IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

MERCK SHARP & DOHME CORP.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 14-874-SLR
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	

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OPINION

Dated: November 16, 2016
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of Abbreviated New Drug Application ("ANDA") No. 205149 by defendant Teva Pharmaceuticals USA, Inc. ("Teva") seeking to produce and market a generic mometasone furoate nasal spray. (D.I. 123) On July 3, 2014, plaintiff Merck Sharp & Dohme Corp. ("Merck") brought this action alleging infringement of U.S. Patent No. 6,127,353 ("the '353 patent").[1] (D.I. 1) Merck filed an amended complaint on August 17, 2015, which Teva answered on Aubust 31, 2015. (D.I. 123; D.I. 130) The court held a *Markman* hearing on July 31, 2015 and issued a claim construction order on September 3, 2015 construing certain disputed limitations. (D.I. 133) The court held a final pretrial conference on May 4, 2016 and a two-day bench trial on June 24 and 27, 2016 on the issues of infringement and validity. The parties have since completed post-trial briefing. The 30-month stay of FDA final approval on Actavis's ANDA expires on November 22, 2016. (D.I. 182, ex. 1 at ¶ 71) The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Technology at Issue

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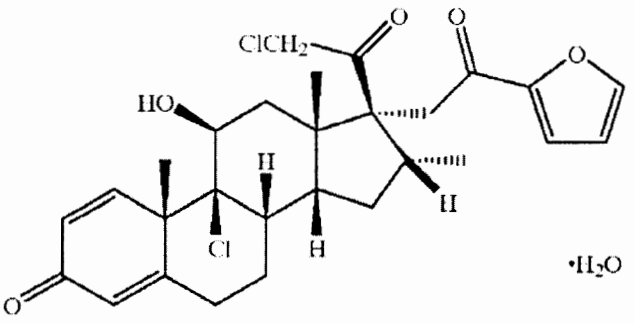
[1] The '353 patent is listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for Nasonex® ("Nasonex"). (D.I. 182, ex. 1 at ¶ 37) Merck holds an exclusive license under the '353 patent and has standing to enforce the '353 patent against Teva in this action. (*Id.* at ¶ 36)

1. Development of MFM

Anhydrous mometasone furoate ("MFA") was first synthesized and patented by a Merck chemist, Dr. Elliot Shapiro, in the early 1980s. (D.I. 191 at 6) After MFA was discovered, its unique physical properties that prevented it from dissolving in water or known pharmaceutically acceptable compounds kept it on the "backburner" for further research. (*Id.*) Years later, scientists found that MFA dissolved in a new pharmaceutical solvent and developed MFA for the treatment of psoriasis, a skin condition. (*Id.* at ¶ 5)

In the late 1980s, a formulator at Merck, Dr. Yuen, led a project seeking to develop mometasone furoate for nasal applications. As a result of this project, mometasone furoate monohydrate ("MFM") was developed. MFM has the chemical name, 9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione-17-(2'-furoate) monohydrate and the following chemical structure:



(D.I. 191 at 3-7; '353 patent)

MFA and MFM are polymorphs. MFM differs from MFA in that every molecule of MFM is associated with a molecule of water, whereas no water is present in the crystal lattice structure of MFA. The difference between the molecular structures of MFM and MFA causes changes to the solid structure of the two crystalline forms. MFA has

acicular morphology, with needle or rod-shaped crystals. MFM has more plate-like crystals. (D.I. 191 at 7; PTX 19)

2. Development of Nasonex

Upon discovering MFM, Dr. Yuen determined that using MFM as a suspension in water with other excipients provided a stable formulation. (D.I. 182, ex. 1 at ¶¶ 12-13) The formation was further developed and ultimately was approved as Nasonex. The formulation is protected by the '353 patent. (*Id.* at ¶14)

Nasonex is indicated for the treatment of perennial allergenic rhinitis, seasonal allergic rhinitis, nasal polyps, and congestion associated with the nasal symptoms of allergic rhinitis (*Id.* at ¶ 15) The product insert for Nasonex states: "[Nasonex] Nasal Spray 50 mcg is a corticosteroid demonstrating potent anti-inflammatory properties." (*Id.* at ¶ 24) It further states: "The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types . . . and mediators . . . involved in inflammation." (Id.) Nasonex contains MFM as its active pharmaceutical ingredient ("API"). (*Id.* at ¶ 39)

3. The '353 Patent

The '353 patent, titled "Mometasone furoate monohydrate, process for making same and pharmaceutical compositions," issued on October 3, 2000. (JTX 1) Merck asserts independent claims 1 and 6 and dependent claims 9-12. The patent claims MFM, a process for preparing MFM by crystallization from a saturated aqueous water miscible organic solution, and aqueous stable pharmaceutical compositions of

