IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB COMPANY and PFIZER INC.,	:	
Plaintiffs,	:	
v.	:	C.A. No. 17-374-LPS (CONSOLIDATED)
AUROBINDO PHARMA USA INC. and AUROBINDO PHARMA LTD.,	:	
Defendants.	:	

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OPINION

August 5, 2020
Wilmington, Delaware

STARK, U.S. District Judge:

Plaintiffs Bristol-Myers Squibb Co. and Pfizer Inc. ("BMS" or "Plaintiffs") brought this action under the Hatch-Waxman Act against Defendants Sigmapharm Laboratories, LLC ("Sigmapharm"), Sunshine Lake Pharma Co., Ltd. and HEC Pharm USA Inc. ("Sunshine Lake"), and Unichem Laboratories Ltd. ("Unichem") (collectively, "Defendants").[1] BMS alleges that Defendants seek to bring to market new drugs that are bioequivalent to BMS's Eliquis® drug product ("Eliquis"), which treats and reduces the risk of certain cardiovascular conditions. BMS specifically alleges that: (1) Sigmapharm and Unichem infringe claims 13 and 104 of U.S. Patent No. 6,967,208 (the "'208 Patent"), which claim apixaban, the active chemical compound in Eliquis; and (2) all three Defendants infringe claims 21 and 22 of U.S. Patent No. 9,326,945 (the "'945 Patent"), which claim certain compositions containing apixaban. Defendants brought counterclaims alleging that the asserted claims of both the '208 and '945 patents are invalid.

The Court held a nine-day bench trial between October 23 and November 13, 2019. (*See* D.I. 692-700) ("Tr.") Thereafter, the parties submitted proposed findings of fact (D.I. 706, 708, 710, 717, 719-22) and post-trial briefs (D.I. 686, 688, 702, 705, 707, 709, 712-16, 718).

Pursuant to Federal Rule of Civil Procedure 52(a), and having considered the entire record in this case, the Court concludes that: (1) Sigmapharm's proposed drug products infringe the asserted claims of the '208 patent;[2] (2) Sigmapharm, Sunshine Lake, and Unichem's

[1] Plaintiffs originally brought this action against at least 25 pharmaceutical companies. By the time of trial, they had resolved their disputes with all but Sigmapharm, Sunshine Lake, and Unichem.

[2] Plaintiffs and Unichem entered into a stipulation of infringement with respect to the asserted claims of the '208 patent. (D.I. 672 Ex. 1 ("Parties' Statement of Uncontested Facts" ("UF")) at ¶ 17)

proposed drug products infringe the asserted claims of the '945 patent; and (3) the asserted claims of the '208 patent and '945 patent are not invalid.

The Court's findings of fact and conclusions of law are set forth in detail below.

FINDINGS OF FACT

I. Introduction

1. These consolidated cases concern U.S. Patent Nos. 6,967,208 and 9,326,945, both of which are listed in the United States Food and Drug Administration's ("FDA") *Orange Book* in connection with BMS's Eliquis product. (UF ¶ 51)

2. Eliquis is an FDA-approved anticoagulant that is indicated to treat and reduce the risk of certain cardiovascular disorders. (Kowey Tr. 1281)[3]

3. Apixaban is the active ingredient in Eliquis. (UF ¶ 35) The chemical name for apixaban is 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1- piperidinyl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo-[3,4-c]pyridine-3-carboxamide. (UF ¶ 36)

4. Sigmapharm submitted ANDA No. 210053 ("Sigmapharm's ANDA") to the FDA seeking approval to engage in the commercial manufacture, use, and sale of apixaban oral tablets, 2.5 mg and 5 mg ("Sigmapharm ANDA product(s)"). (UF ¶ 54) Sigmapharm's ANDA contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for both the '208 and '945 patents. (*Id.*)

5. Sunshine Lake submitted ANDA No. 209994 ("Sunshine Lake's ANDA") to the FDA seeking approval to engage in the commercial manufacture, use, and sale of apixaban oral tablets, 2.5 mg and 5 mg ("Sunshine Lake ANDA product(s)"). (UF ¶ 63) Sunshine Lake's

[3] Citations to trial testimony are in the form "[Witness Last Name] Tr. [page number]."

