IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., and BRISTOL-MYERS SQUIBB PHARMA CO.,	:	
Plaintiffs/Counterclaim-Defendants,	:	
v.	:	C.A. No. 09-651-LPS
MYLAN PHARMACEUTICALS INC., MATRIX LABORATORIES LTD.,	:	**REDACTED-PUBLIC VERSION**
Defendants/Counterclaim-Plaintiffs.	:	
v.	:	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	:	
Counterclaim Defendants.	:	

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MEMORANDUM OPINION

September 30, 2013
Wilmington, Delaware

STARK, U.S. District Judge:

In this patent infringement action, Plaintiffs Bristol-Myers Squibb Co. and Bristol-Myers Squibb Pharma Co. (collectively "BMS"), allege that Defendants Mylan Pharmaceuticals Inc. and Matrix Laboratories Ltd.[1] (collectively, "Mylan") infringe U.S. Patent No. 6,673,372 (the '372 patent").[2] The '372 patent relates to particular forms of crystalline efavirenz and use of those forms to treat human immunodeficiency virus (HIV) infection. (D.I. 191 Ex. 1 (Statement of Uncontested Facts ("SUF")) ¶¶ 8, 32) The Court held a five-day bench trial in this matter in January of 2013. (D.I. 210-214) (hereinafter "Tr.")[3] The parties completed post-trial briefing on April 12, 2013. (D.I. 218, 219, 220, 221, 227, 228)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) BMS has demonstrated by a preponderance of the evidence that Mylan infringes claim 18 of the '372 patent; and (2) Mylan has not proven by clear and convincing evidence that claim 18 of the '372 patent is anticipated or invalid for failing to satisfy the definiteness, enablement, and written description requirements of 35 U.S.C. § 112. The Court's findings of fact and conclusions of law are set forth below.

I. FINDINGS OF FACT

This Section contains the Court's findings of fact on the issues raised by the parties during trial. However, to avoid duplication, certain additional findings of fact are provided only

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[1]Matrix Laboratories was dismissed from the suit by a joint stipulation of the parties. (D.I. 180)

[2]Mylan filed a counterclaim against BMS and Counterclaim-Defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp. (collectively "Merck") seeking, *inter alia*, a declaratory judgment of non-infringement and invalidity with respect to the '372 patent. (*See* D.I. 47)

[3]Certain portions of the trial testimony were sealed, and appear in a separate transcript. (*See* D.I. 208) (hereinafter "Conf. Tr.")

in connection with the Court's conclusions of law.

A. The Parties

1. Bristol-Myers Squibb Company is a corporation organized and existing under the laws of the State of Delaware, having a place of business at Route 206 and Province Line Road, Princeton, New Jersey 08540. (SUF ¶ 1)

2. Bristol-Myers Squibb Pharma Company, an indirect wholly-owned subsidiary of Bristol-Myers Squibb Co., is a general partnership organized and existing under the laws of the State of Delaware, having its principal place of business at Route 206 and Province Line Road, Princeton, New Jersey 08540. (SUF ¶ 2)

3. Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of West Virginia, with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. (SUF ¶ 3)

4. Matrix Laboratories Ltd. is a wholly-owned indirect subsidiary of Mylan Inc., formally known as Mylan Laboratories, Inc., operating and existing under the laws of India, with its principal place of business at 1-1-151/1, 4th Floor, Sal Ram Towers, Alexander Road, Secunderabad – 500 003, Andhra, Pradesh, India. (SUF ¶ 4)

5. Merck & Co., Inc., is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at One Merck Drive, P.O. Box 100, Whitehouse Station, New Jersey 08889. (SUF ¶ 5)

6. Merck Sharp & Dohme Corp. is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at One Merck Drive, P.O. Box 100, Whitehouse Station, New Jersey 08889. (SUF ¶ 6)

B. U.S. Patent No. 6,673,372

7. The '372 patent issued from U.S. Patent Application No. 09/329,421 ("the '421 application"), which was filed on June 10, 1999. (SUF ¶ 21; JTX-001) The '372 patent, entitled "Crystalline Efavirenz," was issued by the USPTO on January 6, 2004 and expires on June 10, 2019. (SUF ¶¶ 22, 25) The USPTO issued two Certificates of Correction for the '372 patent, on July 13, 2004 and April 17, 2012. (SUF ¶ 23)

8. The inventors of the '372 patent are Lilian A. Radesca, Michael B. Maurin, Shelley R. Rabel, and James R. Moore. (SUF ¶ 27) The '372 patent was assigned to Bristol-Myers Squibb Pharma Company on October 1, 2001. (SUF ¶ 28)

9. The '372 patent is directed to various forms of crystalline efavirenz. (SUF ¶¶ 26, 32) Crystalline efavirenz exists in several polymorphic forms, which are designated Forms 1, 2, 3, 4, and 5. (SUF ¶ 32)

10. A polymorph of a given compound is a distinct entity with its own structure and intrinsic properties. (Tr. at 142, 153-54, 323, 325-27) The structure and properties of crystalline forms can be characterized using a number of different techniques, including x-ray powder diffraction ("XRPD") and differential scanning calorimetry ("DSC"). (JTX-001 at col. 1, ll. 8-11; Tr. at 146-56, 324-33) Running the appropriate XRPD and DSC tests is within the skill of one of ordinary skill in the art. (Tr. at 707-08, 646-47, 726)

11. An XRPD analysis is conducted using a diffractometer. (JTX-001 at col. 21, ll. 33-44; Tr. at 150) The results of an XRPD analysis are typically represented as a plot with diffraction angles (2θ values) and relative intensities. (Tr. at 149-50) The 2θ values represent intrinsic properties of a crystal, meaning that the 2θ values for a given polymorph are generally

different from the 2θ values for a different polymorph. (Tr. at 153, 325-26)

12. DSC is used to measure thermal properties of compounds. (Tr. at 330) The output of a DSC experiment is a thermogram, in which endothermic peaks point in one direction and exothermic peaks point in the other direction. (Tr. at 331-32) If two thermograms of a given compound have a peak in the same position, but one peak is exothermic and the other peak is endothermic, one of ordinary skill in the art would conclude that the thermograms are of two different polymorphs. (Tr. at 794)

13. Various factors, such as preparation of the sample, length of collection time, and the presence of impurities, may affect the accuracy of the XRPD or DSC measurement. (Tr. at 457-59, 695-96) For example, the presence of impurities in a sample can affect its powder x-ray pattern and generate peaks not associated with the particular polymorph of interest. (Tr. at 458-459, 695-96)

14. BMS contends that Mylan infringes claim 18 of the '372 Patent. (D.I. 200) Claim 18 of the '372 Patent depends from claim 16. (JTX-001) Claim 16, as corrected by the Certificate of Correction issued on April 17, 2012, reads:

> 16. Form 5 of crystalline Efavirenz which is characterized by an x-ray powder diffraction pattern comprising six or more 2θ values selected from the group consisting of 10.2±0.2, 11.4±0.2, 11.6±0.2, 19.1±0.2, 20.6±0.2, 21.3±0.2, 22.8±0.2, 24.8±0.2, 27.4±0.2, 28.2±0.2, and 31.6±0.2. (JTX-001)

15. Claim 18 reads:

> 18. The compound of claim 16, which is characterized by a differential scanning calorimetry thermogram having a peak at about 108 °C to about 110 °C. (JTX-001)

16. The specification of the '372 patent discloses all eleven 2θ values listed in claim

16 and states that in a "preferred embodiment, Form 5 crystalline Efavirenz is characterized by a differential scanning calorimetry thermogram having a peak at about 108° C to about 110° C." (JTX-001 at col. 8, ll. 50-53; SUF ¶ 46)

C. Efavirenz

17. The chemical name for efavirenz is (S)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one. (SUF ¶ 29) Efavirenz is also known by the chemical name (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one. (SUF ¶ 29)

D. Sustiva®

18. BMS is the holder of New Drug Application ("NDA") No. 21-360, which relates to tablets containing a 600 mg dose of efavirenz. (SUF ¶ 7)

19. On February 1, 2002, the United States Food and Drug Administration ("FDA") approved the marketing of the tablets described in NDA No. 21-360 in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. (SUF ¶ 8)

