB Draco is the record owner of the '602 Patent by virtue of an assignment recorded on April 30, 1992 and May 13, 2008.

C. Entocort EC

10. AstraZeneca LP is the holder of an approved NDA No. 21-324 for Entocort[2] EC ("Entocort"). That NDA was approved on October 2, 2001. The active ingredient in Entocort is budesonide.

11. The '602 Patent is listed in the Food and Drug Administration ("FDA") publication *Approved Drug Products with Therapeutic Equivalence Evaluation* (the "*Orange Book*") in relation to Entocort.

12. AstraZeneca sells Entocort in the United States pursuant to NDA No. 21-324.

D. The Asserted Claims

13. The plaintiffs are asserting claims 1, 5-7, 9, 10, 12, 14, 22, 24 of the '602 Patent (the "asserted claims") against Mylan.

14. Claim 1 of the '602 Patent is an independent claim, whereas the remaining asserted claims depend upon claim 1 and/or non-asserted claims 2 and 3 of the '602 Patent.

E. Mylan's ANDA No. 90-410

15. Mylan filed an Abbreviated New Drug Application ("ANDA") with the FDA under 21 U.S.C. § 355(j)(1), which was assigned No. 90-410. ANDA 90-410 was filed to obtain approval for Mylan to engage in the commercial manufacture, use, and sale of budesonide enteric coated capsules in 3 milligram strength (the "Mylan ANDA product") prior to the expiration of the '602 Patent.

[2] Although "Entocort" is a registered trademark, the "®" symbol will be omitted herein.

16. ANDA No. 90-410 contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), which states that in Mylan's opinion and to the best of its knowledge, the '602 patent is invalid, unenforceable, or will not be infringed by the manufacture, use, sale, offer for sale, or importation of the Mylan ANDA product ("Paragraph IV Certification"). Mylan sent the plaintiffs written notice of ANDA No. 90-410 and Mylan's Paragraph IV Certification in a letter dated June 9, 2008.

F. Mylan's ANDA Product

17. As required by 21 C.F.R. 314.94(a)(8)(iv), the proposed product insert or label submitted with ANDA No. 90-410 identifies Mylan as the manufacturer of the Mylan ANDA Product.

18. As set forth in ANDA No. 90-410, the Mylan ANDA Product contains budesonide as the active ingredient.

III. DISCUSSION

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338 and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that Mylan's ANDA product does not infringe the asserted claims of the '602 Patent. The court's reasoning follows.

The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed.Cir.1995). The patent owner has the burden of proving infringement by a preponderance of

the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984) (*citing Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). "Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F .3d 1562, 1569 (Fed. Cir. 1997).

Claim 1 of the '602 patent covers two separate and mutually exclusive embodiments. The first embodiment requires a core consisting of a "non-pareil seed," which is surrounded by an intermediate coating containing a glucocorticosteroid (namely budesonide) and a release-controlling polymer, which is in turn surrounded by an enteric coat. ('602 Patent at 13:30-14:39.) The second, alternative embodiment requires a seed in which the glucocorticosteroid is homogeneously distributed, which is surrounded by an intermediate coating containing a release-controlling polymer, which is in turn surrounded by an enteric coat. ('602 Patent at 13:30-14:39.) AstraZeneca argues that Mylan's ANDA product infringes the first of these embodiments. (See, e.g., D.I. 126 at 8, 13.) In response, Mylan argues that its product is non-infringing because: 1) it does not contain a "core consisting of a non-pareil seed;" and 2) it does not contain a "layer surrounding said core" containing a glucocorticosteroid and a release-controlling polymer. (See, e.g., D.I. 127 at 5, 11.)