ANDA contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for the '945 patent. (*Id.*)

6. Unichem submitted ANDA No. 210108 ("Unichem's ANDA") to the FDA seeking approval to engage in the commercial manufacture, use, and sale of apixaban oral tablets, 2.5 mg and 5 mg ("Unichem ANDA product(s)"). (UF ¶ 72) Unichem's ANDA contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) for both the '208 and '945 patents. (*Id.*)

II. Patents-in-Suit

A. The '208 Patent

7. BMS owns the '208 Patent. (UF ¶ 13) The '208 patent's priority date is no later than September 21, 2001. (UF ¶ 19) The '208 patent is entitled, "Lactam-Containing Compounds and Derivatives Thereof As Factor Xa Inhibitors." (JTX 001 at -3348)

8. BMS asserts claims 13 and 104 of the '208 patent against Sigmapharm and Unichem. (UF ¶ 16)

9. Claim 13 recites:

> A compound according to claim 8, wherein the compound is:
>
> 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide
>
> or a pharmaceutically acceptable salt form thereof.

'208 patent at 269:1-6. That is, claim 13 recites apixaban or a pharmaceutically acceptable salt form of apixaban. (MacMillan Tr. 279)

10. Non-asserted claim 8, from which claim 13 depends, recites "[a] compound according to claim 1, wherein the compound is selected from" among 41 chemical compounds, "or a pharmaceutically acceptable salt form thereof." '208 patent at 265:39-268:41.

11. Non-asserted claim 1, from which claim 8 depends, recites a structure that includes many chemical compounds, one of which is apixaban. (MacMillan Tr. 281-83)

12. Claim 104 of the '208 patent recites:

> A compound according to claim 13, which is a crystalline compound.

('208 patent at Certificate of Correction page 11 of 13) (D.I. 1-1 at 152 of 154)

13. The Court construed one claim term from the '208 patent. "Pharmaceutically acceptable salts" means "derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio." (UF ¶ 23) The parties agreed that all other claim terms in the '208 patent have their plain and ordinary meaning to a person of ordinary skill in the art ("POSA"). (*Id.*)

14. Sigmapharm contests infringement of the '208 patent. However, Sigmapharm does not dispute that Sigmapharm's ANDA products contain apixaban. (UF ¶ 57)

15. Unichem has stipulated to infringement of the asserted claims of the '208 Patent. (UF ¶ 17)

B. The '945 Patent

16. BMS and Pfizer jointly own the '945 patent. (UF ¶ 26) The '945 patent's priority date is no later than February 24, 2011. (UF ¶¶ 29-30) The '945 patent is entitled: "Apixaban Formulations." (JTX 002 at 3687)

17. Plaintiffs assert claims 21 and 22 of the '945 patent against Sigmapharm, Sunshine Lake, and Unichem. (UF ¶ 28; Atwood Tr. 322) Claims 21 and 22 depend from

independent claim 12 and add that the compositions comprise 2.5 or 5 mg of apixaban, respectively. '945 patent at 10:46-49.

18. Specifically, claim 12 recites:

> A solid pharmaceutical composition comprising a therapeutically effective amount of apixaban and a pharmaceutically acceptable diluent or carrier,
>
> wherein apixaban comprises crystalline apixaban particles,
>
> wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 μm, and
>
> wherein, as measured using a USP Apparatus 2 at a paddle rotation speed of 75 rpm in 900 ml, of a dissolution medium at 37° C., at least 77 wt % of apixaban in the pharmaceutical composition dissolves within 30 minutes in the dissolution medium, and the dissolution medium is 0.05 M sodium phosphate at a pH 6.8 containing 0.05% sodium lauryl sulfate.

'945 patent at 10:13-27.

19. During claim construction, the Court construed "apixaban particles have a D_{90}" to have its plain and ordinary meaning. (UF ¶ 34) The parties agreed that all other claim terms in the '945 patent have their plain and ordinary meaning to a POSA. (*Id.*)

20. Sigmapharm, Sunshine Lake, and Unichem contest infringement of the '945 patent.

21. Sigmapharm and Sunshine Lake dispute infringement of two limitations: "wherein apixaban comprises crystalline apixaban particles" and "wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 microns." (Zaworotko Tr. 964; Brittain Tr. 1100)

22. Unichem disputes infringement of only the latter limitation: "wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 microns." (Berkland Tr. 603; Genck Tr. 1144, 1190)

III. Witnesses

A. BMS's Experts

23. Dr. Jerry Atwood is a Professor of Chemistry at the University of Missouri. (Atwood Tr. 318) Dr. Atwood has worked on the preparation and analysis of pharmaceutical formulations for about 40 years. (*Id.* at 319) The Court recognized Dr. Atwood as an expert in pharmaceutical formulation and analysis. (*Id.* at 321)

24. Dr. David MacMillan has taught organic chemistry for 21 years, most recently at Princeton University. (MacMillan Tr. 271) The Court recognized Dr. MacMillan as an expert in organic and medicinal chemistry. (*Id.* at 274)

