IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

MERCK SHARP & DOHME CORP.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 15-250-SLR
	)	
AMNEAL PHARMACEUTICALS LLC,	)	
	)	
Defendant.	)	

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OPINION

Dated: January 30, 2017
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of Abbreviated New Drug Application ("ANDA") No. 207989 by defendant Amneal Pharmaceuticals LLC ("Amneal") seeking to produce and market a generic mometasone furoate nasal spray. (D.I. 56) On March 20, 2015, 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 September 4, 2015,[2] which Amneal answered on September 18, 2015. (D.I. 56; D.I. 59) 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. 107[3]) The court held a final pretrial conference on June 7, 2016, and a two-day bench trial on June 21 and 22, 2016 on the infringement issue. The parties have since completed post-trial briefing. The 30-month stay of FDA final approval on Amneal's ANDA expires on August 4, 2017. (D.I. 142, ex. 1 at ¶ 46) 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).

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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. 56 at ¶ 15)

[2] Agreed to by stipulation (D.I. 51) and so ordered by the court.

[3] The parties agreed to be bound by the claim construction and invalidity decisions in the co-pending litigation *Merck Sharp & Dohme Corp. v. Teva Pharmaceuticals USA, Inc.*, Civ. No. 14-874-SLR (D. Del.). The court concluded that the asserted claims of the '353 patent were valid. (Civ. No. 14-874, D.I. 133, 204, 205)

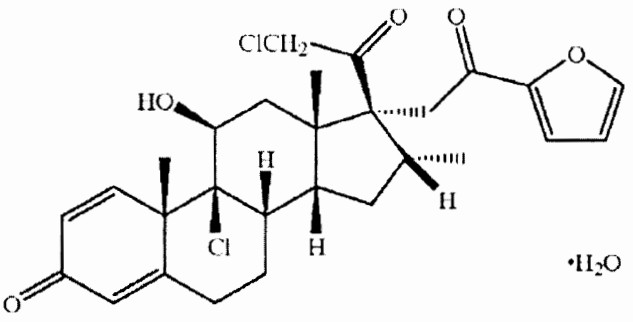
II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. Technology at Issue

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. 163 at 4) 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.*)

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. 163 at 46; '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. (D.I. 163 at 5; PTX 18[4])

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. 163 at 6) The formation was further developed and ultimately was approved as Nasonex. The formulation is protected by the '353 patent. (*Id.*)

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 (D.I. 142, ex. 1 at ¶ 26) The product insert for Nasonex states: "[Nasonex] Nasal Spray 50 mcg is a corticosteroid demonstrating potent anti-inflammatory properties." (*Id.* at ¶ 35) 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 ¶ 34)

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 alleges infringement of independent claims 1 and 6 and dependent claims 9-12. (D.I.

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[4] Xioming Chen et al., *Solid State Characterization of Mometasone Furoate Anhydrous and Monohydrate Forms*, 94 Journal of Pharmaceutics Sciences (2005) ("the Chen article"). (PTX 18)

142, ex. 1 at ¶ 15) 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."

4. The accused ANDA product

Amneal's ANDA product is a generic mometasone furoate nasal spray, 50 mcg, using MFA as the active pharmaceutical ingredient. Amneal's ANDA product has a proposed shelf-life of two years. Merck does not allege that the pre-formulation active pharmaceutical ingredient used in Amneal's ANDA product contains MFM or otherwise infringes the '353 patent. (D.I. 142, ex. 1 at ¶¶ 43-47; D.I. 163 at 3; PTX 23)

B. Infringement 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 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).

C. Analysis

The question for infringement is whether Amneal's ANDA product (an aqueous suspension made with prior art MFA) contains any patented MFM during the product's two-year shelf life.[5]

1. Samples

Amneal produced samples of Batch Nos. BB-ST-13003A (manufactured October 28, 2013), 13005A (manufactured November 22, 2013), and 13006A (manufactured December 9, 2013) (collectively "the Exhibit Batches") and samples of Batch No. RD-3965-162 ("the R&D Batch") to Merck.[6] (JTX 8-10, 14-16) The samples were packaged in nasal spray bottles, Amneal's finished product form. (D.I. 176 at 55:17-23, 110:23-111:5) Amneal produced samples from Batch No. RD-3965-157 ("the Commercial Batch"), after which Amneal changed its manufacturing process. The court ruled that evidence of MFM in such samples could not be used to show infringement.[7] (D.I. 89,

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[5] Merck contends that the MFA in Amneal's product will eventually convert to MFM and the only question is "when" the conversion will occur. (D.I. 163 at 45) Amneal disputes both "if" and "when" the MFA in its ANDA product will convert to MFM, arguing in part that even Merck's expert, Dr. Adam Matzger ("Dr. Matzger"), opined that there are some MFA formulations that will not convert. (D.I. 165 at 29-30; D.I. 176 at 125:22-126:1) The parties spend considerable energy discussing the evidence put forth regarding conversion and disputing the issue of "if" conversion will occur. The court only addresses the arguments material to the infringement question.