20. The tablets described in NDA No. 21-360 are sold in the United States by BMS using the trademark Sustiva®. (SUF ¶ 9) Sustiva® contains the polymorphic form of crystalline efavirenz known as Form 1. (SUF ¶ 10)

21. The FDA's entry for Sustiva® in the "Approved Drug Products with Therapeutic Equivalence Evaluations" ("Orange Book") lists U.S. Patents Nos. 6,639,071 ("the '071 patent") and 6,939,964 ("the '964 patent"). (SUF ¶¶ 13, 18)

22. The '071 patent expires on February 14, 2018. (SUF ¶ 13) The '964 patent

expires on January 20, 2018. (SUF ¶ 18)

E. Mylan's ANDA No. 91-471 and ANDA Product

23. On April 9, 2009, Mylan submitted Abbreviated New Drug Application ("ANDA") No. 91-471 to the U.S. Food and Drug Administration ("FDA"), seeking approval to engage in the commercial manufacture, use, or sale of tablets containing 600 mg of efavirenz ("Mylan's ANDA product"). (SUF ¶ 33) ANDA No. 91-471 also seeks approval to market Mylan's ANDA product in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. (SUF ¶ 34) Mylan refers to the form of efavirenz in its ANDA product as [redacted] (SUF ¶ 33) On March 28, 2011, Mylan received tentative approval from the FDA to market its ANDA product. (SUF ¶ 41)

24. In conjunction with its ANDA filing, Mylan submitted a certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) ("Paragraph IV certification") that the '071 and '964 patents are invalid, unenforceable, and will not be infringed by the manufacture, use, sale, offer for sale, or importation of its ANDA Product. (SUF ¶ 35; JTX-067)

25. By letter dated July 16, 2009 (the "Notice Letter"), Mylan notified BMS and Merck of its Paragraph IV certification, as required by 21 U.S.C. § 505(j)(2)(B)(ii). (SUF ¶ 36; JTX-067) In the Notice Letter, Mylan notified BMS and Merck that it is seeking FDA approval to engage in the commercial manufacture, use, and/or sale of Mylan's ANDA product prior to the expiration of the '071 and '964 patents. (SUF ¶ 37; JTX-067 at p. 04) Within 45 days of receiving Mylan's Notice Letter, BMS brought suit against Mylan alleging infringement of the '372 Patent. (D.I. 1; SUF ¶ 40)

26. On May 26, 2010, BMS and Merck executed a covenant not to sue Mylan for

infringement of the '071 and '964 patents with respect to the filing of ANDA No. 91-471 and the manufacture, use, distribution, sale, offer for sale, or importation by, for, or to Mylan of the products described in, and the subject of, ANDA No. 91-471. (SUF ¶ 38)

F. Facts Relating to Infringement and Validity of the '372 Patent

1. Expert witnesses

27. Dr. Jerry Atwood testified as an expert in "polymorphs, including how to make polymorphs and how to characterize polymorphs," on behalf of BMS. (Tr. at 139)

28. Dr. Harold Kessler testified as a "medical expert in the treatment of HIV and AIDS and the history and treatment of HIV and AIDS," on behalf of BMS. (Tr. at 532)

29. Dr. Mark David Hollingsworth testified as an expert in "organic chemistry and the study of crystal forms, including crystal engineering, crystallography, the identification, characterization, and isolation of crystal forms, organic chemical synthesis, organic solids, and polymorphs," on behalf of Mylan. (Tr. at 320-21)

30. Dr. Craig Eckhardt testified as an expert in "the growth and manipulation of crystalline organic compounds and characterizing and analyzing solid materials, including crystalline materials using laboratory techniques, including differential scanning calorimetry, x-ray diffraction, and powder x-ray diffraction," on behalf of Mylan. (Tr. at 593-94)

2. Person having ordinary skill in the art

31. Dr. Atwood defined a person of ordinary skill in the art as someone with a Ph.D. "in fields relevant to small molecule drug development, such as biochemistry, medicinal chemistry, organic chemistry, or the equivalent, or a bachelor's degree in the same field(s) with four to six years of practical experience." (Tr. at 678)

32. Dr. Hollingsworth defined a person of ordinary skill in the art as one likely to have experience and/or an advanced degree (*i.e.*, a Ph.D. degree) "in fields relevant to small molecular drug development, such as biochemistry, medicinal chemistry, organic chemistry, or the equivalent, and at least one to two years of practical experience in the development and/or characterization of small molecules." According to Dr. Hollingsworth, a person of skill in the art might have a lesser degree (such as a B.S. or B.A. degree in the same fields) with increased time (2-3 years) of practical experience in the research and development and/or characterization of small molecules. (Tr. at 338-39)

33. Both Dr. Atwood and Dr. Hollingsworth agreed that their opinions as to the validity of the patent would remain the same regardless of which definition of the person of ordinary skill in the art the Court ultimately adopts. (Tr. at 340, 678-79)

34. The Court adopts BMS's proposed definition for one of ordinary skill in the art. The Court agrees with Dr. Atwood that the multi-year study and training program associated with an advanced degree, such as a Ph.D., cannot be replaced by a single additional year of work experience. (Tr. at 678) This level of skill is lower than, but consistent with, the skill level of Mr. Moore, an inventor on the '372 patent, who holds a bachelor's degree and worked with pharmaceuticals for over 10 years before discovering Form 5 of crystal efavirenz. (Tr. at 200-11, 228)

3. Mylan's ANDA product

35. Mylan's ANDA product is crystalline efavirenz. (JTX-067 at p. 4)

36. The active pharmaceutical ingredient and Mylan's ANDA product have peaks at the following 2θ values, within the ranges identified: [redacted]

[redacted] (SUF ¶ 43) X-ray powder diffraction testing further indicated that Mylan's active pharmaceutical ingredient and ANDA product have additional peaks at the following 2θ values: [redacted] (*Id.*)

37. Mylan's ANDA product has a DSC thermogram with a peak at about 108° C to about 110° C. (JTX-037 at pp. 06-08; JTX-113 at p. 32)

4. Facts Relating to Anticipation and Indefiniteness

38. United States Patent No. 5,965,729 issued on October 12, 1999 from patent application No. 09/008,824, which was filed January 20, 1998, and is entitled "Process for the Crystallization of a Reverse Transcriptase Inhibitor Using an Anti-Solvent." (JTX-107)

39. The '729 patent is prior art to the '372 patent. (SUF ¶ 12; Tr. at 686)

40. The '729 patent covers certain crystalline forms of efavirenz. (*See* JTX-107) These are Form I, II, and III, which correspond to Forms 1, 4, and 3 of the '372 patent. (Tr. at 367; JTX-004 at p. 205) In particular, BMS has agreed that "Form 3 [of the '372 patent] corresponds to Form III [of the '729 patent]." (JTX-004 at p. 205)

41. The '729 patent shows the full XRPD patterns for Forms I, II, and III in Figures 3, 4, and 5, respectively, as well as a list of 2θ values for each of these forms. (JTX-107 at p. 3-5, col. 5, ll. 15-40) That listing of 2θ values is reproduced below:

Form I	Form II	Form III
6.0800	3.6375	7.2150
6.3900	6.3325	10.9675
10.3950	11.0725	13.7275
10.9875	12.7750	14.5325
12.2850	13.3275	16.7275
13.1900	14.2925	19.0675
14.1700	16.1200	19.6550
15.1925	16.8975	20.8250
16.9000	18.5025	21.7450
18.4375	19.1975	22.2825
19.2275	19.6025	22.8475
20.0925	20.6650	23.1750
21.2100	21.3250	23.8850
22.3600	22.6150	24.4900
23.0725	23.1775	24.9075
24.8900	24.4075	25.8200
25.9500	24.9650	27.0325
26.3575	26.0100	27.6050
27.2550	26.8550	29.2975
28.1150	27.6400	30.2600
28.5850	28.3675	30.7300
29.1325	29.1725	31.3125
29.5625	29.6325	33.3975
30.6850	30.5650	38.4325
32.3725	31.8950	39.2100
38.3125	33.8225	