25. Dr. Eric Jacobsen is the Sheldon Emory Professor of Chemistry at Harvard University, where he has taught for 27 years. (Jacobsen Tr. 1490-91) The Court recognized Dr. Jacobsen as an expert in organic and medicinal chemistry. (*Id.* at 1493)

26. Dr. Peter Kowey is a clinical cardiologist at Main Line Health in Radnor, Pennsylvania. (Kowey Tr. 1272-73) He is also a professor of medicine and clinical pharmacology at the Jefferson Medical College at Thomas Jefferson University and the William Wikoff Smith Chair in Cardiovascular Surgery at the Lankenau Heart Institute. (*Id.* at 1273) The Court recognized Dr. Kowey as an expert in clinical medicine including in particular the treatment of thromboembolic disorders. (*Id.* at 1277)

27. Dr. Allen Myerson is a professor of chemical engineering at the Massachusetts Institute of Technology. (Myerson Tr. 1662-63) The Court recognized Dr. Myerson as an expert in pharmaceutical formulation analysis. (*Id.* at 1664)

28. Dr. Eric Munson is a professor of industrial and physical pharmacy at Purdue University. (Munson Tr. 529) The Court recognized Dr. Munson as an expert in pharmaceutical formulation and analysis. (*Id.* at 530-31)

29. Dr. Cory Berkland is a professor of pharmaceutical chemistry and chemical and petroleum engineering at the University of Kansas. (Berkland Tr. 593) The Court recognized Dr. Berkland as an expert in the preparation and analysis of pharmaceutical formulations. (*Id.* at 594)

B. Defendants' Experts

30. Dr. Harry Brittain is the Institute Director at the Center for Pharmaceutical Physics. (Brittain Tr. 1047) Dr. Brittain has worked in the field of physical pharmacy for over 35 years. (*Id.* at 1049-50) The Court recognized Dr. Brittain as an expert in physical chemistry and physical pharmacy with special expertise in the development and analysis of pharmaceutical formulations and analytical methods, including X-ray powder diffraction. (*Id.* at 1051)

31. Dr. Michael Zaworotko is a professor of crystal engineering at the University of Limerick. (Zaworotko Tr. 903) He has published over 400 peer-reviewed articles whose main subject matter is crystallography and crystallization. (*Id.* at 904-05) The Court recognized Dr. Zaworotko as an expert in the areas of pharmaceutical formulation and analysis, synthesis and structural chemistry, crystallization, crystal engineering, and x-ray crystallography. (*Id.* at 906)

32. Dr. David Apperley has worked in the solid state nuclear magnetic resonance ("NMR") service at the University of Durham Industrial Research Laboratories since 1986.

(Apperley Tr. 723) The Court recognized Dr. Apperley as an expert in NMR testing and analysis. (*Id.* at 726)

33. Dr. Robert Schurko is director of the NMR users program at the National High Field Magnetic Laboratory in Tallahassee, Florida, and was previously a full professor at the University of Windsor in Windsor, Ontario, Canada. (Schurko Tr. 780) The Court recognized Dr. Schurko as an expert in solid state NMR testing and analysis. (*Id.* at 783)

34. Dr. Clayton Heathcock was formerly a chemistry professor at the University of California at Berkeley. (Heathcock Tr. 678) The Court recognized Dr. Heathcock as an expert on organic chemistry and medicinal chemistry. (*Id.*)

35. Dr. Randall Zusman is a noninterventional cardiologist and a faculty member at the Division of Cardiology at the Massachusetts General Hospital. (Zusman Tr. 863-64) The Court recognized Dr. Zusman as an expert in the evaluation, treatment, and care of patients with respect to a broad spectrum of cardiac diseases. (*Id.* at 866)

36. Dr. Wayne Genck is chief engineer and owner of Genck International and has experience in particle size distribution of solid materials. (Genck Tr. 1131, 1136) The Court recognized Dr. Genck as an expert in the field of particle size, measurement distribution, and modification in pharmaceutical preparations. (*Id.* at 1139)

37. Dr. Walter Chambliss is a professor emeritus and research professor in the pharmaceutics department at the University of Mississippi. (Chambliss Tr. 1223) He has experience with the Biopharmaceutical Classification System ("BCS"), dissolution testing, and formulation development. (*Id.* at 1223-24) The Court recognized Dr. Chambliss as an expert in pharmaceutical sciences and pharmaceutical formulations and related fields. (*Id.* at 1226-27)

IV. Person Of Ordinary Skill In The Art

A. '208 Patent

38. Plaintiffs' experts opined that a POSA for the '208 patent is:

> A professional with a graduate degree in organic chemistry, pharmaceutical chemistry, or an equivalent discipline, with experience in the synthesis, purification, and design of pharmaceutical compounds and derivatives thereof as of the date of the claimed inventions. A POSA would have worked with a team of professionals with training in related disciplines, such as pharmacology, pharmacokinetics, metabolism, toxicology, formulation, or clinical medicine as of the date of the claimed inventions.