[6] Merck tested the R&D Batch, but did not analyze the results, because it determined that the R&D batch was not relevant to infringement. (D.I. 176 at 87:10-12)

[7] The court allowed Dr. Matzger to answer a few questions regarding the Commercial Batch, explaining that such information might be appropriate if it pertained to the likelihood of conversion (from MFA to MFM) in the sample environment. Dr. Matzger testified that he identified MFM crystals in the Commercial Batch using both Raman spectroscopy and single crystal XRay diffraction ("SCXRD"), the gold standard for polymorphic identification. He opined that he was able to perform SCXRD, as "the crystals had grown for about a year-and-a-half, so they were larger." (D.I. 176 at 67:2-21, 68:25-69:5, 69:22-70:9) None of the elicited testimony is helpful to the question at bar.

98, 154) Amneal produced samples of another commercial-sized batch, Batch No. BB-ST-16001 ("Batch 16001") in glass bottles. (D.I. 130; D.I. 176 at 110:20-111:5; JTX 5, 13) The samples produced were drawn after manufacture on January 11, 2016 ("Batch 16001 Day 1"). Three days later, on January 14, 2016, the batch was mixed and a certain portion was removed and packaged in nasal spray bottles ("Batch 16001A"). The next day, the batch was mixed, samples were drawn ("Batch 16001 Day 4"), and the remainder was packaged in nasal spray bottles ("Batch 16001A").[8] (JTX 11-12) Amneal stipulated that the Batch 16001 Day 1 samples produced to Merck are representative of its ANDA product. (D.I. 130)

2. Merck's thermodynamic stability study

Merck's expert, Dr. Matzger, conducted a thermodynamic stability test "to establish the thermodynamic stability of the monohydrate relative to the anhydrous form." He added an amount of MFM equal to the amount of MFA in one of the sample bottles from the Exhibit Batches and subjected the bottle to vigorous shaking at 500 RPM. After 27 days, all of the MFA had converted to MFM. He explained that shaking "increase[s] mass transport" to help the conversion from the "less stable form . . . to the more stable form" and "break up the viscosity" of the suspension. Dr. Matzger concluded that "the monohydrate is the more stable form in the environment of Amneal's formulation." He testified that the study established that "conversion will occur," but not "when it will occur." He further explained that he "intentionally added [MFM] so that the conversion could take place with both forms present, and so [he]

[8] The court adopts the parties' nomenclature of referring to the ANDA product packaged in nasal-spray bottles on consecutive days as Batch 16001A. (D.I. 163 at 8-10)

wouldn't know if [MFM] would become present or when it would become present if [he] hadn't added it;" a person of skill in the art would "need to know all of those things to say what the rate would be in the proposed ANDA product."

(D.I. 176 at 60-63, 114:19-23) Amneal's expert, Dr. Robin Rogers ("Dr. Rogers"), does not dispute the findings of the study, opining that the addition of MFM "changed the rate of nucleation" and the kinetics, such that the formulated product "now had a crystal form that it preferred." (D.I. 177 at 427-429)

3. Batch 16001

Merck's expert, Dr. Bernhardt Trout ("Dr. Trout"), explained that polymorphic conversion is governed by the "basic principles of thermodynamics and chemical kinetics." Further, polymorphic conversion involves nucleation, which "is the first step in which the smallest crystal of the new polymorph is formed. And then the second step . . . is growth, where that crystal then grows to a larger crystal." As polymorphic conversion is affected by energy and collisions, "the more one mixes, the more vigorously something is mixed, the more energy [and] the more collisions are imparted."[9] (D.I. 176 at 197-199, 208:16-209:5) An unstable system tends to convert to a stable system. (*Id.* at 222:25-223:8) Dr. Trout opined that it is "very difficult to make