In its *Markman* order, the court construed "a core consisting of a non-pareil seed" to mean "the innermost part of the pellet consisting of a non-pareil seed and optionally one or more pharmaceutically acceptable excipients" (D.I. 60 at 2) and construed "a layer surrounding said core" to mean "a coating enclosing on all sides said core."[3] (Id.) Contrary to AstraZeneca's assertion, the court did not "reject[] Mylan's proposal to limit non-pareil seed to an 'inert sphere

[3] As the court noted in its *Markman* order, "the plaintiffs indicated a willingness to accept a construction of this term that includes 'coating' and 'enclosing on all sides.'" (See D.I. 60 at 2, n.6 (citing D.I. 67 in C.A. 08-305, at 60-61, 158).)

made of sucrose and starch.'" (See D.I. 130 at 1.) As AstraZeneca itself notes, the court was never asked to construe "non-pareil seed" by itself. (See id.) Instead, the parties submitted the entire phrase "a core consisting of a non-pareil seed" for construction. The court explicitly rejected both Mylan's *and* AstraZeneca's proposed constructions of this phrase and left the term "non-pareil seed" intact in its claim construction order – without ruling one way or the other on what constitutes a non-pareil seed.[4] (See D.I. 60 at 2, ¶ 3 and n.4.) Based on its past experience in patent cases, the court believed that the evidence presented at trial likely would allow the court to rule on the issue of infringement without having to construe the meaning of the disputed term beyond giving it its plain and ordinary meaning.

Having considered both the record and the parties' post-trial briefs, the court has indeed concluded that even if the court were to adopt *arguendo* AstraZeneca's position that the lactose particles in Mylan's ANDA product constitute non-pareil seeds, AstraZeneca failed to prove by a preponderance of the evidence that the lactose particles in Mylan's proposed product are enclosed by a glucocorticosteroid/polymer layer. On the contrary, the court finds that the evidence at trial demonstrates that Mylan's product consists solely of: 1) an active core in which budesonide is homogenously distributed and 2) an enteric coating, and further finds that the

[4] The court's decision not to specifically rule on the meaning on "non-pareil seed" was made in part because the dispute over the meaning of this term did not appear to develop until after the parties' joint claim chart was submitted. (See D.I. 33, D.I. 38, D.I. 39, and D.I. 40.) Mylan filed a motion to amend the joint claim chart to include its proposed construction of "non-pareil seed," and AstraZeneca opposed that motion. The court struck the motion from the docket and ordered the parties to resolve the issue on their own. (See Oral Order dated 07/21/2009.) The parties were unable to do so, and Mylan ultimately presented their proposed construction, which would have limited "non-pareil seed" to "inert sphere made of sugar and starch," at the *Markman* hearing. At the hearing, AstraZeneca vehemently opposed Mylan's proposal. In the end, as noted in the main text of this memorandum, the court rejected both Mylan's and AstraZeneca's proposed constructions and declined to rule on the meaning of "non-pareil seed."

lactose particles in the active core are not enclosed on all sides by a glucocorticosteroid/polymer coating.[5]

On its face, Mylan's ANDA describes a product with a two-layer design. The ANDA states that the innermost layer consists of a "core pellet" or "mini-tablet" that is "compressed from a blend of (i) homogeneous granules comprised of lactose monohydrate, budesonide drug substance and an ethylcellulose polymer system and (ii) extragranular disintegrant, lubricant, and glidant." (MX-4 at 271.) AstraZeneca does not assert that any portion of Mylan's ANDA describes the lactose particles in the granules as being completely coated, surrounded, or enclosed by the budesonide and ethylcellulose. Despite AstraZeneca's efforts in its post-trial briefs to describe the ANDA as disclosing a "layer" or "coating" of budesonide/ethylcellulose (see D.I. 126 at 13, ¶¶ 38 & 39), none of the sections of Mylan's ANDA cited by AstraZeneca describes the budesonide/ethylcellulose as a "coating," "layer," or any other term indicating that the budesonide and ethylcellulose enclose or surround the lactose particles. (See JTX-7 at 202-03 & 220-21.) Rather, the ANDA describes the top-spraying as a "granulation" process and the pellets that result as "granules" or a "granulating suspension." (See id.) The only "coating" or "layer" described in the ANDA is the enteric coat that surrounds the entire mini-tablet core. (See, e.g., id. at 202.)