(UF ¶ 20)

39. Defendants' experts applied the following definition of a POSA for the '208 patent:

> A person who possesses an advanced degree (Ph.D. or Master's) in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field and at least some experience in the research, design, and development of small molecule drugs or drug candidates, either in academia or industry. The POSA would have substantial knowledge and experience in the design of drugs to meet specific clinical utility, including the understanding of structure-activity relationships, biochemical targets, and the role of physical-chemical properties. The POSA would have consulted and/or collaborated with professionals in related areas of pharmaceutical R&D, including analytical, formulation, preclinical, and clinical research and development and would have a good understanding in these related fields. Additional practical experience could also substitute for the advanced degree. Such a POSA may also work in conjunction with a team that included one or more other POSAs with respect to one or more other aspects with which the other POSA may have expertise and knowledge that was obtained through his or her educational, industrial, or academic experiences. The person (or team) of ordinary skill in the art could have a lower level of formal education if such a person (or team) had a higher degree of experience. The person (or team) of ordinary skill would easily have understood the prior art references referred to herein,

and would have had the capacity to draw inferences from the prior art and from others skilled in the art.

(UF ¶ 21)

40. The parties agree that "[t]he opinions offered by each side's experts as to the validity and infringement of the '208 Patent do not change based on which of the two definitions . . . is applied." (UF ¶ 22) The Court agrees with the parties' agreement on this point.

B. '945 Patent

41. Plaintiffs' experts opined that a POSA for the '945 patent is:

> A person that has a Ph.D. or Master's degree or a Bachelor's degree with commensurate experience in chemistry, chemical engineering, pharmacy, pharmaceutical science or an equivalent discipline and has an understanding of the properties of active pharmaceutical ingredients, the design of solid pharmaceutical dosage forms, and knows or has access to techniques to characterize solid pharmaceutical products.

(UF ¶ 31)

42. Defendants' experts opined that a POSA for the '945 patent is:

> A person that has a Ph.D. in pharmaceutical sciences or a closely related field with two or more years of experience in that field or a master's degree in pharmaceutical sciences or a closely related field and five or more years of experience, or the equivalent, in pharmaceutical formulation, or a bachelor's degree in chemistry, pharmaceutics, or chemical engineering, and significant work experience in the manufacture and characterization of materials having pharmaceutical interest. That POSA would have been capable of designing and formulating pharmaceutical formulations, including immediate release compositions of low solubility active pharmaceutical ingredients, such as, for example, apixaban for thromboembolic therapy. This POSA at the relevant time had training in, experience in, and/or an understanding of particle size and dissolution testing that frequently accompanies the development of pharmaceutical formulations. Such a person generally would have supervised and/or collaborated with others having skill and/or expertise in the testing discussed above.

(UF ¶ 32)

43. The parties agree that "the opinions offered by each side's experts as to the validity and infringement of the '945 Patent do not change based on which of the two definitions . . . is applied." (UF ¶ 33) The Court agrees with the parties' agreement on this point.

V. Facts Related to Infringement

A. Crystallization

i. General Background

44. Pharmaceutical compositions are made up of an active pharmaceutical ingredient ("API") and one or more excipients. (Atwood Tr. 325) An API is the active ingredient that treats a disease, while an excipient is any component that is not the active ingredient. (*Id.* at 325-26) In Eliquis and in the proposed ANDA products, the API is apixaban. (*Id.* at 325) "Bulk apixaban" refers to apixaban before it is included in a pharmaceutical composition. (Genck Tr. 1148)

45. A crystalline particle contains a substance with molecules in a long-range order called a crystal lattice or array. (Atwood Tr. 326) Long-range order means there are enough ordered molecules to generate an x-ray powder diffraction, or "XRPD," pattern. (Zaworotko Tr. 911)

46. All crystals are particles. (Myerson Tr. 1669)

47. Materials which lack long-range order are called amorphous materials. (Atwood Tr. 326-27) Crystalline and amorphous forms can coexist, although amorphous materials will tend to convert to a lower-energy crystalline form. (*Id.* at 327-29)

48. Crystals form by a process called nucleation, which involves molecules coming together to form a lower-energy crystal array. (*Id.* at 330) When crystals initially form, they are on the order of a few nanometers across in size. (*Id.*) After nucleation, a crystal grows by

converting surrounding amorphous material to crystalline form, as molecules join the lower-energy crystalline array. (*Id.* at 331)