[9] Referencing Chong-Hui Gu, Victor Young, Jr., and David Grant, *Polymorph Screening: Influence of Solvents on the Rate of Solvent-Mediated Polymorphic Transformation*, 90 Journal of Pharmaceutical Sciences 11, (2001) ("the Gu article"). (DTX 180) Dr. Trout explained that the Gu article is an example of "one solid crystalline form transforming to another and the effects of agitation" thereon. (D.I. 176 at 258:2-7) Dr. Trout admitted that the Gu article did not specifically study MFA or MFM and focused on solvent mediated transformation of a chemical called SMZ. Moreover, the mixing was done with a wrist shaker. (D.I. 176 at 232-233) The court concludes that the Gu article is not helpful to the issue at hand, i.e.,whether mixing would facilitate the conversion of MFA to MFM in the aqueous pharmaceutical suspension at bar.

predictions" on how mixing would affect a specific system, and "to verify in a given sample whether there was conversion, it needs to be tested empirically." (*Id.* at 199:12-17, 207:11-18, 236:11-237:21) Applying these principles to Batch 16001, he concluded that "[m]ore vigorous mixing enhances the likelihood of nucleation. And once nucleation has occurred, for example, as Dr. Matzger said in the [Batch] 16001 Day 1 sample, the additional mixing, the vigor of the mixing, the collision imparted [and] the energy imparted by this industrial mixing would increase the likelihood of growth of [MFM] in the nucleated system." (*Id.* at 208:14-209:3) He also concluded that "as a whole, the vigor of the mixing of the 16001 Batch was greater than that of the Exhibit Batches." Moreover, the concentration of the MFA varied within the manufacturing process, which might also affect the conversion. (*Id.* at 201-204, 265:22-268:3; PTX 97, 98)

Dr. Matzger testified that "the way you mix something [and] the vigor with which you mix something affects the polymorphic conversion." (D.I. 176 at 108:8-16) Therefore, he "would expect to see at least as much" MFM in the later samples of Batch 16001 as in the Batch 16001 Day 1 sample, and would expect that "the amount would have increased," because "the additional mixing, if anything, would be expected to increase conversion."[10] (*Id.* at 111:20-112:23) Dr. Matzger admitted that he did not investigate a rate of conversion in response to mixing speed, and stated that the conversion is a solution mediated process. (*Id.* at 135-137)

Dr. Rogers disagreed with Dr. Trout's opinions, testifying that the conversion of MFA to MFM is difficult, as there is a high energy barrier. He explained that in a

[10] The actual mixing speeds and times for the various samples are redacted. (JTX 7-10; DTX 26)

solution, conversion is a three-part process – dissolution of the crystal form, nucleation, and crystal growth of the new form. He opined that MFA "has very good physical stability under humidity."[11] (D.I. 177 at 417-420) He described that the Exhibit Batches and the 16001 Batch "were subjected to the highest energy stirring" for the same amount of time. Therefore, if the high energy could cause conversion, there should have been MFM present in the Exhibit Batches.[12] As to the 16001 Batch, he opined that Dr. Trout's "cumulative mixing" theory fails to take into account the periods of rest in between the later mixing steps. (*Id.* at 433-440, 444:23-445:17) He agreed that concentration can be related to how fast a material crystalizes and that "theoretically, it is possible" that "increasing mixing or agitation[] sometimes can result in an increase of the nucleation rate of a crystal." (*Id.* at 465-466)

The parties dispute whether Amneal should have provided samples from Batch 16001 Day 4 and Batch 16001A ("additional samples") to Merck.[13] Amneal asserts that the additional samples would be cumulative to those provided (Batch 16001 Day 1 and the Exhibit Batches). Merck requests that the court conclude that the additional samples would have contained MFM because of the additional mixing. From the expert testimony, the court concludes that generally additional (or faster) mixing tends to promote conversion of MFA to MFM. Neither party, however, has offered a

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[11] Referencing the Chen article. (PTX 18) Dr. Trout criticized reliance on the Chen article because it studied the physical stability under humidity, which is completely different than an aqueous suspension. (D.I. 176 at 250-51)

[12] Dr. Rogers also opined that agitation can increase or decrease the rate of nucleation in a particular system. J.W. Mullin, *Crystallization: Chapter 5, Nucleation*, 191 (4th ed. 2001). (DTX 84) Dr. Trout criticized the reliance on this reference, opining that it focuses on nucleation in a solution not in an aqueous suspension. (D.I. 177 at 492-93)