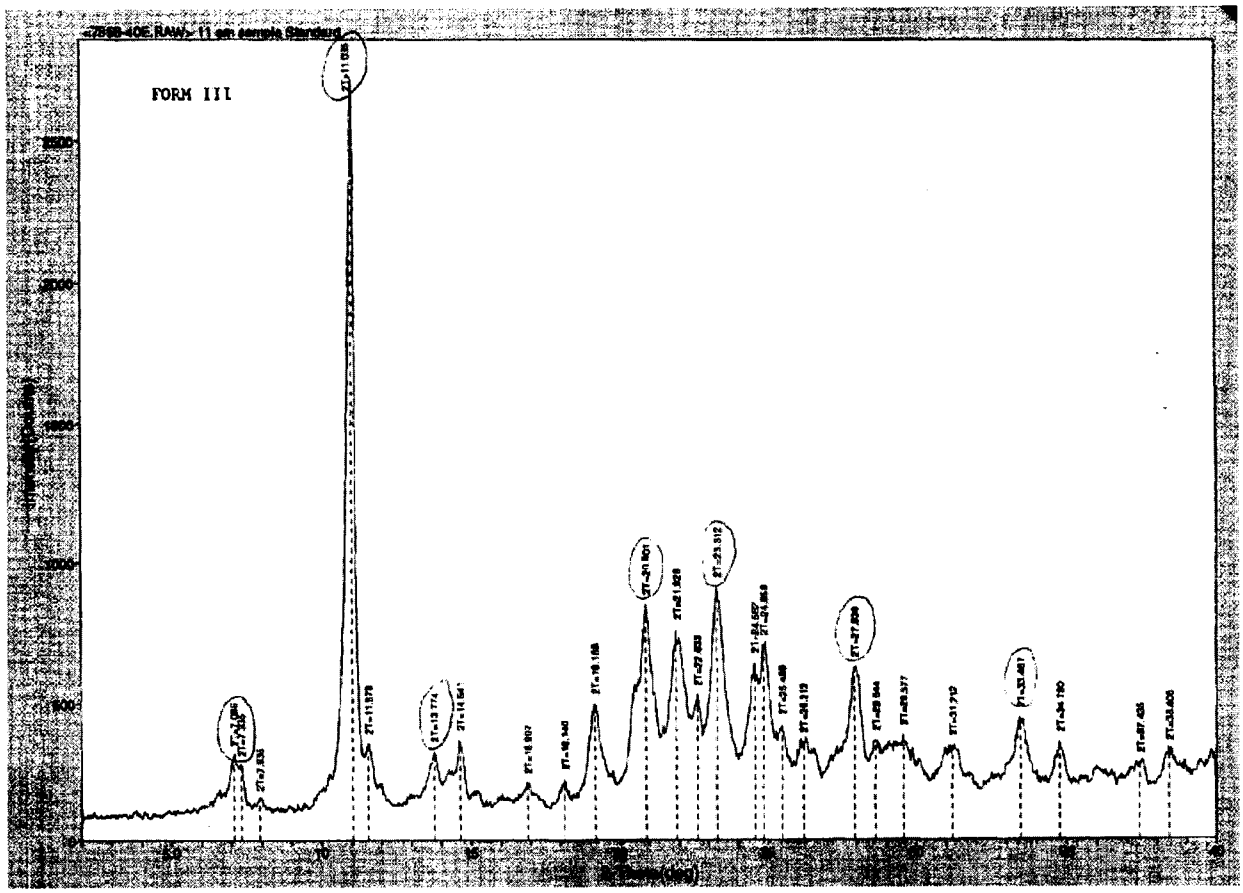
42. As illustrated above, the listing of 2θ values for Form III in the '729 patent includes: 19.1, 20.8, 22.8, 24.9, and 27.6. (JTX-107 at col. 5, ll. 15-50) These five 2θ values match five of the recited 2θ values of Claim 16 of the '372 patent. (Tr. at 371)

43. The '729 patent also provides the DSC of Form III in Figure 6. (JTX-107 at p. 6; Tr. at 367-68) According to the '729 patent, DSC results show a peak at 118° C. (JTX-107 at col. 5, ll. 55-59) The '372 patent, on the other hand, states that Form 3 has a DSC peak at about 108° C to about 110° C. (JTX-001 at col. 6, ll. 49-61)

44. BMS publishes an "Encyclopedia of Solid State Forms" (JTX-019), which contains an x-ray powder diffraction pattern for "pure" Form III, and serves as a BMS reference standard for Form III. (Tr. at 700) JTX-117 is a computer analysis of the x-ray powder diffraction pattern for Form III in the BMS Encyclopedia. Dr. Atwood testified that Dr.

Radesca's XRPD pattern for Form III, identified as Sample No. 7858-40E, is the same form contained in the BMS Encyclopedia. (Tr. at 700-01; 768-69; JTX-117 at p. 6; JTX-019 at p. 15)

45. The Form III XRPD pattern from page 6 of JTX-117 is reproduced below:



46. Mylan's experts did not conduct any independent tests in connection with this litigation. (Tr. at 472-73)

5. Facts Relating to Enablement and Written Description

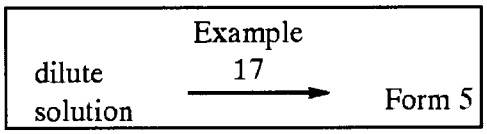
47. The '372 patent teaches that the appropriate solvent system for crystallizing Form 5 efavirenz is THF/heptane. (Tr. at 715; JTX-001 at col. 13, ll. 28-30, col. 27, l. 67 to col. 28, l. 22) Specifically, Example 17 teaches that Form 5 can be crystallized from a slurry of "1% v/v

THF/heptane" (i.e., 1% THF, 99% heptane). (Tr. at 711-12, 723-24; JTX-001 at col. 27, l. 67 to col. 28, l. 22) A slurry is prepared by adding efavirenz to the solvent until no more efavirenz dissolves. (Tr. at 723) Example 17 uses approximately 70 grams of efavirenz in either one liter or 1.5 liters of 1% v/v THF/heptane. (JTX-001 at col. 27, l. 67 to col. 28, l. 22)

48. The '372 Patent states that "Form 5 is the most thermodynamically stable form below 40° C." (JTX-001 at col. 13, ll. 24-26) Example 17 illustrates three experiments in which Form 5 is crystallized at room temperature, which is below 40° C. (Tr. at 718; JTX-001 at col. 27, l. 67 to col. 28, l. 22)

49. Scheme 4 of the '372 Patent teaches that Form 5 can be obtained using slow crystallization from a dilute solution. (Tr. at 720; JTX-001 at col. 13, ll. 28-60) The third paragraph of Example 17 describes an experiment in which the dilute solution was "allowed to cool to room temperature overnight and Form 5 crystals were then collected by filtration." (JTX-001 at col. 28, ll. 19-22)

50. The specification of the '372 patent states that "[Form 5] crystals may be obtained by recrystallization from a dilute solution of THF/heptane. The crystals may be obtained from solutions in which either Form 1 or Form 4 have already been isolated." (JTX-001 at col. 13, lines 28-32; SUF ¶ 48) Scheme 5 then directs one skilled in the art to apply the teachings of Example 17 to this dilute solution, as illustrated below. (Tr. at 736; JTX-001 at col. 26, ll. 1-25)



(JTX-001 at col. 26, Scheme 5; *see also* JTX-001 at col. 28, ll. 19-22)

51. Example 17 of the '372 patent discloses that the slurry was seeded "periodically

with Form 5 until the seeds no longer dissolved (63° C), then allowed to cool to 45° C and filtered." (JTX-001 at col. 28, ll. 17-19) Mr. Moore testified that if efavirenz is dissolved in solution, the "crystal form is gone." (Tr. at 234) The filtering step of Example 17 removes whatever seeds have not dissolved into the slurry. (Tr. at 252-53, 736-38)

52. After his discovery of Form 5, Mr. Moore investigated how to reproduce it. (Tr. at 234) Mr. Moore ran ten experiments in order to determine how to make Form 5. (*See* Tr. at 235-57) Mr. Moore described these experiments on pages 142-64 of his laboratory notebook, Notebook No. DMP 7051. (JTX-056 at pp. 149-71)