Since Mylan's ANDA does not explicitly disclose the existence of an intermediate layer that completely encloses the lactose particles, AstraZeneca had to show by other means that

[5] The court further notes that adopting AstraZeneca's position would essentially require the court to accept that the scope of claim 1 encompasses formulations containing multiple non-pareil cores within a coating that percolates throughout and between the cores. The language of claim 1 itself, however, contemplates a three-layer product, with the layers positioned, in the words of Dr. Elder, "one on top of the other." (Tr. 5/19 at 114:22-115:4.) The claims cover formulations containing "*a* core" surrounded by "*a* layer" and, in the court's view, do not contemplate a formulation containing multiple individual cores, with the intermediate "layer" scattered throughout and between the individual cores. The court need not decide the issue of infringement on this basis, however, since even if such a dispersed "layer" falls within the meaning of the claim, the court finds that the individual lactose particles in Mylan's actual ANDA product are not completely enclosed by the budesonide/ethylcellulose "layer," for the reasons stated in the main text of this memorandum.

Mylan's ANDA product met the "layer surrounding said core" limitation of claim 1. As AstraZeneca stated in its post-trial brief:

> There is . . . no dispute that the lactose particles are sprayed with an aqueous dispersion of budesonide with ethylcellulose in a top-spray fluid bed granulator/dryer during "Step #2 Part II Granulation/Drying." The parties disagree as to whether this spraying process results in lactose particles that are enclosed on all sides by the budesonide-ethylcellulose aqueous dispersion . . . or lactose particles that are merely connected by "binder bridges" made from the budesonide-ethylcellulose dispersion . . . .

(D.I. 126 at 5.) "Binder bridges" between particles are the result of the conventional granulation process. (See Tr. 5/19 at 63:10-13 (Davies) & 142:2-23 (Elder).) Such binder bridges, which in Mylan's product would be formed from a mixture of ethylcellulose and budesonide, cover only a portion of the surface area of the particles and would not result in a film completely coating the individual particles, as required by the asserted claims. (See Tr. 5/19 at 63:14-21 (Davies) & 142:22-25 (Elder).)

The parties agree that the top-spray "wet granulation" process that Mylan describes in its ANDA can be used in both granulation and coating processes and, by extension, can be used to form either binder bridges or complete film coatings. (See D.I. 126 at 14; D.I. 129 at 7.) AstraZeneca cites the "Remington" reference (JTX-83) for the proposition that wet granulation can be used for coating. (E.g., D.I. 126 at 13.) The issue in this case, however, is not whether such a granulation process *could* be used for coating, but rather whether Mylan's ANDA product itself *actually contains* such a coating. In other words, AstraZeneca faced the burden of proving by a preponderance of the evidence that Mylan's top spray fluid bed granulator actually coats lactose monohydrate particles so that they are "completely enclosed" *and*, if so, that such a coating survives the later processing steps in Mylan's manufacturing process. Put another way, AstraZeneca had to show that the existence of a complete coating in Mylan's ANDA product "is

more probable than its non-existence." *See Bosies v. Benedict*, 27 F.3d 539, 542 (Fed. Cir. 1994) (*citing In re Winship*, 397 U.S. 358, 371-72 (1970)). The court finds that AstraZeneca did not meet this burden.