[13] This has been an ongoing dispute. (D.I. 130, 131, 134)

quantification of how the additional (or faster) mixing might affect the dissolution of MFA, or the nucleation and crystal growth of MFM in Amneal's ANDA product. The experts agree that the thermodynamic study does not inform this determination, as it is not representative of the ANDA product (because of the addition of MFM) and did not measure the effect of mixing speed or time on the rate of conversion. The expert testimony – that conversion is system-dependent and the additional mixing performed on Batch 16001 likely would have promoted conversion – renders any conclusion regarding Batch 16001 Day 4 and Batch 16001A theoretical.[14] On the evidence presented, the court concludes that Merck has not demonstrated that the additional samples would yield different results.[15] Consequently, the court denies Merck's

[14] The Müller article (acknowledging funding by Merck) describes the selection and SCXRD testing of a crystal to determine which polymorph was present in a sample of Apotex nasal spray marketed in Canada. The testing identified an MFM crystal present in the sample before the expiration date of the product. Peter Müller, *Mometasone fuorate revisited, or how did the hydrate get in the bottle?*, C71 Acta Cryst., 1080 (2015). (PTX 12) Merck argues that this article establishes "that MFA can convert to MFM within the shelf life of an aqueous pharmaceutical suspension that is formulated with MFA." (D.I. 163 at 16) Merck points to Amneal's counsel argument that the formulation at bar is virtually identical to that found non-infringing in the *Apotex* litigation. (D.I. 176 at 39:12-20); *Schering Corp. v. Apotex Inc.*, 2012 WL 2263292 (D.N.J. June 15, 2012) ("the *Apotex* litigation"). The court does not find such argument persuasive as the experts at bar have testified that conversion from MFA to MFM is particular to a system. The court will not (without expert testimony) conclude that the formulation at bar would behave in the same fashion as that tested in the article.

[15] Nor has Merck demonstrated that Amneal's failure to produce additional samples of Batch 16001 warrants an adverse inference. Indeed, Merck did not respond to Amneal's arguments against such an inference in its reply brief. (D.I. 163 at 53-54; D.I. 165 at 54; D.I. 168 at 28-29); *Braintree Labs., Inc. v. Novel Labs., Inc.*, 2015 WL 3492936 at *13 (D.N.J. June 1, 2015) (citation omitted) (An imposition of adverse inference was not required when defendant "ha[d] not shown any prejudice, surprise, or bad faith on the part of" plaintiff.).

alternative request for the production of 16001 Day 4 and 16001A samples and a new trial.[16]

4. Raman spectroscopy

Raman spectroscopy is a vibrational spectroscopy technique, which looks at the way a molecule vibrates in a crystal. A microscope is coupled to an excitation laser and a spectrometer. The laser is used to generate a Raman spectrum, which indicates the vibrational modes of molecules and is used to differentiate between crystalline forms. A Raman spectrum is a plot of the intensity (vertical axis) as a function of the vibrational frequency (horizontal axis). Raman maps are a collection of Raman spectra (from a hundred to over a million), which may then be analyzed by algorithms (or viewed individually) to determine potential matches to a reference standard. Reference standards are Raman spectra of known compositions. (D.I. 176 at 64-67, 78:20-79:6)

5. Merck's testing of the Exhibit Batches

Dr. Matzger used a Renishaw Raman spectrometer with point focus mapping ("point focus spectrometer"). This technique focuses the laser on a point and then steps the laser to different positions on the sample to generate the Raman spectra. In December 2015, Dr. Matzger switched to using a Renishaw StreamLine® Raman spectrometer ("StreamLine spectrometer"), which allows for the collection of more data by elongating the laser into a line and moving the sample continuously. (D.I. 176 at 75:20-23, 76:4-9, 106:1-4; *see also* D.I. 177 at 318:23-319:9) According to Dr. Matzger,

[16] Merck asserts that whether Amneal should produce the samples is governed by Federal Rule of Civil Procedure 26(b)(1), and contends that "it has established that the additional mixing that the 16001 Day 4 and 16001A samples underwent increases the likelihood of formation of MFM, thereby making those samples relevant to infringement." (D.I. 168 at 26)

the StreamLine spectrometer "spreads [the laser] power out more evenly over the sample, so it tends to reduce the chance of damaging the sample with the laser." (D.I. 176 at 76:18-20)