MFM. ('353 patent, 1:31-48) Independent claim 1 recites "9α,21-dichloro-16α-methyl-1,4-pregnadiene-11β,17α-diol-3,20-dione-17-(2'-furoate) monohydrate" and independent claim 6 recites "[a] pharmaceutical composition comprising mometasone furoate monohydrate in a carrier consisting essentially of water." The '353 patent incorporates U.S. Patent No. 4,472,393 ("the '393 patent") by reference. ('353 patent, 1:15-18)

4. The accused ANDA product

Teva's ANDA product is a generic mometasone furoate nasal spray, 0.05mg/spray, using MFA as the active pharmaceutical ingredient. Teva's ANDA product has a proposed shelf-life of two years. Merck is not alleging that the pre-formulation active pharmaceutical ingredient used in Teva's ANDA product contains MFM or otherwise infringes the '353 patent. (D.I. 191 at 3-5; D.I. 194 at 6)

B. Invalidity

1. Non-Statutory double patenting

As recently reiterated in *Abbvie Inc. v. Mathilda and Terence Kennedy Institute of Rheumatology Trust*, 764 F.3d 1366 (Fed. Cir. 2014), "'a rejection based upon double patenting of the obviousness type' is 'grounded in public policy (a policy reflected in the patent statute).'" *Id.* at 1372 (citing *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985)). "If an inventor could obtain several sequential patents on the same invention, he could retain for himself the exclusive right to exclude or control the public's right to use the patented invention far beyond the term awarded to him under the patent laws." *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014). "[O]bviousness-type double patenting prohibits 'claims in a later patent that are not

patentably distinct from claims in a commonly owned earlier patent.'" *Sun Pharmaceutical Industries, Ltd. v. Eli Lilly and Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010) (citing *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1375 (Fed. Cir. 2008)).

In *Gilead Sciences*, the Federal Circuit applied the above policy considerations and concluded that:

> Looking instead to the earliest expiration date of all the patents an inventor has on his invention and its obvious variants best fits and serves the purpose of the doctrine of double patenting. Permitting any earlier expiring patent to serve as a double patenting reference for a patent subject to the URAA guarantees a stable benchmark that preserves the public's right to use the invention (and its obvious variants) that are claimed in a patent when that patent expires.

753 F.3d at 1216.

At bar, the '353 patent issued on October 3, 2000 from U.S. Patent Application No. 07/984,573[2] (the '573 application), which was a U.S. national phase application of PCT Application No. PCT/US91/06249 (the '249 PCT application) that was filed on September 6, 1991. The '781 patent issued from U.S. Patent Application No. 08/422,479[3] ("the '479 application") as a continuation of the '573 application. Thus, the '781 patent is in the same patent family as the '353 patent, and is a direct continuation of the '353 patent. (D.I. 182, ex. 1 at ¶¶ 32, 41) The parties agree on the following timeline:

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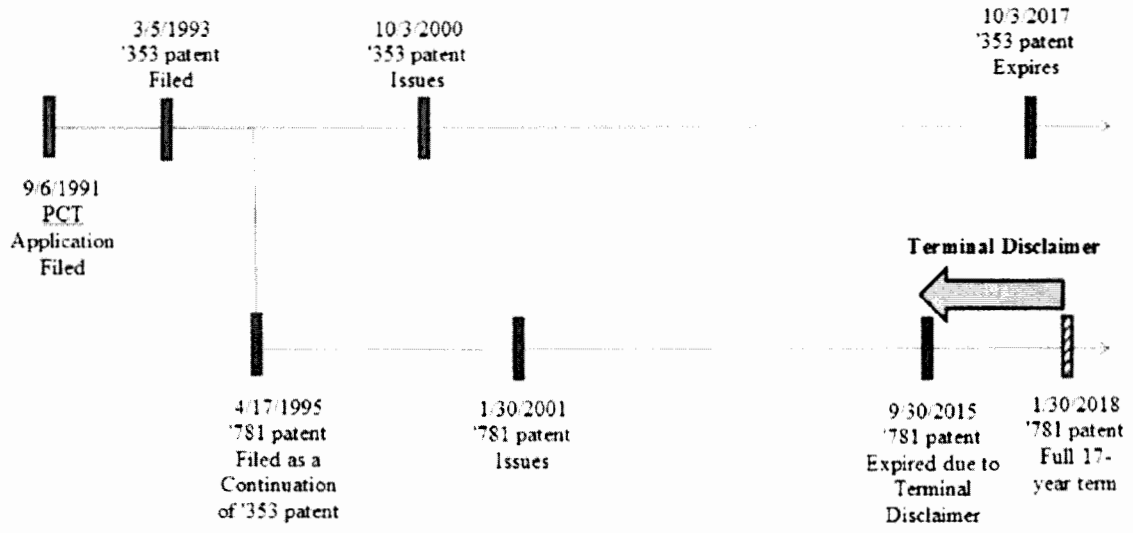
[2] Filed on March 5, 1993.

[3] Filed on April 17, 1995.