49. The classical models of nucleation and crystal growth were known in the art as of 2010 and apply to solid pharmaceutical compositions. (*Id.* at 332-33) Amorphous materials can generally convert to crystalline materials in a tablet formulation. (Brittain Tr. 1104)

50. Crystal growth is limited by the amount of material able to be converted to crystalline form. (Atwood Tr. 332) When excipients surround a region of crystalline and amorphous material, the excipients will limit the ultimate size of the crystalline particle. (*Id.*)

51. For example, povidone, or PVP, is an excipient that is well-known in the art for inhibiting and preventing nucleation and crystallization in an amorphous solid dispersion. (Brittain Tr. 1057, 1098)

ii. Identifying Crystalline Apixaban Particles

a. X-ray Powder Diffraction (XRPD)

52. X-ray Powder Diffraction ("XRPD") is an accepted method for distinguishing between crystalline and amorphous materials and, thus, for identifying the presence of crystalline apixaban particles. (Atwood Tr. 335-36; Zaworotko Tr. 914)

53. The United States Pharmacopeia ("USP") teaches that identification of the phase composition of an unknown sample by XRPD can be based on visual comparison of a portion of its XRPD pattern to a known reference. (Atwood Tr. 338-40)

54. The '945 patent lists six characteristic peaks of crystalline apixaban form N-1 and establishes a margin of error of 0.1 degrees. (*Id.* at 340-41, 353-54; '945 patent at 4:66-5:3 & Table 2)

55. Sigmapharm's expert, Dr. Zaworotko, admitted that "a single sharp peak" is indicative of crystallinity. (Zaworotko Tr. 969) He agreed that "if there is a sharp peak in an XRPD, this indicates long-range order." (*Id.*)

56. Each XRPD scan is referred to as a "step." (Atwood Tr. 359) Each step is performed at a different angle. (*Id.*)

57. The parties' experts agreed that it is not necessary to match all peaks in an XRPD pattern in order to identify a crystalline material. (*Id.* at 341-42; Zaworotko Tr. 972-73)

58. The amount of time programmed for each step is known as "count time." (Atwood Tr. 359)

59. Count time and step time are synonymous. (Zaworotko Tr. 982)

60. The count number on the Y axis is the number of photons collected by the detector at a certain angle during an XRPD experiment. (Atwood Tr. 334, 342) The standard deviation in a measurement is the square root of the number of counts collected. (*Id.* at 342-43)

61. There is no dispute that increasing the count time is an appropriate method to detect components that are a small portion of a sample. (*Id.* at 360; Zaworotko Tr. 917, 976-77; Brittain Tr. 1112)

62. As the number of counts collected increases, the standard deviation decreases relative to the number of counts, so scans with higher count times are more sensitive than scans with lower count times and are, therefore, better able to detect material that is present in only small amounts. (Atwood Tr. 342-43) Accordingly, performing slower scans by increasing the count time per step increases the sensitivity of an XRPD test. (*Id.* at 343)

b. Solid-State Nuclear Magnetic Resonance (SSNMR)

63. The parties' experts agreed that solid state nuclear magnetic resonance ("SSNMR") is a useful tool to distinguish crystalline and amorphous materials in pharmaceutical compositions. (Apperley Tr. 754-55; Schurko 817)

64. Crystalline peaks in SSNMR spectra are characterized by sharp peaks, which are visually distinguishable from broad peaks created by amorphous material. (Munson Tr. 532-33) Crystalline peaks in a mixture of amorphous and crystalline material appear as sharp peaks overlaid on broader peaks. (*Id.* at 562-64) Peak line widths should be visually comparable, but it is not necessary to measure line widths because a POSA can simply compare the line widths of an observed peak to peaks in a reference API. (*Id.* at 561-62, 564, 585; Schurko 851-52)

iii. Determining Crystalline Apixaban Particle Size

65. There are many methods for measuring particle size. (Myerson Tr. 1671) These methods include laser light scattering, imaging, and many others. (*Id.* at 1671-72)

66. Scanning electron microscopy ("SEM") is a type of imaging that uses a high-powered microscope with an electron beam as its energy source. (Berkland Tr. 597-98) The electron beam is projected onto the surface of a sample and electrons are reflected back up to a detector. (*Id.*) The detector converts the electrons into an image. (*Id.*) At the same time, imaging software produces a scale bar on the image which can be used to measure particle size. (*Id.* at 598)

67. The prior art describes the use of imaging techniques, such as SEM, to measure particle size. (*Id.* at 605-06) The prior art specifically describes the use of imaging techniques such as SEM to measure particle size of pharmaceutical compositions. (*Id.* at 609)