Dr. Matzger tested samples from four bottles of the Exhibit Batches over a period of eight months starting in June 2015. He agreed that he did not find MFM in any of the samples, and that some of the tested samples were over two years old. (*Id.* at 71:11-72:5, 87:5-9, 127:13-128:13; PTX 40) He testified that he used both point focus spectroscopy (for samples tested prior to December 2015) and StreamLine spectroscopy (for samples tested after December 2015) to test the Exhibit Batches and there was no difference in the results. (*Id.* at 123:20-24, 178:13-181:10)

The parties disagree on whether the Exhibit Batches are representative of the ANDA product.[17] Merck argues that the Exhibit Batches are not representative of the ANDA product, as they were not packaged according to the current Master Packaging Batch Record and were mixed significantly less vigorously than the Batch 16001 Day 1. (D.I. 163 at 18-19; D.I. 176 at 202-203) Dr. Matzger tested the Exhibit Batches, but did not rely on the results for his ultimate infringement opinion. (D.I. 163 at 28) Amneal, on the other hand, maintains that the Exhibit Batches are its ANDA product, arguing that it used the Exhibit Batches to conduct testing (including the bioequivalence studies) required by the FDA. (JTX 4, 5) For these reasons, Amneal references Dr. Matzger's testing of the Exhibit Batches in its non-infringement arguments. (D.I. 165 at 31)

[17] Merck states that on the record at bar, the Exhibit Batches were mixed at one-third to one-half of the lowest acceptable values specified by Amneal's current ANDA. (D.I. 168 at 1-2) Although Amneal's counsel represented that typographical errors existed regarding the mixing speeds, on the evidence presented, the court accepts Merck's representations. (D.I. 165 at 15, 32-33)

There can be no dispute that Amneal provided data to the FDA obtained by testing the Exhibit Batches. The court addressed the issue of additional (or faster) mixing above. The court concludes that the testing of the Exhibit Batches (some of which were tested after the two-year expiration) is relevant to the question of infringement.

6. Merck's testing of Batch 16001 Day 1

Dr. Matzger tested seven slides prepared from one bottle of Batch 16001 Day 1. Specifically, he briefly shook the glass bottle, used a pipette (or poured) to transfer some material to the slide, allowed the slides to dry, and stored them in Petri dishes. (D.I. 176 at 73:10-74:18, 101:11-25) He performed StreamLine spectroscopy on the slides and generated Raman maps made up of millions of individual spectra. He compared certain individual spectra (under 10% of spectra generated) to reference spectra of MFM and MFA generated on the same equipment.[18] (*Id.* at 74:24-76:9, 78:20-79:22, 168:25-169:16; PTX 40) He explained that MFM has a characteristic peak (not shared) around 1709 cm^{-1}, MFA has a characteristic peak at 1725 cm^{-1}, and the two polymorphs share a peak in the range of 1640-1680 cm^{-1}. (D.I. 176 at 81:17-83:4; PTX 70)

By the characteristic peak at 1709 cm^{-1}, Dr. Matzger identified five MFM crystals on three slides (the slide prepared February 8, 2015 had three particles and the slides

[18] Dr. Matzger explained that a reference standard is collected with a high signal to noise ratio, allowing the visualization of "all of the peaks that would be different between the two forms" and the identification of "other maybe minor characteristic peaks." (D.I. 176 at 188:7-189:3)

prepared on March 13 and 19, 2016 each had one particle).[19] Each of the spectra indicated the presence of both MFM (characteristic peak at 1709 cm^{-1}) and MFA (from characteristic peaks including the one at 1725 cm^{-1}).[20] (D.I. 176 at 89-98, 158:4-13; PTX 75-76, 79-80, 84-87) Dr. Matzger testified that he could not see any other characteristic peaks for MFM "because of the signal to noise limitation." (D.I. 176 at 158:12-13, 160:22-161:5) He opined that noise occurs in all spectra and, in a pharmaceutical product with a small amount of active ingredient, "noise will always be present." (*Id.* at 190:10-16) He explained that he took into account the signal to noise ratio in his analysis and that a peak is considered significant if the ratio exceeds 2/1 or 3/1.[21] The signal to noise ratio in one spectra was 4.3/1 and, after "smoothing," it "improved somewhat to" 4.7/1. (*Id.* at 93:6-24) Dr. Matzger explained that "smoothing" increases the signal to noise value of a particular spectrum, at the expense of resolution. It is accomplished by taking "three adjacent peaks and averag[ing] them