A terminal disclaimer was required to revive the application for the '781 patent during prosecution (relating to the amount of time during which the application was abandoned, not to the subject matter of the claims). (D.I. 196 at 12-13) The parties dispute whether the '781 qualifies as a double patenting reference because it expired before the '353 patent.

The patents-at-issue are from the same family, indeed the '781 patent is a continuation of the '353 patent. The patents were examined by the same examiner at the PTO. Under the particular circumstances, the oddity of using the '781 patent as a reference patent to cut short the '353 patent's (the first issued parent patent) term of exclusivity is rejected. This is not an instance of a patentee seeking to extend the patent term with "sequential" applications.[4] The '353 patent is not invalid for double patenting.

[4] "[T]he doctrine of double patenting was primarily designed to prevent such harm by limiting a patentee to one patent term per invention or improvement." *Gilead Sciences*, 753 F.3d at 1212.

2. Written description

a. Standard

The statutory basis for the written description requirement, § 112 ¶1, provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

A patent must contain a written description of the invention. 35 U.S.C. § 112, ¶ 1. *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2011). It ensures that "the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005). The Federal Circuit has stated that the relevant inquiry – "possession as shown in the disclosure" – is an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351.

This inquiry is a question of fact. "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citation omitted). In this regard, defendant must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the

claimed invention. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-17 (Fed. Cir. 2008) (citation omitted).

b. Analysis

> Incorporation by reference "provides a method for integrating material from various documents into a host document . . . by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein." "To incorporate material by reference, the host document must identify with **detailed particularity** what specific material it incorporates and **clearly indicate where** that material is found in the various documents." Whether material has been incorporated by reference into a host document, and the extent to which it has been incorporated, is a question of law. In making that determination, "the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity."

Zenon Envtl., Inc. v. U.S. Filter Corp., 506 F.3d 1370, 1378-79 (Fed. Cir. 2007) (citations omitted). The '353 patent provides that "[m]ometasone furoate is known to be useful in the treatment of inflammatory conditions. The compound is prepared by procedures disclosed in U.S. Patent No. 4,472,393 ["the '393 patent"], which patent is hereby incorporated by reference." ('353 patent, 1:14-17) Contrary to Teva's argument, the incorporation is not limited to material disclosing a procedure for making mometasone furoate, but, rather, the citation incorporates the patent.

To the extent Teva criticizes Merck for not affirmatively presenting evidence of the '393 patent at trial, it is Teva's burden to prove, by clear and convincing evidence, that the disclosures in the '353 patent lack written description.[5] Teva's expert, Dr. Dash, declined to consider the '393 patent in reaching his opinions, testifying that "[t]here is nowhere in the specification [that] a person of ordinary skill in the art will be finding a

[5] *See* D.I. 192 at 47 n.25. The court finds that Merck did refer to the '393 patent in its contentions, albeit somewhat ambiguously. (D.I. 55 at 38)

composition that contains mometasone furoate monohydrate in a subtherapeutic amount and another agent . . . present in that composition that acts as an API." He concluded that claim 6 of the '353 patent does not disclose pharmaceutical compositions using another API in combination with MFM and, thus, was invalid for lack of written description. (D.I. 203 at 281:25-288:10)

The court, however, has concluded that the '353 patent incorporates by reference the full scope of the '393 patent, including its disclosures explaining that "[t]he pharmaceutical dosage forms . . . may contain other active ingredients, e.g. neomycin sulfate in cream for topical use" and "[t]he compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics." ('393 patent, 8:10-13, 47-50) Claims 6 and 9-12 of the '353 patent are directed to an array of pharmaceutical compositions containing MFM. Without evidence on the disclosures of the '393 patent, Teva has not carried its burden of establishing lack of written description by clear and convincing evidence.[6]

3. Conclusion

For the reasons articulated above, the court concludes that the asserted claims of the '353 patent are valid.

C. Infringement

1. Standard

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35

[6] At trial, Merck moved under Rule 52(c) for judgment that Teva had failed to prove its defense of lack of written description. (D.I. 203 at 322:17-21)

U.S.C. § 271(a). To prove direct infringement, the patentee must establish that one or more claims of the patent read on the accused device literally or under the doctrine of equivalents. *See Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope, a question of law. *See id.* at 976-77; *see also Teva Pharms. USA, Inc. v. Sandoz, Inc.*, _ U.S. _, 135 S. Ct. 831, 837 (2015). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1337 (Fed. Cir. 2015) (citing *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998)). "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (quoting *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007)). "If any claim limitation is absent . . ., there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *Ferring B.V. v. Watson Labs., Inc.-Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (citing *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1552 (Fed. Cir. 1989) ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim.")). However, "[o]ne may infringe an independent claim and not

infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). The patent owner has the burden of proving literal infringement by a preponderance of the evidence. *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, _ U.S. _, 134 S. Ct. 1749, 1758 (2014).