53. In his first experiment, Mr. Moore took isolated efavirenz and dissolved it in a mixture of about 20% v/v THF/heptane. (Tr. at 235; JTX-056 at p. 149) He then concentrated it to a paste at less than 40° C, in order to remove the solvent and encourage crystallization. (*Id.*) The resulting polymorph was Form 2. (Tr. at 236; JTX-056 at p. 149) Next, he reconstituted the paste with additional THF and heptane and warmed the mixture up to 70° C. (*Id.*) He cooled it slowly to 40° C and nothing crystallized, so he concentrated it to a paste once again. (*Id.*) The resulting polymorph this time was Form 4; so Mr. Moore reslurried again, splitting the sample into two and adding acetic acid to one of the samples. (*Id.*) No crystals formed in either sample, so he opened the flasks and allowed the solvent to evaporate. (Tr. at 237; JTX-056 at p. 150) Small rings formed at the solvent lines for each sample, but no crystals. (Tr. at 237) He then seeded both samples with his originally discovered Form 5 crystals and a few days later both samples had crystals in them – and the crystals in the sample without acetic acid were Form 5. (Tr. at 237; JTX-056 at p. 150)

54. Mr. Moore's second polymorphic experiment is described on page 146 of his

laboratory notebook (JTX-056 at p 153) In this experiment, he took the mother liquor from a previous synthesis reaction and seeded it with his originally isolated Form 5 crystals several times; he did not obtain Form 5 crystals. (Tr. at 242-43; JTX-056 at p. 153)

55. Mr. Moore proceeded to do seven more experiments, described at pages 161-64 of his laboratory notebook (Experiments #1-7 below). (JTX-056 at p. 168-71) In these experiments, he was studying crystallization in 1% v/v THF/heptane. (Tr. at 245-46)

56. In Experiment #1, Mr. Moore took a sample of efavirenz and slurried it in one liter of 1% v/v THF/heptane, filtered out the residual solids, and seeded it. (Tr. at 246; JTX-056 at p. 168) The experiment resulted in the formation of Form 5 crystals. (*Id.*)

57. In Experiment #2, Mr. Moore added the solids that had been filtered out of Experiment #1 to 1.5 liters of 1% v/v THF/heptane and warmed it to 40° C. (Tr. at 248; JTX-056 at p. 168) He then filtered out residual solids while the mixture was still warm and seeded with Form 5 crystals. (*Id.*) The resulting Form 5 crystals formed quickly, yielding about ten times more material than had been obtained in Experiment #1. (*Id.*)

58. In Experiment #3, Mr. Moore reslurried the solids that had been filtered out of Experiment #2 and warmed the mixture to 79° C. (Tr. at 249; JTX-056 at p. 168) He then filtered out the residual solids, seeded with Form 5, and let the mixture cool. (*Id.*) The result was a mixture of Forms 2 and 5. (*Id.*) Mr. Moore testified that he believes he got the mixture because the temperature was too high. (Tr. at 250) The next day, the mother liquor from the sample had formed "crystals in long needles." (JTX-056 at p. 169) An XRPD analysis found that these crystals were Form 5. (JTX-056 at p. 169; JTX-055 at p. 187)

59. In Experiment #4, Mr. Moore concentrated the leftover materials from the

previous experiments into a paste, reslurried the paste in the solvent mixture, and warmed it to 80° C. (Tr. at 250; JTX-056 at p. 169) He then cooled it slowly, seeding periodically until the seeds no longer dissolved. (*Id.*) He continued cooling and solids precipitated – they were Form 2, not Form 5. (Tr. at 250-51; JTX-056 at p. 169)

60. In Experiment #5, Mr. Moore reconcentrated everything from Experiment #4 into a paste, dissolved it into heptane, and added THF to make a 1% v/v THF/heptane solution. (Tr. at 251-52; JTX-056 at p. 169) He warmed the mixture to about 80° C and, at about 85° C, everything was dissolved. (Tr. at 252; JTX-056 at p. 169) He then cooled the mixture slowly to 63° C and seeded. (*Id.*) The resulting samples were Form 1, so Mr. Moore reheated it to dissolution and cooled it very slowly, seeding until the solids precipitated out at 50° C. (Tr. at 252; JTX-056 at p. 170) He filtered out the seeds and solids at 45° C, resulting in a clear mother liquor with no solids or seeds in it. (*Id.*) He then let the mother liquor sit overnight without seeding and found that the resulting solids were Form 5. (Tr. at 252-53; JTX-056 at p. 170)

61. In Experiment #6, Mr. Moore warmed a sample of efavirenz in a 1% v/v THF/heptane solution to 40° C. (Tr. at 253-54; JTX-056 at p. 170) He filtered out the residual solids and separated the resulting mother liquor into two flasks. (Tr. at 254; JTX-056 at p. 170) On the next day, there were Form 5 crystals in both flasks. (*Id.*)

62. In Experiment #7, Mr. Moore combined the remaining mother liquors and non-Form 5 solids from the previous experiments, concentrated those into a paste, and chased it with heptane to remove any residual THF. (Tr. at 255; JTX-056 at p. 171) He then reconstituted it in one liter of 1% v/v THF/heptane and warmed it to 85° C. (*Id.*) After cooling it to 50° C, he filtered out the precipitate that had formed, and then seeded the solution with Form 5. (Tr. at

255-56) He held it at room temperature overnight and Form 5 resulted. (Tr. at 256; JTX-056 at p. 171) Given the results of his experiments, Mr. Moore concluded, "Excellent. Produced Form V Repeatedly." (Tr. at 256-57; JTX-056 at p. 171)

II. INFRINGEMENT

BMS contends that Mylan's planned commercial manufacture, use, sale, or offer for sale in the United States and importation into the United States of Mylan's ANDA product will infringe claim 18 of the '372 patent. The Court agrees with BMS.

A. Legal Standards

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). A two-step analysis is required before making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly construed claims with the accused infringing product. *See id.*

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. CardinaliG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

B. Discussion

There are no factual disputes with respect to infringement. Mylan's non-infringement argument concerns only the appropriate application of the Court's construction of the Markush

group language in claim 18 to the undisputed facts. (*See* Tr. at 838, 885-86)

Claim 18 depends from claim 16, which requires:

> 16. Form 5 of crystalline Efavirenz which is characterized by an x-ray powder diffraction pattern comprising six or more 2θ values selected from the group consisting of: 10.2±0.2, 11.4±0.2, 11.6±0.2, 19.1±0.2, 20.6±0.2, 21.3±0.2, 22.8±0.2, 24.8±0.2, 27.4±0.2, 28.2±0.2, and 31.6±0.2.

(JTX-001) The Court has construed the Markush group language "selected from the group consisting of" to mean that "the x-ray powder diffraction pattern must include at least [6] of the 2θ values selected from 10.2±0.2, 11.4±0.2, 11.6±0.2, [] 19.1±0.2, 20.6±0.2, 21.3±0.2, 22.8±0.2, 24.8±0.2, 27.4±0.2, 28.2±0.2, and 31.6±0.2."[4] (D.I. 179 at ¶ 9)

Mylan contends that the phrase "selected from the group consisting of" limits the x-ray powder diffraction pattern to the eleven 2θ values specifically recited in the claim, and nothing more. (D.I. 220 at 2-8) According to Mylan, if a crystal sample has an x-ray powder diffraction pattern with more than the eleven claimed 2θ values, that sample is outside the scope of claim 16. (D.I. 220 at 3) BMS, on the other hand, contends that the word "comprising" in claim 16 renders the claim open-ended and that the transitional phrase "consisting of," used in the Markush group, closes only the group of alternative 2θ values, not the entire claim. (*See* D.I. 218 at 6) (citing *Maxma v. ConocoPhillips Inc.*, 2005 WL 1690611, at *5 (E.D. Tex. July 19, 2005)) The Court agrees with BMS.[5]

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[4]Claim 16 was amended by a Certificate of Correction to delete "12.6±0.2" from the list of possible 2θ values. (*See* JTX-001) Hence, the Court's construction should also not include this 2θ value and is hereby modified to eliminate the 12.6 value.