68. SEM can be used to determine particle size simply by taking a picture and

measuring the size of the particles in that picture using the scale bar. (*Id.* at 606)

69. Energy-dispersive X-ray spectroscopy ("EDS") is an analytical technique that uses the same SEM instrument to identify the atoms present in a sample. (*Id.* at 598-99) Using the same electron beam as is involved in SEM, a separate detector collects x-rays emitted from the sample. (*Id.*) Each element emits a particular x-ray and can be used to identify that element. (*Id.*) For example, carbon emits a specific x-ray, oxygen has its own x-ray, and nitrogen another distinct x-ray. (*Id.*) The detector can convert the x-ray signals into colors. (*Id.*) The image generated is also known as an elemental map. (*Id.* at 600)

70. SEM-EDS is the combination of SEM and EDS on the same analytical machine. (*Id.* at 599) To use the two techniques together, SEM is used to image the sample while EDS superimposes the elemental maps onto that image to identify the elements that make up the sample. (*Id.*)

71. The prior art discloses the use of SEM-EDS with pharmaceutical compositions. (*Id.* at 606-09)

72. SEM can be used by itself to measure particle size when the identity of a substance is known. (*Id.* at 599-600) SEM-EDS can be used to measure particle size of a particular component of a mixture. (*Id.* at 600) A POSA can use the EDS technique to determine the identity of a particular particle and then overlay that elemental map on top of an SEM image to measure the size of that particular particle. (*Id.* at 598, 600)

73. SEM-EDS is a routine and well-understood technique. (*Id.* at 600, 609-10) As of the priority date of the patents-in-suit, a POSA would have known that SEM-EDS was an available method to measure the size and composition of pharmaceutical particles. (*Id.* at 605, 609-10)

74. The SEM-EDS technique does not permit one to view apixaban particles that are below the surface of the granules. (Genck Tr. 1180-81)

B. Sigmapharm

i. Sigmapharm's Manufacturing Process

75. Sigmapharm's Drug Master File No. 030774 states that Sigmapharm uses "Apixaban . . . crystalline Form I" as the "starting material" for manufacturing its ANDA products. (PTX 1068 at -820; *see also* MacMillan Tr. 292-93) Sigmapharm's ANDA specifies that Sigmapharm manufactures its ANDA products in Bensalem, Pennsylvania. (PTX 1011 at 3; MacMillan Tr. 293-94)

76. Sigmapharm's CEO, Spiridon Spireas, testified that Sigmapharm used crystalline apixaban to manufacture its apixaban drug product: "Look, we're using a Medichem material with crystalline particles." (Spireas Tr. 262; *see also id.* at 260-63)

77. Sigmapharm attempts to avoid crystallization of its end product by using a process designed to make an amorphous dispersion with the polymer povidone, which is known to inhibit crystal growth. (Zaworotko Tr. 908, 934-35, 969-71)

78. Sigmapharm starts by dissolving crystalline apixaban in a solution with povidone. (Atwood Tr. 381-82) The mixture containing the apixaban and povidone is spread into trays and vacuum dried. (*Id.* at 382) Drying forms a drug intermediate that contains 6.6% apixaban and 93.1% povidone. (*Id.*) After drying, the drug intermediate is granulated with excipients and compressed into tablets. (*Id.*; Zaworotko Tr. 935-36)

79. Sigmapharm's manufacturing process limits the size of the crystalline apixaban particles that form in Sigmapharm's ANDA products. (Atwood Tr. 382-83) Apixaban is thoroughly mixed in the solution (*id* at 452), and rapid drying leaves the apixaban

uniformly dispersed in pockets in the polymer povidone (*id.* at 383).

80. Due to the small amount of apixaban in the intermediate, the pockets of apixaban must be small, such that large crystalline apixaban particles cannot form. (*Id.* at 383) Dr. Atwood testified "there's just not going to be enough apixaban in these pockets to form particles of 89 microns" or larger. (*Id.* at 384)