2. Analysis

The question for infringement is whether Teva's ANDA product (an aqueous suspension made with prior art MFA) contains any patented MFM during the product's two-year shelf life. Teva produced samples from six different batches of its accused ANDA product to Merck. Merck performed testing on batch no. 3A911005S, "the development batch," manufactured in November 2009; batch no. 3A102095S, "the exhibit batch," manufactured in February 2011; and batch no. 3A508014S, a commercial-sized batch of Teva's ANDA product ("the commercial batch), manufactured in August 2015.[7] (D.I. 182, ex. 1 at ¶¶ 65-70)

a. Optical microscopy and single x-ray diffraction

"Polarized light microscopy . . . should be considered as a primary tool to support other solid-state characterization techniques, such as X-ray diffraction . . . ." "The optical properties of a crystal are controlled by its crystal structure and chemistry and so they can provide valuable analytical data to support structural data derived using other

[7] Teva also produced samples (not tested by Merck) of batch no. 3A102094S, a development batch manufactured in February 2011; batch no. 3A104011S, an exhibit batch manufactured in April 2011; and batch no. 3A111035S, an exhibit batch manufactured in November 2011.

techniques." (DTX 19[8] at 168) Polarized light microscopy is an analytical tool that may be used to determine the optical properties of crystals. (*Id.*) Interference colors "in crystals viewed between crossed polarizer are the result of the constructive and destructive interference of white light as one wave is retarded relative to the other" after they pass through the crystal and are "recombined in the analyzer." "Crystals having more than one refractive index are doubly refracting and are said to be birefringent. Birefringence is the numerical difference between the highest and lowest refractive indices." "When birefringent crystals are viewed between crossed polarizers and are rotated on the specimen stage, they become black every 90° due to extinction (when the vibration directions in the crystal are aligned with the vibration direction of the polarizer and the analyzer)." "When the extinction position is determined in relation to the shape of a crystal, it can be used as an indication of its crystal system." Crystals showing complete extinction are indicative of a "good quality, strain-free specimen." (*Id.* at 177-181)

Polymorphs "can often be distinguished from each other by their optical properties when observed using plane polarized light and crossed polarizers." Light microscopy "can provide chemists with an insight to the atomic structures of materials." "Optical crystallographic methods can also be used to indicate which of the seven crystal systems a crystal might belong to and, in some cases, can give clues about its crystal structure. A mixture containing different polymorphs can be examined and each could be distinguished because of their different optical properties." "[T]he most

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[8] G. Nichols, *Light Microscopy in Polymorphism in the Pharmaceutical Industry*, 167 (Hilfinker ed., 2006).

important accessory for a light microscope . . . is the eye-brain combination of the microscopist who has the experience to observe, understand and interpret images in a meaningful and analytical way. (DTX 20[9] at 290)

Although "[d]ifferent polymorphic forms of a compound are often characterized by having different shapes, . . . [d]ifferent crystal shapes shown by a compound . . . most likely reflect differences in the way they grew." (*Id.* at 304; see also DTX 16[10]) Processing may also affect crystal shape:

> During the development and production scale-up of a compound, the crystal shape or the length to breadth aspect ratio can vary between batches because of changes in the solvent, the saturation of the crystallizing solution, the cooling rate, or the stirring speed. A difference in the crystal shape for a compound may be recognized by light microscopy and this could be indicative of a different polymorphic form. In this case, another analytical technique (such as X-ray diffraction, Raman spectroscopy or solid state NMR) should be used to confirm that the crystal structure is actually different to that expected.

(DTX 19 at 192-93) The "United States Pharmacopoeia (USP) test for crystallinity describes a crystalline substance as one that shows interference colors and extinguishes every 90° of rotation. For most samples examined, the USP test is adequate." But it is not infallible. "The drug particles [dried with toluene] shown . . . are hexagonal prisms and are crystalline according to the USP test because they display interference colors and have extinction positions every 90° of rotation. However, powder X-ray diffraction pattern shows that they are highly disordered and practically amorphous." (*Id.* at 185-86)

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[9] G. Nichols et al., *Microscopy in Solid State Characterization of Pharmaceuticals*, 287 (Storey et al. eds.) (2011).

[10] Differences in external crystal shape may not necessarily indicate a change in the polymorphic crystal structure, as such variation may result from changes in crystal growth conditions. Joel Bernstein, *Polymorphism in Molecular Crystals*, 46-47 (2002).