[5]To the extent the Court's holding involves a clarification of its prior claim construction, such clarification is permissible. *See Guttman, Inc. v. Kopykake Enters.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002) ("District courts may engage in a rolling claim construction, in which the court revisits and alters its interpretation of the claim terms as its understanding of the technology evolves.").

Claim 16 is directed to Form 5 of crystalline efavirenz. The Court has construed the term "Form 5" as: "A polymorphic crystal form of [efavirenz] that can be distinguished from other forms." (D.I. 179 ¶ 4) According to the claim, Form 5 is distinguished from other crystal forms by certain 2θ values in an x-ray powder diffraction pattern. The "consists of" language defines a group of possible 2θ values in an x-ray powder diffraction pattern that can be used to characterize the crystal form. As explained in the Court's Markman Opinion (D.I. 178 at 9), the Markush group is closed with respect to the 2θ values that can be used to characterize Form 5. Read in context, however, neither the claim itself nor the Court's construction of the claim precludes an x-ray powder diffraction pattern having additional 2θ values. Because the claim also includes the transitional phrase "comprising," additional 2θ values are permissible, but those 2θ values cannot be used to characterize the crystal form.

The Court's conclusion is consistent with the Federal Circuit's reasoning in *In re Crish*, 393 F.3d 1253, 1257 (Fed. Cir. 2004). There, the claim at issue included both "comprising" and "consisting of" as transitional phrases, requiring: "A purified oligonucleotide ***comprising at least a portion*** of the nucleotide sequence of SEQ ID NO: 1, wherein ***said portion consists of*** the nucleotide sequence from 521 to 2473 of SEQ ID NO: 1." *Id.* at 1254-55 (emphasis added). The Federal Circuit concluded that the transitional phrase "consists of" modifies the "said portion" language of the claim, while the word "'comprising' means that the claim can include that portion plus other nucleotides." *Id.* at 1257. As in *In re Crish*, the phrase "consists of" restricts only the 2θ values that may be used to characterize Form 5, while the term "comprising" allows for the possibility of additional 2θ values in an XRPD pattern, although those additional values may not be used to characterize Form 5.

The Court is also guided by the claim construction principles set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (internal quotation marks omitted):

> Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.

The '372 patent discloses different polymorphic forms of crystal efavirenz, which are characterized by certain 2θ values on an x-ray powder diffraction pattern. (JTX-001 at col. 1, ll. 7-11) As Dr. Hollingsworth explained, the 2θ values on an XRPD pattern represent intrinsic properties of a crystal structure. (Tr. at 325-26) As a result, different polymorphs of the same compound will have different XRPD patterns. (Tr. at 153) However, "the number of peaks that one gets [on an XRPD pattern] depends in large measure on how much time one spends carrying out the experiment, taking the pattern itself;" depending on how long one runs the experiment, there could be as many as "2,100 possible peaks on an XRPD pattern." (*See* Conf. Tr. at 49-50) In other words, a crystalline form of a compound will always have the same XRPD pattern, but running the experiment for a longer period of time will result in additional peaks appearing in the pattern.[6] In this context, adopting Mylan's proposed construction would mean that running the diffractometer for a short amount of time could result in a finding of infringement, but running the same experiment for a different (longer) amount of time could result in pattern that does not infringe. Such a result would not be sensible, nor would it "align[] with the patent's description

[6]Mylan's expert, Dr. Eckhardt, acknowledged that he is not aware of any polymorphic form of crystal efavirenz with fewer than 11 total peaks in its XRPD pattern. (Tr. at 641)

of the invention."[7] *Phillips*, 415 F.3d at 1316.

Having resolved the claim construction dispute in favor of BMS, the Court concludes that BMS has proven that Mylan infringes claim 18 of the '372 patent by a preponderance of the evidence. Mylan's ANDA product is crystalline efavirenz. (JTX-067 at p. 4) [redacted] Mylan's ANDA product has a DSC peak between 108° and 110° C. (JTX-037 at pp. 06-08; JTX-113 at p. 32) In sum, BMS has proven that all of the limitations of claim 18 are present in Mylan's ANDA product, so BMS has proven that Mylan's ANDA product infringes that claim.

III. VALIDITY

Mylan has raised four separate invalidity challenges to claim 18 of the '372 patent: (1) anticipation; (2) indefiniteness; (3) enablement; and (4) written description. The Court will address these in order.

A. Anticipation

Mylan asserts that claim 18 of the '372 patent is invalid as being anticipated by a different prior art crystal form of efavirenz, Form III. (D.I. 220 at 14, 26-27) In view of the evidence presented at trial and for the reasons that follow, the Court concludes that Mylan has not proven

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[7]The Court disagrees with Mylan's contention that adopting BMS's proposed construction would result in the "recapture" of subject matter recited in claim 158, which was canceled during prosecution. (*See* D.I. 228 at 4) At the time claim 158 was canceled, the claim included the same Markush group language as remains in present claim 18. (JTX-004 at pp. 169, 196) The amendment proposed by applicants was never entered, since the claim had previously been canceled.

anticipation by clear and convincing evidence.

1. Legal Standards

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Inherent anticipation, which is the theory Mylan asserts here, requires that every element of the claim must "necessarily and inevitably" be present in the anticipating reference, even though those elements are not expressly disclosed. *See id.* at 1378. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Bettcher Indus. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011).

An issued patent is presumed valid. *See* 35 U.S.C. § 282. Whether a prior art reference anticipates a patent claim is a question of fact, and proving anticipation requires clear and convincing evidence. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted).

2. Discussion

Mylan contends that the inherent physical characteristics of Form III crystalline efavirenz disclosed in the '729 patent (JTX-107) satisfy each limitation of claim 18 of the '372 patent.[8] BMS responds that Mylan has failed to prove by clear and convincing evidence that Form III:

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[8]The '729 patent was considered by the Patent Examiner during prosecution of the '372 patent. (JTX-004 at p. 189)

(1) necessarily has a DSC peak between 108° and 110° C; and (2) inherently includes at least six of the 2θ values required by claim 18. (D.I. 218 at 11-12) The Court agrees with BMS.

At trial, the parties agreed that a polymorph of a given compound is a distinct entity with its own structure and intrinsic properties. (Tr. at 142, 153-54, 323, 325-27) The parties also agreed that the structure and properties of those crystalline forms can be evaluated using x-ray powder diffraction and differential scanning calorimetry. (Tr. at 145-47, 154-55, 324) The parties further agreed that various factors, such as preparation of the sample, length of collection time, or the presence of impurities could affect the accuracy of the XRPD or DSC measurement. (Tr. at 457-59, 695-96)

Claim 18 of the '372 patent requires a DSC peak between 108° and 110° C. There is no dispute that the '729 patent describes Form III as having a DSC peak at 118° C (JTX-107 at col. 5, ll. 55-61), which the experts agree is clearly different from the claimed range. (*See* Tr. at 469-70, 686-87) The '372 patent, however, describes Form 3 as having a DSC peak at about 108° C to about 110° C. (JTX-001 at col. 6, ll. 49-61) Mylan contends that the DSC peak for Form 3 in the '372 patent should also be attributed to Form III of the '729 patent, because BMS has previously agreed that "Form 3 [of the '372 patent] corresponds to Form III [of the '729 patent]."[9] (D.I. 220; JTX-004 at 205)

Mylan's expert, Dr. Hollingsworth, testified that there is a "conflict" as to which of the DSC patterns – the one in the '729 patent, showing a peak at 118° C, or the one in the '372 patent, showing a peak at about 108° to 110° C – is correct. (Tr. at 470) Dr. Hollingsworth

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[9]This statement was made in the context of a dispute between BMS and Merck as to the ownership of Form 3.

opined that because the '372 patent was filed after the '729 patent, one of ordinary skill in the art would expect the '372 patent to be correct.[10] (Tr. at 471-72) This is not persuasive.

The record includes documents created by BMS prior to this litigation describing Form III as having a DSC peak at 117° C. For example, BMS's Encyclopedia of Solid State Forms ("BMS Encyclopedia") describes Form III as having a DSC peak at 117° C. (JTX-019 at p. 23) This is consistent with the disclosure of Merck's independently developed '729 patent. Taken together, this evidence supports a finding that Form III has a DSC peak at about 117° C.