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[19] Dr. Matzger opined that he did not find MFM particles on the other four slides, but did not perform extensive searches of those slides, as the searches were time consuming. He "didn't see the point of doing additional searching" after identifying MFM on the other slides. (D.I. 176 at 87-88, 153:24-154:9) He also explained that he would not have had time to perform an extensive analysis of the other four slides. (*Id.* at 186:24-187:20) He testified that when particles are very small (as in the samples at issue), "[t]he search algorithms are just not that reliable," and potential matches must be inspected by hand. (*Id.* at 67:25-68:5)

[20] Dr. Matzger opined that none of the excipients would have a peak at 1709 cm^{-1}. He did not analyze pure samples of the excipients in the ANDA formulation, nor a placebo containing all of the ingredients except the API to determine if any other peaks existed in the general vicinity of 1709 cm^{-1} to 1711 cm^{-1}. He stated that he "had a number of experiments where there was excipient and [he] did not identify peaks at that location." (*Id.* at 165-167) He also relied on Amneal's ANDA stating that "excipient spectra will not have peaks at wave numbers 1725±3 (or 1705), 1611 cm-1." (PTX 26 at AMLMF 4670)

[21] Validation of Compendial Procedures, USP 37. (PTX 67 at 3)

together."[22] He indicated for a particular spectra that "the[] two peaks are well resolved. You can see the separation between them well enough that the reduction in resolution is not an issue." (*Id.* at 90:6-91:11; PTX 80) Dr. Matzger testified that he also considered the width and shape of the peak to evaluate whether the peak was MFM as opposed to an artifact.[23] (*Id.* at 94:7-20)

Amneal's expert, Dr. Brian Marquardt ("Dr. Marquardt"), analyzed the five spectra from Dr. Matzger's report and opined that a "shoulder peak" indicative of MFA "could be easily misinterpreted . . . as a peak in that space and be misrepresented as MFM," given the concentrations and the signal to noise levels. He further explained that the spectra show that "this is primarily the MFA form, which is indicated by th[e] secondary doublet and the primary peaks . . . , which are indicative of both forms. And it is my opinion that Dr. Matzger misinterpreted this data as MFM." He concluded that MFM was not present. (*Id.* at 310-311; DTX 138) Dr. Marquardt testified that in his study of the API particles, the Raman spectra were "well above" a signal to noise ratio of 20/1. (*Id.* at 308:5-10)

Dr. Matzger opined that a single characteristic peak is sufficient to distinguish between MFM and MFA, as "based on the inspection of the reference patterns, you can find one where they're well separated." When asked if a single peak was sufficient to distinguish between MFM and MFA in Amneal's product, Dr. Matzger responded that Amneal "did a similar analysis . . . and . . . also relied on a single peak in order to

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[22] In contrast, Dr. Marquardt opined that applying a smoothing algorithm to high resolution Raman spectra, like that of Dr. Matzger, "can actually cause [one] to misinterpret, possibly even generate [an] artificial peak." (D.I. 177 at 309:8-20)

[23] Dr. Matzger opined that his spectra are "essentially the same" as certain of Amneal's spectra from a limit of detection study. (D.I. 176 at 100:22-101:10; PTX 39, 84)

differentiate the monohydrate and the anhydrate."[24] He testified that he uses a single peak "commonly to generate Raman maps." (D.I. 176 at 82-83; PTX 70) In contrast, Dr. Marquardt testified that he "standardly use[s] three peaks" to identify a compound in a complex mixture, because "using three peaks gives us an absolute confirmation of its presence, and it provides us the specificity we need to confirm." He opined that it would be appropriate to rely on one peak "at times," for example "in the determination of the limit of detection . . . where we add the material to the system, and we watch it actually come in and grow into the system because we're adding known amounts." (D.I. 177 at 301:20-302:12)

Dr. Matzger testified that the particles of MFM were in the range of 1-2 microns, but he was unable to measure the size. (*Id.* at 169:17-170:12) Dr. Marquardt explained that using a scale factor, Raman instrumentation allows the visualization of particles that are one to ten microns in diameter. (D.I. 177 at 323:7-16; *see also* 463:22-464:6)

Dr. Matzger testified that he would expect the amount of MFM to increase over time due to crystal growth, but he did not analyze whether the identified MFM particles did so.[25] (D.I. 176 at 129:11-14, 167-169) Dr. Rogers reviewed Dr. Matzger's laboratory notebook, noting that Dr. Matzger prepared a slide on February 8, 2016 and performed spectroscopy on it gathering data from February 8-10, and identifying three micron sized particles of MFM. He testified that Dr. Matzger prepared slides on