After a crystal is selected, single crystal X-ray diffraction ("SCXRD") may be used to confirm the structure. A crystal is mounted and a beam of X-rays is passed through the crystal and measured from various angles. The data is compared to known standards to determine the identity of the crystal. Both MFA and MFM "show good birefringence, which indicates that both are highly crystalline material. The morphology is clearly distinct for these materials." MFM belongs to the orthorhombic crystal system and MFM to the triclinic system. MFA has acicular morphology and is needle and rod shaped, whereas MFM has plate-like crystals. (PTX 19[11] at 2499-502)

b. The expired samples

Merck's expert, Dr. Victor Young ("Dr. Young"), tested the development batch between September and November of 2015, approximately four years after its expiration date of November of 2011. In November 2015, he also tested the exhibit batch, approximately two and a half years after its expiration date of February 2013. To perform his testing, Dr. Young gave the bottle containing the product a small shake in order to disperse the suspension inside the spray bottle and sprayed a sample on a clean glass slide. He selected a particular crystal using optical microscopy; withdrew the crystal; mounted it onto a MiTeGen loop; and performed SCXRD on the crystal. (D.I. 201 at 57-63) Dr. Young indexed 10 MFM crystals in the expired batches – seven MFM crystals in the development batch and three MFM crystals in the exhibit batch. The crystals from the development batch were approximately 70-75 microns by 35-45

[11] X. Chen et al., *Solid State Characterization of Mometasone Furoate Anhydrous and Monohydrate Forms*, 94:11 J. Pharm. Sci., 2496 (November 2005).

microns. One of the crystals was 8 microns and one was 25 microns thick.[12] (*Id.* at 73-78; PTX 28) Dr. Leonard Chyall ("Dr. Chyall"), Teva's expert, did not dispute the crystallography findings. (D.I. 203 at 189)

Dr. Young opined, based on "looking at the development, exhibit batch and the commercial batch,"[13] that "the size of the crystals . . . roughly tracked the amount of time that product has been in the bottle," and concluded that MFM "forms at manufacture or shortly thereafter." (D.I. 201 at 51:15-19, 70:14-71:9, 242:18-243:7) Dr. Young did not see a "reason to even think to do" experiments to determine how much mometasone furoate was dissolved in the commercial batch at the time he tested it. Nor did he do or see a reason to do any kinetics studies. He admitted that he is not an expert in kinetics. He disputed his deposition testimony, wherein he stated that he was not an expert in nucleation and crystal growth, by testifying that he taught graduate courses in crystallography. (*Id.* at 126:17-127:6, 131-132) As Dr. Chyall explained, "Dr. Young didn't do any type of experiments to understand the kinetics of nucleation and crystal growth of MFM in these bottles, so he cannot extrapolate results that he obtained in 2015 back in time to provide evidence that the MFM was present in these batches during their shelf life."[14] The court agrees with Dr. Chyall's conclusions that "Dr. Young

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[12] Merck did not specifically call out the dimensions of the crystals from the exhibit batch.

[13] The testing of the commercial batch is discussed below. Dr. Young testified that if he had been able to test the commercial product after January 2016, the crystals would have been larger, as "crystal growth tracks the time in the Teva bottle." (D.I. 201 at 91:24-92:11)

[14] Nor did Dr. Young perform any testing to determine if the expired development and exhibit batches still met the stability specifications set forth in the ANDA. (D.I. 201 at 129:13-130:17; JTX 5 at 348-351)

just does not know when these crystals formed," and the testing "does not tell us anything about whether MFM was present before expiry." (*Id.* at 189:24-190:11) Instead, the testing of the expired samples only reveals that the MFM "appears at some point between when it was manufactured and when it was tested." (*Id.* at 215:11-16)

c. The non-expired sample

i. Testing

Dr. Young attempted to follow the same process to determine whether MFM was present in the commercial batch, but was unable to find large enough crystals for SCXRD analysis. He explained that "the crystals that were forming of [MFM] were very small in comparison to the" expired batches. The crystals were on the order of 10 microns and could not easily be extracted off of a wet glass slide. The extraction was made more difficult by the viscous and "soupy" nature of the liquid product. He stated that the crystals "needed to grow a little bit more over time" before he could "actually extract one and competently determin[e] its unit cell constants." (D.I. 201 at 76) He testified that in October 2015, he "found a putative crystal of [MFM], but it was less than ten microns." (*Id.* at 79:12-16) On October 5, 2015, Dr. Young wrote that he "looked for similarly shaped plates as found" in one of the expired samples. He selected a larger specimen which indexed to MFA. He wrote: "Comparing both specimens it was noted that the anhydrate crystals were more needle-like versus the squarish plates/blocks of the monohydrate. Also, the colors passing through as the polarizer is rotated near extinction appears different to the eye: the anhydrate is more colorful while the hydrate appears to gray-out at extinction." (PTX 28 at 6) On October 8, 2015, Dr. Young wrote that "it was relatively easy to distinguish [MFM] from MFA based on crystal shape and

colors using polarized light." On October 9, 2015, he wrote that "[i]t would be useful to have a better understanding of the morphology of the [MFM] specimens by indexing crystal frames." (*Id.* at 8)

On November 10, 2015, he found two "possible" MFM crystals, which were ultimately too small for X-ray crystallography. On November 11, Dr. Young looked for MFM in the commercial batch, but recorded that some "cells indexed to MFA or did not index at all due to small specimen sizes." (*Id.* 12) When asked about this entry, Dr. Young testified that he found some "broken blocks" or "glassy orthorhombic blocks" that he thought were MFA or something else and were worth investigating. He also testified that he rotated the crystals and looked for extinction properties, but "these were oddball crystals." He did not write details of this testing or describe his findings. (D.I. 201 at 138-139; 252) On November 18, 2015, he noted that he found two "putative" MFM crystals, which he transported to Argonne National Laboratory[15] on November 19. The crystals yielded "inconclusive data." (*Id.* at 107-113; PTX 28)