The court is persuaded by the testimony of Mylan's expert witness, Dr. Edwin J. Elder, regarding the nature of Mylan's accused ANDA product and the manufacturing process that produces it. Dr. Elder testified that the expansion chamber on Mylan's granulator is configured to force particles into the random motion that is required for granulation. (Tr. 5/19 at 121:22-123:8 & 124:8-10; Tr. 5/20 at 23:19-25:18.) He contrasted this with the configuration shown in Remington, which Elder said would lead to recirculation of the materials in the chamber; such recirculation is consistent with a coating process, not a granulation process. (Tr. 5/19 at 122:22-123:8; Tr. 5/20 at 25:11-18.) In addition, Dr. Elder testified that the location of Mylan's spray nozzle (above the lactose particles) maximizes particle interactions for granule formation (Tr. 5/19 at 122:18-21), unlike the configuration shown in Remington which depicts particles traveling above the spray nozzle within the expansion chamber. (Tr. 5/19 at 122:11-123:5; JTX-83 at 936, Fig. 46-6.) The court therefore finds based on the evidence presented at trial that the manufacturing process described in Mylan's ANDA results in granules where the lactose particles are connected by binder bridges that only cover a portion of the surface area of the lactose particles in the granules, not a "coating" or "layer" that surrounds or encloses the lactose particles.

Even if some of the lactose particles are completely coated (which, for the reasons stated above, the court finds unlikely), the court finds that such coatings would be broken during the milling step that occurs after the granulation step of Mylan's manufacturing process.[6] To ensure

[6] The milling step appears as "Step 1C" in the flow chart in the ANDA depicting Mylan's manufacturing process. (See MX-4 at 288.)

uniform size distribution, Dr. Elder explained, the granules must go through a milling step that breaks down any granules larger than the desired size range. (Tr. 5/19 at 150:17-23.) This is accomplished by using a round impeller to force the granules through holes in a mill. (See Tr. 5/19 at 127:17-129:17; MX-4 at 291.) Similarly, even in the unlikely event that a coating was formed and somehow remained intact after the milling process, the court finds that, due to the friability (*i.e.*, brittleness) of lactose, such a coating would be fractured by the pressures the milled granules are exposed to during the tableting process.[7] (Tr. 5/19 at 172:21-173:2.) During the tableting process, the granules are exposed to extreme pressure in order to compress them into mini-tablets of the desired size. (Id. at 149:10-150:8; MX-4 at 292.) Thus, by the time the Mylan's pharmaceutical dosage form is complete, it is highly unlikely that any of the lactose particles in Mylan's ANDA product would have a budesonide-polymer layer surrounding them. The initial top-spray granulation process is not likely to result in a complete coating of lactose particles, and if by chance some lactose particles did become coated, those coatings would be fractured and broken down after the granules are milled and compressed into the mini-tablets that form the homogeneous and active core of Mylan's two-layer product.

To advance its theory that the lactose particles are indeed completely coated by the dispersion, AstraZeneca relied on the testimony of Dr. Martin C. Davies. In his testimony, Dr. Davies described experimental tests that he ran on Mylan's ANDA product after dissolving it in simulated intestinal fluid; other than measuring the size of Mylan's mini-tablets, Dr. Davies did not rely on any evidence in his report or at trial based on testing of Mylan's ANDA product before it was dissolved. (Tr. 5/19 at 64:12-17.) After dissolving away the lactose, Dr. Davies examined the remnants of Mylan's product, and presented an optical micrograph at trial depicting either: 1) "intact, ethylcellulose-budesonide film coatings," according to the testimony

[7] The tableting process appears as "Step 1E" in Mylan's flow chart. (See MX-4 at 288.)

of Dr. Davies and the proposed findings submitted by AstraZeneca (see Tr. 5/18 at 87:10-23; D.I. 126 at 14); or 2) "porous clumps of rehydrated and coagulated ethylcellulose bridges" (D.I. 129 at 9-10), according to the testimony of Dr. Elder and the proposed findings submitted by Mylan (see Tr. 5/19 at 132:18-133:6; D.I. 127 at 14). Specifically, Dr. Elder noted that the material depicted in the disputed micrograph was highly porous, and opined that the polymeric material in the disputed micrograph was actually coagulated clumps of ethylcellulose binder bridges rather than intact films.[8] (See Tr. 5/19 at 131:16-133:6.)