Mylan could have attempted to rebut this evidence, but – despite having the burden of proof – it did not. For example, Dr. Hollingsworth testified that he "could make Form 3," and had the equipment necessary to conduct a DSC test, but he did not do so. (Tr. at 472-73) Given the state of the record – which by even Dr. Hollingsworth's estimation shows only a "conflict" – the Court concludes that Mylan has failed to establish by clear and convincing evidence that Form III in the '729 patent has a DSC peak between 108° and 110° C, as required by claim 18 of the '372 patent.

The asserted patent claim further requires "an x-ray powder diffraction pattern compris[ing] six or more 2θ values selected from the group consisting of 10.2±0.2, 11.4±0.2, 11.6±0.2, 19.1±0.2, 20.6±0.2, 21.3±0.2, 22.8±0.2, 24.8±0.2, 27.4±0.2, 28.2±0.2, and 31.6±0.2." (JTX-001) Mylan concedes that the '729 patent includes only five – not six or more – of the 2θ values required by claim 18. (JTX-107 at col. 5, ll. 16-39; Tr. at 371, 694) According to Mylan, however, the inherent physical characteristics of Form III result in additional 2θ values that

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[10]Dr. Hollingsworth also testified that the DSC peak of between 108° and 110° C "could be a mistake in the '372 patent." (Tr. at 471)

correspond to the 2θ values of claim 18. To establish the "inherent" characteristics of Form III, Mylan relies on an x-ray powder diffraction pattern from an internal BMS file labeled as Form III (JTX-075), the BMS Encyclopedia (JTX-019), and a computer analysis of Form III disclosed in the BMS Encyclopedia (JTX-117). (D.I. 220 at 16-18)

Dr. Hollingsworth testified that the x-ray powder diffraction pattern for Form III in the internal BMS file (Exhibit JTX-075) disclosed eight peaks[11] that match the 2θ values required by claim 18. (Tr. at 377) According to Dr. Hollingsworth, JTX-075 discloses the same five peaks as the '729 patent, as well as three additional peaks at 11.6, 28.0, and 31.7. (Tr. at 373-77; JTX-075 at p. 10) BMS's expert, Dr. Atwood, disagrees with Dr. Hollingsworth's analysis for two reasons. First, according to Dr. Atwood, at least four of the peaks identified by Dr. Hollingsworth do not have sufficient intensity to qualify as a peak. Second, the peaks identified by Dr. Hollingsworth could have been caused by the presence of impurities in the sample tested in JTX-075. (Tr. at 695-98) Because there is no purity information for the sample in JTX-075, Dr. Atwood contends that the peaks shown in JTX-075 do not necessarily represent any inherent characteristic of Form III. (*Id.*)

At trial, neither party presented evidence of the purity of the Form III sample tested in JTX-075. (Tr. at 462-63) However, both sides' experts agreed that the presence of impurities in a sample can lead to the presence false peaks in an x-ray powder diffraction pattern. (Tr. at 459, 696-97) For instance, Dr. Hollingsworth agreed that "if we look at a . . . x-ray powder diffraction pattern for a given sample and it's not pure, we may see peaks that aren't due to the polymorph of interest to us." (Tr. at 459) Dr. Hollingsworth also agreed that "noise" present in the x-ray

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[11]For purposes of this discussion, the term "peaks" is interchangeable with the term "2θ values."

powder diffraction patterns can make it difficult to distinguish smaller peaks from the noise itself. (Tr. at 457-58) While it is possible that the eight peaks identified by Mylan in the XRPD of Form III contained in JTX-075 represent inherent physical characteristics of Form III, it is likewise possible that one or more of those peaks may be attributed to noise, or to the presence of impurities in the JTX-075 sample.[12] Mylan, as the party with the burden of proof, simply has not presented sufficient evidence to eliminate, or even discount, these latter possibilities. Accordingly, the Court cannot agree that Form III in JTX-075 "necessarily and inevitably" includes at least six 2θ values required by claim 18 of the '372 patent. *See Bettcher*, 661 F.3d at 639 (explaining that inherency "may not be established by probabilities or possibilities").

Mylan also relies on the BMS Encyclopedia of Solid State Forms (JTX-019), which contains an x-ray powder diffraction pattern for "pure" Form III, and serves as a BMS reference standard for that form. (Tr. at 700) JTX-117 is a computer analysis of the x-ray powder diffraction pattern for Form III in the BMS Encyclopedia. Only four 2θ values in the diffractometer in JTX-117 match the 2θ values recited in claim 18. One of those values (11.6) is not disclosed in the listing of 2θ values disclosed in the '729 patent. (Compare JTX-117 and JTX-107) Mylan contends that it is appropriate to combine the 2θ values from the Form III sample in JTX-117 with the 2θ values for Form III in the '729 patent because those 2θ values purportedly represent intrinsic physical characteristics of Form III. (D.I. 220 at 17-18)

In the Court's view, however, Mylan may not pick and choose 2θ values from different

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[12]Mylan contends that the purity of the Form III sample is "irrelevant" because claim 18 "does not include a purity limitation." (D.I. 228 at 11) The Court does not agree. Mylan's argument is inherent anticipation. If the Form III sample contains some impurities, then the 2θ values in an XRPD pattern for that sample do not necessarily and inevitably represent any inherent property of Form III.

samples in order to arrive at a conclusion of anticipation. Because x-ray powder diffraction patterns of different samples of Form III have appeared to result in different 2θ values – perhaps due to the presence of impurities or noise – the Court cannot conclude that any single 2θ value necessarily represents an inherent physical characteristic of the crystal structure itself. Instead, it is possible that one or more of the 2θ values in the '729 patent may be the result of the presence of impurities or noise. Mylan has not offered any single x-ray powder diffraction pattern that, on its own, contains at least six of the 2θ values recited in claim 18. Even the "pure" reference standard sample of Form III in BMS's Encyclopedia contains only four matching 2θ values. (JTX-117 at p. 6)

Thus, the Court finds that Mylan has failed to prove by clear and convincing evidence that Form III in the '729 patent "necessarily and inevitably" has six or more of the 2θ values required by claim 18 of the '372 patent. Accordingly, for this reason as well (in addition to the DSC finding described earlier), the Court concludes that claim 18 of the '372 patent is not anticipated by Form III as disclosed in the '729 patent.

B. Indefiniteness

Mylan contends that claim 18 of the '372 patent is indefinite and, therefore, invalid. (D.I. 220 at 14-21) For the reasons below, the Court disagrees.

1. Legal Standards

The definiteness requirement is set forth in 35 U.S.C. § 112, ¶ 2, which states that a patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The Federal Circuit has explained that:

> Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims.

Halliburton Energy Servs. v. M-I LLC, 514 F.3d 1244, 1249 (Fed. Cir. 2008). Again, because the claims of a patent are presumed to be valid, "the evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence." *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1345 (Fed. Cir. 2007).

2. Discussion

Claim 18 of the '372 patent is directed to Form 5 of crystalline efavirenz. (JTX-001) The Court has construed the term "Form 5" to mean "[a] polymorphic crystal form of [efavirenz] that can be distinguished from other forms." (D.I. 179 at ¶ 4) Mylan contends that claim 18 is indefinite because one of ordinary skill in the art could not "clearly differentiate" Form 5 from prior art forms of crystalline efavirenz described in the '729 patent, specifically Form III and/or a combination of several forms (*e.g.*, Form I and Form III). (D.I. 228 at 9) According to Mylan, "'[s]uch differentiation is an important consideration in the definiteness inquiry because in attempting to define a claim term, a person of ordinary skill in the art is likely to conclude that the definition does not encompass that which is expressly distinguished as prior art.'" (*Id.*) (quoting *Halliburton*, 514 F.3d at 1252) However, as explained in connection with Mylan's anticipation argument above, claim 18 of the '372 patent does clearly differentiate Form 5 of crystalline efavirenz from Form III alone and from a combination of Form I and Form III, at least because claim 18 requires "a differential scanning calorimetry thermogram having a peak at about 108° C to about 110° C." (JTX-001)

Moreover, Mylan's contention that if a claim cannot be distinguished from the prior art, that claim is indefinite (Tr. at 908-10) is incorrect. This is evident from *Halliburton*, a case relied on by Mylan, which states:

> Of course, that is not to suggest that a claim can never be definite and yet read on the prior art. For example, a claim that recites a specific numeric range for a physical property may be definite even though prior art products fell within that range. In such a case, a person of ordinary skill in the art would know the boundaries of the claim, and the focus would properly be on other validity challenges (e.g., anticipation).