Dr. Young prepared wet slides on January 7, 2016 and saw dozens of MFM crystals. He performed a limited inspection noting crystals about 25 microns. The slides were stored in "snap top containers" in a storage area. On January 8, he reexamined the slides (now dry) and identified two crystals – one appeared to fracture and one measured 34 by 34 by 4 microns. This crystal indexed to MFM. On January 14, using the same slides, Dr. Young identified and harvested four more crystals. Two of these indexed to MFM and two yielded inconclusive data. (D.I. 201 at 81:9-20, 122:20-123:21, 244:3-7)

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[15] To use a more powerful SCXRD.

ii. SCXRD

The parties dispute whether the drying of the slides promoted crystal growth or "created an uncontrolled experiment." Dr. Young explained that he was not able to harvest MFM crystals from a wet slide

> because of the difficulty of withdrawing a crystal from the slide. The crystals were, more or less, at the edge of their detectability. They were . . . 25 to 35 microns in diameter, but . . . still rather thin plates of crystals. Being so thin, it was difficult to withdraw them from the glass slide while it was wet. I really did not want to run into a situation where I had debris adhering to the crystal or had Avicel or other crystals from the matrix occlude on them. So it was much easier to let the crystals dry on the slide, then peel back the film on top of the crystal and very carefully harvest it.

(D.I. 201 at 82:11-21) Dr. Young "viewed lots of slides where they were drying and . . . noticed no formation of new crystals of any sort, including [MFM]." He testified that "[d]rying itself doesn't provide a crystal. It's not part of our standard crystallographic practice. It doesn't happen." He saw "no reason" to track the crystal growth on the slides as they were drying, because "once the crystals are on the glass slide, they don't change." He also stated that dust could not have caused crystal growth. (*Id.* at 85-87) Dr. Young explained that he periodically sprayed some slides on December 9, 23, and 30, 2015 from the first bottle. He sought to determine "if the crystals were changing or growing or getting larger from spray to spray, and . . . would go back and look at the previous slides for comparison. [He] noticed no crystal growth and . . . no changing of the product from inspection to inspection . . . in December 2015."[16] (*Id.* at 80:11-81:8)

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[16] The Müller article (acknowledging funding by Merck) describes the selection and testing of a crystal to determine which polymorph was present in a particular product. Peter Müller, *Mometasone fuorate revisited, or how did the hydrate get in the bottle?*, C71 Acta Cryst., 1080 (2015). (PTX 23) A spray was applied to a glass slide; the slide was examined "under a polarizing microscope[, which] showed the presence of several

In Dr. Young's estimate, if new MFM crystals formed as the slide dried, they "would form a very uniform powder as the puddle dried from the edge to the center, or if it was anything else, it would be sort of a glassy material." Such crystals would be poor candidates for SCXRD.[17] (*Id.* at 244-245)

Dr. Chyall criticized Dr. Young's method and conclusions. In analyzing Dr. Young's laboratory notebook, he remarked upon the larger size of the crystal found on January 8, 2016. He opined that when Dr. Young allowed the wet slides "to dry over extended period of time, he provided an uncontrolled experiment," which "was actually conducive to formation of MFM on the microscope slide." Specifically, Dr. Chyall explained that "nucleation is the aggregation of molecules that form the starting point for the formation of a crystalline solid." In Dr. Chyall's opinion, the environment of drying slides "cause[s] concentration of the solutions and nucleation of MFM on the slide." He explained further that "[n]ucleation can occur just by having a highly concentrated solution or it could be facilitated by an imperfection on the slide, another solid impurity

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crystals of sufficient size and quality for X-ray structure determination and" a crystal was chosen; the crystal was then mounted and SCXRD performed. After determining that the product contained a monohydrate, it stated that it "is beyond the scope of this study to determine exactly how the monohydrate crystals may have formed" in the product tested. Dr. Young testified that the journal publication guidelines require that an experimental section "be very explicit for any particular methodology that is needed to reproduce the experiment." (D.I. 201 at 90:5-22) Merck concludes that the Müller article would have reported if harvesting crystals from a wet slide were important or if drying could affect crystal growth. (D.I. 191 at 36-37) The court does not find such argument persuasive, as the Müller article describes the methodology by which the crystal was harvested (from a wet slide) and the analysis of such crystal. Crystal growth on slides is simply not part of the article's focus.