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[24] Amneal performed and provided the results of certain testing to the FDA, including Raman spectroscopy. (PTX 38) One of Amneal's scientist agreed that they "would look at 1705 for monohydrate and 1725 for anhydrate" during testing. (D.I. 176 at 278:20-279:4, 283:6-8; PTX 26, 38)

[25] Merck points out that it asked Amneal multiple times if it would be allowed to supplement the testing and Amneal refused, therefore, Merck did not request supplementation of the expert record from the court. (D.I. 176 at 171:3-23)

February 15, March 5, and March 12, and performed spectroscopy on each without identifying any MFM particles. Dr. Matzger then prepared a sample on March 13 and another on March 19. For each of these slides, Dr. Matzger performed spectroscopy six days later identifying one micron-sized particle on each slide. Dr. Matzger prepared a seventh slide on March 26, 2016 and performed spectroscopy on it, but did not identify any MFM particles. Dr. Rogers disagrees with Dr. Matzger's conclusion about the presence of MFM in Batch 16001 Day 1, explaining that "it can't be correct because if MFM had been in there, it would have grown in both size and number. It would have been easier to detect and he would have found a lot of it by the end." (D.I. 177 at 431:9-433:5)

Dr. Matzger relied on his identification of one peak on a Raman spectra to conclude that MFM particles were present in the tested Batch 16001 Day 1 samples. He opined that a single peak is sufficient to identify MFM in the ANDA product, but admitted that he could not see any other characteristic peaks for MFM because of the signal to noise limitation. In contrast, Dr. Marquardt testified that three peaks are generally used to identify a polymorph in an unknown sample. 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. 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.[26, 27] *Id.* at *7-10. The court assigns little weight to Dr. Matzger's identification of MFM based on a single peak under these circumstances.

7. Amneal's testing of Batch 16001 Day 1

Dr. Marquardt[28] analyzed ten samples from two bottles of Batch 16001 Day 1. Specifically, five drops of material were placed on a slide, the slides were dried and viewed under a HORIBA Scientific LabSpec 6 Raman microscope. Thirty API particles were measured on two slides. Point focus spectroscopy was performed – two slides with wide area mapping (4.5 micrometers steps) and six slides with high spatial resolution mapping (2.5 micrometers steps). (D.I. 177 at 314-318; DTX 79, 133) Dr. Marquardt analyzed the Raman spectra and compared them to reference spectra of MFM and MFA, obtained using "individual points at the same accumulation time and integration time." He examined 200 API particles using the three methods and did not identify any MFM in the samples. (D.I. 177 at 323-326, 330, 333:3-334:7, 390:20-23)

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[26] 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 the *Apotex* litigation 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).

[27] The court declines to reach Amneal's collateral estoppel argument.

[28] Dr. Marquardt is the CEO and founder of MarqMetrics, a company providing measurement solution services and developing Raman technology. (D.I. 177 at 297:17-298:3) Dr. Marquardt's assistant at MarqMetrics, Dr. Andrew Knight ("Dr. Knight"), prepared the slides and performed the Raman testing under Dr. Marquardt's direction. Dr. Knight has experience in crystalline materials. (*Id.* at 327, 389:5-8) Having reviewed Dr. Marquardt's background information, the court disagrees with Merck's representation that Dr. Marquardt is only an expert in Raman spectroscopy "in a general sense," and that neither he nor MarqMetrics has the requisite experience or skill to conduct any meaningful tests of Amneal's ANDA product. (D.I. 163 at 38-41) The court separately addresses Merck's specific concerns regarding Dr. Marquardt's testing.

The particles were selected by scanning the microscope stage in real-time and viewing a "very noisy, very fast Raman spectrum" until observing "large indicator peaks" at 1470 cm^{-1} and 1660 cm^{-1}. (*Id.* at 326:8-327:1) Dr. Marquardt testified that he was not "trying to perform a massive amount of scans and not look at the data." Instead, he tried to do "a fundamental objective design of experiments, where we could assess the quality of the information that we collected, and then be able to make a conclusive determination about whether there was or was not the presence of MFM in our Raman data." (*Id.* at 319:18-25) Dr. Marquardt agreed that his testing of Batch 16001 Day 1 reflects the content of the sample at the time of testing. (*Id.* at 349:16-25)