On this point, as is often the case in patent trials, the court was presented with the testimony of two remarkably well-qualified experts in the relevant field who came to completely different conclusions regarding a key factual dispute in the case. Here, the court found the testimony of Dr. Elder to be the most credible. For the reasons described above, the court finds it highly unlikely that Mylan's ANDA product would contain a complete layer surrounding the lactose particles. Certainly, Dr. Davies' explanation regarding the nature of the polymeric material he found after his tests is not sufficient to overcome the strong evidence indicating that

[8] To illustrate for the court the manner in which this coagulation occurs, Dr. Elder analogized the ethylcellulose to pasta, which has a tendency to hydrate, swell, and eventually clump together when overcooked. (See Tr. 5/19 at 131:22-132:16.) AstraZeneca mocked Dr. Elder's analogy, dismissing Dr. Elder's analogy as a "creative explanation [that] was supported by no experimental results or scientific observations (from either the laboratory or the kitchen)" (D.I. 130 at 8-9) and criticizing Dr. Elder for failing to provide evidence in support of his assertions. (D.I. 126 at 15.) The statement that Dr. Elder failed to produce "evidence" supporting his explanation is somewhat peculiar given that Dr. Elder's opinion testimony – based on over 24 years of industry and academic experience with granulation and coating equipment, including the equipment used by Mylan – is itself evidence. The court shudders to think how long patent trials would last if experts had to present independent evidence verifying every assertion they make while providing opinion testimony in court.

AstraZeneca's sarcasm is particularly ironic given that their own expert, Dr. Davies, also used such metaphors without producing independent "evidence" verifying his statements. For instance, when explaining the function of the disintegrant in Mylan's product, Dr. Davies used the metaphor of a "little time bomb" that "blows up." (Tr. 5/19 at 76.) Just as the court did not begrudge Dr. Davies his "time bomb" analogy, it does not frown upon Dr. Elder's pasta analogy. On the contrary, the court found both analogies beneficial in helping it understand the technical processes that the experts were describing.

AstraZeneca was not alone in adopting a condescending tone in its briefs. Mylan's post-trial brief similarly mocked Dr. Davies' explanation of the material he examined, beginning the final section of their reply brief with the phrase "In their excitement to hear that Dr. Davies found something in the bottom of his Petri dish . . ." (See D.I. 129 at 9.) The court notes for the sake of future parties that such condescension is unbecoming an attorney appearing before a federal court, and is in no way constructive or beneficial to the court's task of weighing the evidence presented at trial and reaching its findings of fact and conclusions of law.

Mylan's ANDA product would not contain complete coatings, particularly given Dr. Elder's contrasting explanation of the nature of the disputed material.

For these reasons, the court finds that even if the court accepts *arguendo* that the lactose particles in Mylan's accused ANDA product are non-pareil seeds, the accused product does not literally contain a budesonide/polymer layer surrounding the core, as required by claim 1. AstraZeneca did not assert infringement via the doctrine of equivalents with respect to this limitation. (See, e.g., D.I. 130 at 1, n.2.) Consequently, the court concludes that Mylan's accused ANDA product does not infringe claim 1 of the '602 Patent or any of the asserted dependent claims.

IV. CONCLUSION

Based on the factual record in this case, the documentary and testimonial evidence presented at trial, including the expert testimony on the issue of infringement, the court concludes that the plaintiffs have not proven by a preponderance of the evidence that manufacture, use, or sale of Mylan's proposed generic budesonide product would infringe the asserted claims of the '602 patent.

Dated: June 23, 2011

CHIEF, UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA LP, et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	C.A. No. 08-453-GMS
	)	
MYLAN PHARMACEUTICALS INC.,	)	
	)	
Defendant.	)	
	)	

ORDER

At Wilmington, this 23rd day of June, 2011, consistent with the memorandum opinion issued this same date, IT IS HEREBY ORDERED THAT:

1. Mylan's accused ANDA product does not infringe the asserted claims of the '602 Patent.

2. The Clerk of Court is directed to enter judgment in favor of Par and against the plaintiffs.

CHIEF, UNITED STATES DISTRICT JUDGE