[17] Merck's additional argument that slides used in Teva's internal testing dried during such testing, making Dr. Young's procedure proper, is inapposite. The slides for the internal testing were prepared differently and for a different purpose. (D.I. 191 at 43-44, redacted)

that's in the formulation, or even something from the ambient environment, such as a particle of dust." After MFM is nucleated, "it can continue to grow and form the crystalline species that Dr. Young analyzed a day to a week later." He concluded that "the drying is what promoted the nucleation of MFM on the slide such that the MFM crystal that [Dr. Young] analyzed a day later is not representative of what is in Teva's file of ANDA product." (D.I. 201 at 195-203)

iii. Optical microscopy

According to Merck, Dr. Young was ultimately able to reliably distinguish between MFM and MFA crystals based on their shape, extinction, and birefringence using optical microscopy, but first he needed a "learning period." The "learning period" (from when Dr. Young first began looking at the commercial batch in October 2015 to November 11, 2015) allowed him to get comfortable with the commercial batch.[18] (D.I. 201 at 78:11-79:9) As to why such a period was not noted in his laboratory notebook entry of November 5, 2015, Dr. Young testified that he "wasn't aware that [he] was going to have a learning period with this material at that point." (*Id.* at 101-102; PTX 28)

Dr. Young explained that the MFA material is micronized (mechanically ground) before being used in the ANDA product. MFM "grows clean out of the solution" and, therefore, cleanly extinguishes in 90-degree increments. (D.I. 201 at 64-65) He explained that

> the micronized material definitely appeared gray on the cross-polarized lens. And then when I say birefringence is consistent here, it's not just that

[18] It is not entirely clear when the "learning period" ended, as Merck's brief characterizes "[o]n November 10 and 18, 2015," as being "towards the end of the learning period." (D.I. 191 at 26) Dr. Young testified that the slide made on November 10, 2015 "would be the last slide" of his learning period, but also that his November 11, 2015 entry was "part of his learning experience." (D.I. 201 at 80:2-5, 108:19-24)

> it would blink on and blink off like we talked about before, rotating at 90 degrees. The thinner crystals would definitely have very, very strong coloration, green, blue, yellow, red, depending on how thick the crystal was. So that those differences, including the, the shape of the crystals and sort of the machining of the crystals made a good tool for me to differentiate MFM from MFA. . . . I'm looking for the optical properties of the light traveling through the crystal.

(*Id.* at 246:17-247:6) Following the "learning period," Dr. Young was confident in his ability to visually distinguish between MFM and MFA in the commercial batch. In summarizing his findings, he testified that he had identified "dozens and dozens" of MFM crystals on the wet slides from the commercial batch. Moreover, there was no chance he misidentified the crystals and he was one hundred percent confident that at least one of the dozens and dozens of crystals was MFM. (*Id.* at 245:17-247:16; 255:17-21)

Dr. Chyall disagreed with Dr. Young's reliance on visual observation alone, testifying that such observation "has to be coupled with X-ray crystallography of that same crystal in order to have any confidence of the chemical identity in the solid form of that crystal." (*Id.* at 188:12-20) Dr. Chyall explained that Dr. Young's notebook entries highlighted "the difficulty associated with just looking at crystals, especially when they are quite small." (*Id.* at 192:17-22) He opined that Dr. Young identified multiple "possible" MFM crystals, which he was then unable to index as MFM. (*Id.* at 192-195) Dr. Chyall also based his opinions on the literature (described above), which also specifies coupling optical microscopy with a more accurate method of measurement. (*Id.* at 205:1-20, 227:6-10; DTX 16, DTX 19)

Merck would like the court to conclude that MFM was present in the commercial batch based on Dr. Young's visual identification of crystals, but argues that he required

a "learning period" to get comfortable with the material.[19] Merck contends that the crystal shapes are different (MFA as needle or rod-shaped and MFM as plate-like) and, paired with other optical properties (like extinction), are sufficient for Dr. Young to conclusively tell the polymorphs apart. However, the literature explains that the shape of crystals may be affected by processing and even Dr. Young testified that the micronized MFA has a variety of shapes. (D.I. 201 at 118:16-22) Dr. Young did not document his findings regarding the shapes and extinction properties with much detail – compare his laboratory notebook entry of November 11, 2015 (no details on shape and extinction) with his testimony (details regarding both). Most significantly, the literature (and Dr. Young)[20] repeatedly describe optical microscopy as used in conjunction with another method (here SCXRD) for crystal identification.

d. Teva's internal testing

In *Schering Corp. v. Apotex Inc.*, 2012 WL 2263292 (D.N.J. June 15, 2012), the court evaluated expert testimony regarding Raman spectroscopy results performed on the product at issue in that case. Raman spectroscopy provides information about the

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[19] Dr. Young did admit to misidentifying a crystal at his deposition. At trial, he explained that he answered the question incorrectly and that he had not misidentified the crystal. (D.I. 201 at 83:7-16) According to Teva, the misidentification is related to the November 11, 2015 entry. (D.I. 194 at 18)