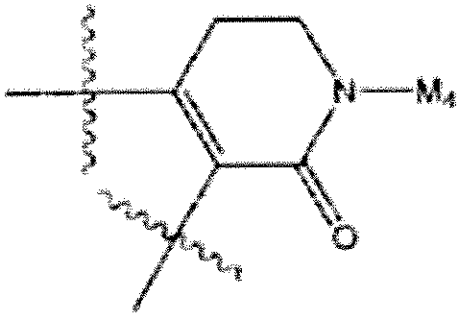
81. Polymer and other excipients prevent pockets of crystalline apixaban from joining to form larger crystalline apixaban particles. (*Id.* at 383-84) Even Sigmapharm's expert, Dr. Zaworotko, testified that there would be "an inhibition of crystallization" in the dispersion. (Zaworotko Tr. 970) Apixaban in Sigmapharm's formulation would be expected to have limited mobility, while "crystal growth requires continued molecular mobility." (*Id.* at 971) Dr. Atwood testified credibly and persuasively that it is not possible for "apixaban as it crystallizes to mix and mingle with other crystal apixaban pockets and form large crystals." (Atwood Tr. 383-84)

ii. Apixaban in Sigmapharm's ANDA Product

82. Sigmapharm's ANDA products will contain 2.5 mg or 5 mg of apixaban. (UF ¶ 57) Sigmapharm disputes that its products' apixaban will satisfy four limitations in claim 1, which are depicted as Rings M, E, A, and Q. (Heathcock Tr. 686-87, 714)

83. Claim 1's Ring M limitation recites:

ring M, including P_1, P_2, M_1, and M_2 is substituted with 0-2 R^{1a} and is



'208 patent at 237:12-24. Claim 1's R^{1a} limitation begins: "R^{1a}, at each occurrence, is selected from H, —$(CR^3R^{3a})r$—R^{1b}, ..." *Id.* at 238:62-63.

84. A POSA would have understood that four hydrogens are present on the chemical structure shown in the Ring M limitation of claim 1. (Heathcock Tr. 715-16) In apixaban, ring M contains the same four hydrogens. (MacMillan Tr. 284-86) A POSA, therefore, would have understood that Ring M in apixaban is substituted with zero R^{1a} groups; that is, there is no difference between the R^{1a} groups for Ring M as recited in the claim and Ring M as it appears in apixaban. (*Id.* at 286)

85. Claim 1's Ring E limitation recites:

> E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and is substituted with 1-2 R . . . .

'208 patent at 237:36-61. Claim 1's R limitation begins: "R is selected from H, C_{1-4} alkyl, F, Cl, Br, I, OH, OCH_3 . . . ." *Id.* at 238:5.

86. In apixaban, Ring E is a phenyl ring. (MacMillan Tr. 1630-31) Because carbon atoms typically form four bonds (*id.* at 284-85), a POSA would have understood the phenyl ring at Ring E to begin with five hydrogens (*id.* at 1630-31). Ring E in apixaban contains four hydrogens and one methoxy group (i.e., OCH_3). (Heathcock Tr. 690-91) A POSA would, therefore, have understood Ring E in apixaban to be substituted with one R group (i.e., the

methoxy group that is substituted for one of the five hydrogen atoms in the phenyl structure recited in claim 1). (MacMillan Tr. 1631)

87. Claim 1's Ring A limitation recites:

> A is selected from:
>
> $C_{3\text{-}10}$ carbocycle substituted with 0-2 R^4 . . . .

'208 patent at 238:20-21. Claim 1's R^4 limitation begins: "R^4, at each occurrence, is selected from H, =O . . . ." *Id.* at 240:47-48.

88. In apixaban, Ring A is a phenyl ring. (MacMillan Tr. 1629) Because carbon atoms typically form four bonds (*id.* at 284), a POSA would have understood the phenyl ring at Ring A to begin with four hydrogens (*id.* at 1629). Ring A in apixaban contains the same four hydrogens. (*Id.*) A POSA, therefore, would have understood Ring A in apixaban to be substituted with zero R^4 groups, as there is no difference between the R^4 groups in the chemical structure for Ring A recited in the claim and Ring A as it appears in apixaban. (*Id.*; *see also id.* at 281-88)

89. Claim 1's Ring Q limitation recites:

> ring Q is a 6 membered monocyclic ring, wherein 0 double bond is present within the ring and the ring is substituted with 0-2 R^{4a} . . . .

'208 Patent at 238:22-37. Claim 1's R^{4a} limitation begins: "R^{4a}, at each occurrence, is selected from H, =O, $(CR^3R^{3a})_rOR^2$, ..." *Id.* at 240:65-66.