According to Dr. Matzger, Dr. Marquardt did not "collect[] a sufficient number of spectra [or] data . . . on a significant number of particles within those spectra to draw the conclusions that he has drawn." Moreover, "[i]f you want to say that something is not present, it's pretty typical to do a limit of detection." (*Id.* at 483:18-485:4) Dr. Marquardt, on the other hand, explained that "collecting millions and millions of spectra doesn't do you much good if you don't actually analyze the data," and "taking a lot of data doesn't say much about your scientific data. It just says you have an instrument that can take data very quickly." (*Id.* at 331:17-332:5) Dr. Marquardt agreed that the detection limit of a technique determines whether a particle may be detected and that he did not do a specific study on the effect of particle size on the detection limit. However, he explained that none of the experts performed limit of detection studies. (*Id.* at 395:22-397:12)

Dr. Matzger testified that samples may be damaged by the laser during Raman spectroscopy because the power densities are so high. A damaged sample cannot be

used for analysis and the damage is not always visible. He opined that a certain crystal examined by Dr. Marquardt was visibly darker after testing, indicating that it was burned. He testified that MFM is more thermally sensitive than MFA, such that less power is needed to burn MFM. (*Id.* at 476-480) Dr. Marquardt admitted that he did not specifically test the sensitivity of MFM to laser exposure. (*Id.* at 389:21-390:8) He disagreed, however, with Merck's theory that his method "burned samples," explaining that the power density of his point focus laser was in line with that used by Dr. Matzger and his method was proper. Moreover, in preparation of a Raman method, they "always perform a . . . sample method prep where [they] look at laser power, . . . at exposure time, and . . . actually test on a test sample to see if [they] are . . . creating any damage and . . . to maximize our signal while minimizing the potential for damage in [the] system." (*Id.* at 317:3-19, 340-341, 402:1-403:3) He opined that the difference in color of a certain sample was "a difference in contrast after ten-and-a-half hours of imaging and bringing that image back in the microscope field of view." (*Id.* at 336:14-19) On cross-examination, he maintained that the difference in color does not "prove[] anything besides the fact that [the pictures were] taken ten hours apart. The Raman spectra were fine." (*Id.* at 379:11-380:20)

Dr. Matzger also criticized Dr. Marquardt's use of a spike filter, opining that it throws away data. For that reason, Dr. Matzger does not use a spike filter during data collection for maps, but might use it during post processing when he is viewing the spectra. (*Id.* at 480:5-21) Dr. Marquardt opined that a spike filter is commonly used in Raman spectroscopy and allows the averaging out of random events. (*Id.* at 343:6-344:4, 345:5-22)

Merck urges the court to assign no weight to Amneal's testing and related testimony based on the fact that such experiments only indicate the presence or lack of MFM at that specific point in time, not whether "MFM forms . . . during the product's proposed two-year shelf life." (D.I. 163 at 37) Neither expert has opined on a "growth rate." In essence, two experts have tested the same samples and come (not surprisingly) to opposite conclusions. Dr. Marquardt's testing is at least as relevant as the conclusions drawn by Dr. Matzger.

8. Conclusion

Merck offers Dr. Matzger's testing of Batch 16001 Day 1 as persuasive evidence of MFM in Amneal's ANDA product. Merck criticizes Dr. Marquardt's testing, arguing that such testing is insufficient to prove a negative – that MFM is not present in the ANDA product. The court observes that Dr. Matzger's testimony and Merck's related arguments are self-serving, i.e., essentially arguing that Dr. Matzger's testing is "more and better," therefore, only his opinion should be believed. The court is not so convinced, and finds Dr. Marquardt's testimony at least as consistent and credible. Weighing the evidence at bar (lack of MFM in the Exhibit Batches[29] and opposing conclusions on the same testing[30] of the 16001 Batch Day 1), the court concludes that Merck has not carried its burden to prove, by a preponderance of the evidence, that MFM is present in Amneal's ANDA product during its two-year shelf life.

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[29] The court addressed Merck's concerns regarding the relevance of the Exhibit Batches above.

[30] The court recognizes that Dr. Matzger used a different testing protocol (StreamLine spectroscopy) and has addressed Merck's concerns about Dr. Marquardt's testing above.

III. CONCLUSION

For the foregoing reasons, the court finds that Amneal does not infringe the asserted claims.[31] An appropriate order shall issue.

[31] The court does not reach Merck's contributory infringement arguments. (D.I. 163 at 58)