514 F.3d at 1252. Here, as in *Haliburton*, claim 18 of the '372 patent contains specific numeric requirements that define the physical characteristics of Form 5: an x-ray powder diffraction pattern with six or more of the specified eleven 2θ values and DSC peak at about 108° C to about 110° C. (JTX-001) These limitations are sufficiently clear to "inform the public of the bounds of the protected invention." *Halliburton*, 514 F.3d at 1249. For this reason, claim 18 is not indefinite, regardless of the prior art.

Mylan also contends that claim 18 is indefinite because it does not specify whether the DSC peak is endothermic or exothermic and, thus, could conceivably cover more than one compound. (D.I. 220 at 20-21) Mylan has not offered evidence of any other compound that satisfies the other requirements of claim 18 (e.g., 2θ values) and would render the endothermic/exothermic distinction pertinent. Mylan's hypothetical speculation does not constitute clear and convincing evidence of indefiniteness.

C. Enablement

Mylan contends that claim 18 of the '372 patent is invalid under 35 U.S.C. §112, ¶ 1 for failing to satisfy the enablement requirement. The Court disagrees.

1. Legal Standards

A patent specification must set forth "the manner and process of making and using [the invention] . . . 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." 35 U.S.C. § 112. To satisfy the enablement requirement of § 112, the disclosure in a patent application must enable a person skilled in the art to make and use the claimed invention without "undue experimentation" as of the filing date of the application. *See In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988); *see also Genetech, Inc. v. Novo Nordisk AIS*, 108 F.3d at 1361, 1365 (Fed. Cir. 1997). Enablement is "not precluded where a 'reasonable' amount of routine experimentation is required to practice the claimed invention." *ALZA Corp. v. Andrx Pharms., L.L.C.*, 603 F.3d 935, 940 (Fed. Cir. 2010). While the knowledge generally available in the art can supplement an application's specification, "[i]t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genetech, Inc.*, 108 F.3d at 1366.

In determining whether "undue" experimentation is required to make and use a claimed invention, courts may, but are not required to, consider such factors as: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *See In re Wands*, 858 F.2d at 737. Not all of the factors need to be reviewed when determining whether a disclosure is enabling. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that *Wands* factors "are illustrative, not

mandatory. What is relevant depends on the facts"). Mylan has the burden of proving lack of enablement by clear and convincing evidence. *See Morton Int'l v. Cardinal Chem. Co.*, 5 F.3d 1464, 1469 (Fed. Cir. 1993).

2. Discussion

Mylan contends that claim 18 fails the enablement requirement because: (1) the '372 patent specification does not teach one of ordinary skill in the art how to make Form 5 without seeding; and (2) the '372 patent specification does not teach one of ordinary skill in the art how to make Form 5 with an exothermic peak at about 108° C to about 110° C. (D.I. 220 at 21) The Court will address these two arguments in order.

Mylan first contends that the '372 patent does not provide any independent means of making Form 5. According to Mylan, every example of making Form 5 disclosed in the '372 patent requires a step of seeding the solution with Form 5, meaning that "you can only make Form 5 if you already have Form 5 on hand." (D.I. 220 at 22) In Mylan's view, there is no example that discloses making Form 5 from scratch. (*Id.*) It follows, according to Mylan, that to make Form 5 without seeding would require undue experimentation by one of ordinary skill in the art. The Court does not agree.

The '372 patent explains that Form 5 "crystals may be obtained by recrystallization from a dilute solution of THF/heptane. The crystals may be obtained from solutions in which either Form 1 or Form 4 have already been isolated." (JTX-001 at col. 13, ll. 28-32) Mylan's expert, Dr. Hollingsworth, testified that this guidance is too "vague" because it does not provide the necessary conditions such as: (1) the make-up of the solvent system; (2) the temperature of crystallization; (3) the time frame for formation of the crystal form; (4) the amount of material to

use; and (5) the methods for characterizing the resulting form. (Tr. at 388-90) While acknowledging that Example 17 of the '372 patent discloses many of these conditions, Dr. Hollingsworth believes that one of ordinary skill in the art would likely ignore this example because it requires a step of seeding with Form 5. (Tr. at 395-96) The Court does not find this reasoning persuasive.

Instead, the Court finds that Plaintiff's expert, Dr. Atwood, testified credibly that, "The purpose of using seeding in an experiment such as this is to control the rate at which the crystals grow. If one seeds the solution, the crystals would grow rather quickly. If one does not, they'll grow more slowly." (Tr. at 713) The Court agrees that one of ordinary skill in the art would not ignore the crystallization conditions described in Example 17 simply because the example includes a seeding step. *See generally* Manual of Patent Examining Procedure § 2164.01 ("Any part of the specification can support an enabling disclosure, even a background section that discusses, or even disparages, the subject matter disclosed therein.") (citing *Callicrate v. Wadsworth Mfg., Inc.*, 427 F.3d 1361 (Fed. Cir. 2005)).

Moreover, credible testimony from Dr. Atwood and Mr. Moore established that Example 17 does not require one of ordinary skill in the art to seed with Form 5 (or seed at all) to make Form 5. Mr. Moore testified that the form of the seed in the slurry does not matter, because "when it goes into the solution, the crystal form is gone." (Tr. at 234) Also according to Mr. Moore, the filtering step removes whatever seeds are not dissolved. (*See* Tr. at 254) Dr. Atwood agreed. (Tr. at 725, 729) This is consistent with the explanation in the '372 patent, that the slurry "was seeded periodically with Form 5 ***until the seeds no longer dissolved*** (63° C.), then allowed to cool to 45° C. and ***filtered***." (JTX-001 at col. 28, ll. 17-19) (emphasis added)

Because the seed is either dissolved or filtered out, the crystallization step in Example 17 occurs without any seed present in the solution. (JTX-001 at col. 28, ll. 17-19; Tr. at 737-38) Additionally, the '372 patent explicitly discloses a method of making Form 5 by recrystallization of a dilute solution, which is defined as a "solution[] in which either Form 1 or Form 4 have already been isolated." (JTX-001 at col. 13, ll. 28-32)

When considered as a whole, the '372 patent provides one of ordinary skill in the art with information about the solvent system ("1% v/v THF/heptane"); the temperature ("room temperature"); the time ("overnight"); and the amount of material ("approximately 70g" of efavirenz) to make a slurry. The '372 patent also provides a method of characterizing the form – using x-ray powder diffraction and differential scanning calorimetry.[13] (JTX-001 at col. 1, ll. 8-11) Given these teachings, and in view of the high level of ordinary skill in the art, any additional experimentation required to make Form 5 would be "routine" and, therefore, not undue.[14] *See ALZA Corp.,* 603 F.3d at 940.

The Court's conclusion that the '372 patent enables one of ordinary skill in the art to make Form 5 crystal efavirenz without seeding is further supported by the nearly

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[13]For the reasons provided above in connection with Mylan's indefiniteness argument, the Court does not agree that claim 18 of the '372 patent is too broad to differentiate Form 5 from other prior art forms of crystalline efavirenz. The Court also does not agree that there are "thousands of distinct characterizations of material that would be considered Form 5." (D.I. 220 at 24 n.9) At trial the evidence established that only one existing form of material satisfies the requirements of claim 18: Form 5 of crystalline efavirenz. Accordingly, the "breadth of the claims" factor supports the Court's conclusion. *See In re Wands,* 858 F.2d at 737

[14]While other factors, such as "solution concentration, degree of supersaturation, system volume, temperature, solvent, presence or absence of impurities, and/or the time the system is allowed to stand unperturbed" may play a role in crystal formation (Tr. at 488-92), the record does not support a conclusion that these factors would require one of ordinary skill in the art to undergo undue experimentation to make Form 5.

contemporaneous experiments carried out by Mr. Moore. (*See* JTX-056 at pp. 148-71) For example, in experiment number 5, which used largely the same method (i.e., solvent system, temperature, time, and amount of material) as described in Example 17 of the '372 patent, but ***without*** seeding, Mr. Moore was able to make Form 5 successfully. (Tr. at 252-53; JTX-056 at pp. 169-70) Indeed, after running ten different experiments, Mr. Moore concluded that the results were "Excellent" and that he "Produced Form V repeatedly." (JTX-056 at p. 171) Mr. Moore confirmed this fact at trial:

> **Q.** So based on your experimental work, was it your belief that you could make Form 5 crystals at will, as you said, with or without seeding?
>
> **Mr. Moore.** Yes.