[20] When asked if "optical microscopy alone [was] sufficient to identify distinctions between" MFM and MFA, Dr. Young responded that "we have to couple that with X-ray crystallography to get a definitive result." Optical microscopy shows "the shapes of crystals to select, but it does not show . . . the crystal structure that's underlying it." SCXRD "is the gold standard" for "determining the three-dimensional crystal structure of a particular material" and it provides "the complete crystal structure." (D.I. 201 at 65:23-66:15) "I am always coupling my X-ray crystallography and optical microscopy together." (*Id.* at 105:1-4) "I've always coupled optical microscopy with X-ray crystallography. Optical microscopy is the first point for selecting a crystal that would ever go on an X-ray diffractometer. . . . They must be paired together for any useful crystallographic result." (*Id.* 114:13-23)

vibrational modes of bonds in a molecule and may be used for sample identification. The court concluded (based on expert testimony) that at least three peaks on a spectra must be used to identify material based on accepted practices.[21] *Id.* at *7-10. At bar, Merck presents the testimony of Teva's 30(b)(6) deposition witness, Dr. Ayoub, who was asked questions regarding certain Merck generated print-outs from Teva's Raman spectroscopy data. Having reviewed the testimony, the court concludes that Dr. Ayoud did not, as Merck argues, admit that the data showed the presence of MFM; instead, he simply testified that he could see a peak at 1710 cm^{-1}. He explained that such visual observation was not a proper interpretation of the results of Raman spectroscopy, instead, the system's software analyzes the data and provides a determination of the content of the sample. Setting aside the lack of expert testimony,[22] and having also reviewed the confidential arguments and exhibits,[23] the court concludes that the internal testing does not establish the presence of MFM in Teva's ANDA product.[24]

3. Conclusion

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[21] Merck argues that the need for three peaks only applies to the x-ray crystallographic powder diffraction pattern analysis opined on by the expert in *Apotex* and not to Raman spectroscopy. The Federal Circuit heard the same argument from Merck and subsequently affirmed the district court's judgment. *See Merck Sharp & Dohme Corp. v. Apotex Inc.*, 517 F. App'x 939 (Fed. Cir. 2013) (Rule 36 affirmance).

[22] Which the court concludes would be necessary for proper analysis of the issue at bar. *Centricut, LLC v. Esab Grp., Inc.*, 390 F.3d 1361, 1369 (Fed. Cir. 2004) ("Where the field or art is complex, we have repeatedly approved the use of expert testimony to establish infringement."). The parties agreed not to present experts on this issue in order to narrow the scope of the trial. (D.I. 174)

[23] Redacted material from D.I. 191, 194, JTX 5, 6, and PTX 4, 5, 7, 12-15.

[24] The court declines to reach Teva's collateral estoppel argument.

The court concludes that the expired samples are not representative of the ANDA product. Without testimony (or evidence) of when the MFM crystals formed in the expired products, the conclusory statements provided by Dr. Young do not establish infringement. Moreover, at no point during his testing of the commercial batch did Dr. Young harvest an MFM crystal from a wet slide (as he did for the exhibit and development batches). (D.I. 201 at 82:5-21) Instead, Dr. Young identified three MFM crystals from slides which had dried. Dr. Chyall has offered up a reasonable criticism of such findings. At bar, Dr. Chyall's testimony is more credible and consistent.[25] Most significantly, the literature and the experts consistently pair optical microscopy with another measurement method before conclusively distinguishing polymorphs. For these reasons, the court finds that Merck has not established, by a preponderance of the evidence, the presence of MFM in Teva's ANDA product during its two-year shelf life.

III. CONCLUSION

For the foregoing reasons, the court finds that the '353 patent is valid and not infringed. An appropriate order shall issue.

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[25] The parties' respective arguments regarding the experts have been considered by the court. (D.I. 191 at 39-41; D.I. 194 at 34-39) Merck's argument that Dr. Chyall does not know how to perform SCXRD is irrelevant. Dr. Chyall did not dispute the crystallography findings, only the manner in which the crystals were collected, an area within his expertise. As to his opinions regarding optical microscopy, that Dr. Chyall did not inspect the product does not foreclose his opinions regarding Dr. Young's methods, particularly when such opinions are supported by the literature. As to Teva's criticisms regarding Dr. Young (misidentification of crystals; testimony regarding the use of optical microscopy alone for identification; less than detailed notebook entries; and "learning period"), the court finds such criticisms go to the credibility of the witness and the weight assigned to such testimony.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

MERCK SHARP & DOHME CORP.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	Civ. No. 14-874-SLR
	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
	)	
Defendant.	)	

ORDER

At Wilmington this 10th day of November 2016, consistent with the opinion issued this same date;

IT IS ORDERED that:

1. The asserted claims of the '353 patent are valid.

2. Defendant does not infringe the asserted claims of the '353 patent.

3. The clerk of court is directed to enter judgment in favor of plaintiff and against defendant as to the validity of the '353 patent, and in favor of defendant and against plaintiff as to the infringement of the '353 patent.

United States District Judge