(Tr. at 257) The Court finds Mr. Moore's testimony credible. By contrast, Mylan's expert, Dr. Hollingsworth, did not attempt to make Form 5 using the guidance of the '372 patent. (*See* Tr. at 472-73)[15]

Mylan also contends that the '372 patent specification does not teach one of ordinary skill in the art how to make Form 5 with an exothermic peak at about 108° C to about 110° C. By following the steps for making Form 5 outlined in the '372 patent, one of ordinary skill in the art will obtain a crystal form with a DSC peak at about 108° C to about 110° C. That peak will be endothermic, which is consistent with the disclosure of the specification that describes Form 5 as having a "melting point" at about 108° C to about 110° C. (JTX-001 at col. 13, ll. 23-24; D.I.

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[15]In its Responsive Brief, Mylan also contends that claim 18 is not enabled because "Mr. Moore admitted at trial [that] Form 5 crumbles and reverts to Form I at room temperature." (D.I. 228 at 15) According to Mylan, this purported fact renders Form 5 "useless" and, therefore, not enabled. (*Id.*) This argument is not persuasive. Mr. Moore stated only that "he believes" Form 5 will revert to Form I after some time – "a lot longer" than three days. (Tr. at 300) This limited evidence is not clear and convincing evidence that claim 18 is not enabled.

220 at 25) Both sides agree that a single polymorph cannot have both an endothermic and an exothermic peak at the same location. (D.I. 220 at 25; Tr. at 794) There is no evidence in the record that a crystal form of efavirenz exists which satisfies the requirements of claim 18, but has an ***exothermic*** peak at about 108° C to about 110° C. Mylan cites no authority for the suggestion that a patent may be found invalid for lack of enablement based on the patent's failure to enable one of skill in the art to make a compound that does not exist.[16]

In sum, the Court rejects Mylan's enablement argument, and concludes that claim 18 is enabled.

D. Written Description

Mylan also contends that claim 18 of the '372 patent is invalid for failing to satisfy the written description requirement of 35 U.S.C. § 112. For the reasons below, the Court disagrees.

1. Legal Standards

To comply with the written description requirement of 35 U.S.C. § 112, the patent disclosure must convey with reasonable clarity to a person of ordinary skill in the art that the inventor was in possession of the claimed invention at the time of the application. *See Ariad Pharms., Inc. v. Eli Lilly &* Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification. It is part of the *quid pro quo* of the patent grant and ensures that the public receives a meaningful disclosure in exchange for being excluded from

[16]Neither party requested for the Court to determine whether the claims are limited to an endothermic peak.

practicing an invention for a period of time." *Id.* at 1353-54 (internal citations and quotation marks omitted).

Whether the written description requirement is met is a question of fact. *See Martek Biosciences Corp. v. Nutrinova, Inc.,* 579 F.3d 1363, 1369 (Fed. Cir. 2009). Mylan must demonstrate by clear and convincing evidence that claim 18 of the '372 patent is invalid for lack of written description. *See ICU Med., Inc. v. Alaris Med. Sys.*, 558 F.3d 1368, 1376 (Fed. Cir. 2009).

2. Discussion

Mylan contends that claim 18 of the '372 patent fails to satisfy the written description requirement because: (1) it fails to distinguish Form 5 from other crystal forms; (2) the specification fails to teach one of ordinary skill in the art how to make Form 5; and (3) the specification contains numerous scientific errors and inconsistencies, which would cause one of ordinary skill in the art to doubt the information contained therein. (D.I. 220 at 27-29) None of these arguments is persuasive.

The specification of the '372 patent discloses all eleven 2θ values listed in claim 16 and states that in a "preferred embodiment, Form 5 crystalline Efavirenz is characterized by a differential scanning calorimetry thermogram having a peak at about 108° C to about 110° C." (JTX-001 at col. 8, ll. 50-61; SUF ¶ 46) For chemical compounds, the written description requirement is satisfied when the application discloses "relevant identifying characteristics" such that the compound can be distinguished from other compounds. *See In re Wallach,* 378 F.3d 1330, 1335 (Fed. Cir. 2004). Moreover, the subject matter of claim 18 appeared in the original claims of the '421 application, which issued as the '372 patent. (JTX-004 at p. 98) (claims 92

and 93) Those "original claims constitute their own description." *In re Koller*, 613 F.2d 819, 823 (CCPA 1980) Hence, the Court concludes that the '372 patent specification provides literal support for claim 18.

Additionally, the Court has already found that the relevant identifying characteristics of Form 5 are sufficient to distinguish Form 5 from the prior art. The Court has also concluded that the disclosure of the '372 patent specification enables one of ordinary skill in the art to make Form 5 without undue experimentation. Finally, the Court is not persuaded that any purported "errors and inconsistencies" in the '372 patent, such as filing the original patent application with incorrect XPRD and DSC patterns for Form 5 (D.I. 220 at 29), lead to the conclusion that the inventors did not possess the claimed invention. Mylan's professed suspicions would not lead one of ordinary skill in the art to ignore the explicit disclosure of the '372 patent specification.

For these reasons, the Court concludes that Mylan has not proven by clear and convincing evidence that claim 18 is invalid for failing to satisfy the written description requirement.

IV. CONCLUSION

BMS has proved by a preponderance of the evidence that Mylan's ANDA product infringes asserted claim 18 of the '372 patent. Mylan has failed to prove by clear and convincing evidence that claim 18 of the '372 patent is invalid. By separate order, the parties will be directed to submit an appropriate form of judgment consistent with this opinion.[17]

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[17]Both parties moved for judgment as a matter of law during trial, pursuant to Federal Rule of Civil Procedure 52(c). (Tr. at 559-66, 667-71; *see also* D.I. 204) The Court deferred ruling on these motions until after trial. (Tr. at 574-75, 676-77) Having now made findings of fact and reached conclusions of law on a full post-trial record, the Court will deny all motions for judgment as a matter of law.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., and BRISTOL-MYERS SQUIBB PHARMA CO.,	:	
Plaintiffs/Counterclaim-Defendants,	:	
v.	:	C.A. No. 09-651-LPS
MYLAN PHARMACEUTICALS INC., MATRIX LABORATORIES LTD.,	:	
Defendants/Counterclaim-Plaintiffs.	:	
v.	:	
MERCK & CO., INC. and MERCK SHARP & DOHME CORP.,	:	
Counterclaim Defendants.	:	

ORDER

At Wilmington this 30th day of September, 2013:

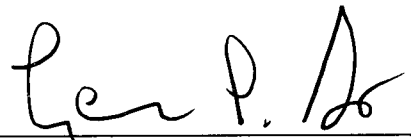
For the reasons set forth in the Memorandum Opinion issued this date, IT IS HEREBY ORDERED that:

1. The parties shall meet and confer and submit, no later than **October 10, 2013**, a proposed form of order consistent with the Memorandum Opinion, to enter final judgment for Plaintiffs and against Defendants, including any appropriate remedy.

2. Defendants' motion for judgment of non-infringement as a matter of law (D.I. 203) is DENIED.

3. Motions for judgment as a matter of law made during trial (*see* Trial Transcript at 559-66, 667-71) are DENIED.

4. The parties shall submit a proposed redacted version of the Memorandum Opinion no later than **October 7, 2013.**



UNITED STATES DISTRICT JUDGE