90. In apixaban and in claim 1, Ring Q is a six membered monocycle. (MacMillan Tr. 1630) Because carbon atoms typically form four bonds (*id.* at 284), a POSA would have understood the monocycle at Ring Q to begin with eight hydrogens (*id.* at 1630). Ring Q in apixaban contains the same eight hydrogens. (Heathcock Tr. 692) Therefore, a POSA would have understood Ring Q in apixaban to be substituted with no R^{4a} groups because there is no

difference between the R^{4a} groups in the chemical structure for Ring Q recited in the claim and Ring Q as it appears in apixaban. (MacMillan Tr. 1629-30; *see also id.* at 281-88)

91. Sigmapharm expert Dr. Heathcock opined that his (and Sigmapharm's) interpretation – that claim 1 requires counting each hydrogen on these four rings as substitutions – means that: (1) "apixaban, which is a compound that the '208 patent is about and which the '208 patent expressly claims, is not within the scope of claim 1;" (2) "none of the compounds that are specifically disclosed in the '208 patent would fall within the scope of claim 1;" and (3) "it's impossible for any compound to fall within claim 1's scope." (Heathcock Tr. 713, 718)

iii. Crystallization in Sigmapharm's ANDA Products

92. Sigmapharm will use the same manufacturing process for its 2.5 mg and 5 mg tablets. (Munson Tr. 555) Dr. Zaworotko and Dr. Schurko do not contest that Sigmapharm's 2.5 mg and 5 mg ANDA products will be the same with respect to composition. (Schurko Tr. 826; Zaworotko Tr. 994-95)

a. Dr. Atwood's XPRD Testing

93. Dr. Atwood received samples of Sigmapharm's 5 mg ANDA product from counsel. (Atwood Tr. 350-51) He performed XRPD scans of varying degrees of sensitivity, including scans with count times of 30 to 100 seconds. (*Id.* at 363-67, 369-70; PTX 1098 at 8, 12, 14)

94. Dr. Atwood identified four characteristic crystalline apixaban peaks in XRPD patterns of Sigmapharm's ANDA product. (Atwood Tr. 363-65; PTX 1098 at 8 (12.3 and 12.9 peaks); PTX 1098 at 14 (27.1 peak); PTX 1098 at 12 (22.1 peak)) Peaks at 12.3, 12.9, and 27.1 are listed in the '945 patent as characteristic of apixaban (Atwood Tr. 354), and a peak at 22.1 degrees appears in Sigmapharm's own XRPD test of its pure crystalline form N-1

apixaban API (*id.* at 367-69; *see also* PTX 1009 at SIGMA_APIX 0017897-98; PTX 1098 at 12). Dr. Atwood identified a peak at 22.0 degrees in his reply report. (Atwood Tr. 506-07)

95. Based on the peaks he identified in XRPD scans of Sigmapharm's ANDA products, Dr. Atwood concluded that Sigmapharm's ANDA products contain crystalline apixaban particles. (*Id.* at 371) The Court found Dr. Atwood's analysis to be credible and persuasive.

96. Sigmapharm's expert, Dr. Zaworotko, testified that no specific number of peaks is required in order to match a measured XRPD pattern to a known reference pattern, as "what is appropriate will vary from sample to sample." (Zaworotko Tr. 972-73) One factor is whether one knows what is in one's sample. For instance, the USP recommends scanning past ten peaks when comparing an unknown sample to the Powder Diffraction File of over 60,000 reference patterns. (*Id.* at Tr. 973-74; PTX 409 at -2473)

97. For his noninfringement analysis, Dr. Zaworotko relied on testing by Catalent, a contract company that conducts testing. (Zaworotko Tr. 931, 964, 978) Catalent's testing of Sigmapharm's drug intermediate used count times of one second. (*Id.* at 978-79)

98. A limit of detection ("LOD") is "the minimum concentration or . . . weight content of the analyte of interest that would allow XRPD to detect the presence of that analyte." (*Id.* at 918) If a component is present above its LOD, it can be detected by XRPD. (*Id.* at 917) In other words, as Dr. Atwood explained, "[a] limit of detection means that if one gets enough material present in the sample to detect it, it's above the limit of detection. If it's below the limit of detection, then one doesn't detect it." (Atwood Tr. 371) Although Sigmapharm's ANDA product contains 3.125 percent apixaban, Sigmapharm's XPRD method used a limit of detection of 5 percent. (Zaworotko Tr. 983) Dr. Zaworotko agreed that "[i]f the limit of detection for an

XRPD test is 5 percent . . . the test method is invalid for analyzing a component that is only 3 percent of a sample." (*Id.* at 977)

99. Dr. Atwood did not perform a limit of detection analysis because he detected the four crystalline peaks. (Atwood Tr. 371-72)

b. Dr. Munson's SSNMR Testing

100. Dr. Munson tested Sigmapharm's 5 mg ANDA product using SSNMR, using BMS's crystalline apixaban API as a reference. (Munson Tr. 533-34, 536) Dr. Munson observed 12 peaks in Sigmapharm's ANDA product that correspond to peaks in the spectra from BMS's crystalline apixaban. (*Id.* at 545-49) Six well-resolved peaks had the same location and shape as those in the crystalline apixaban reference. (*Id.*) The other six crystalline apixaban peaks were partially resolved and appeared as a shoulder or other features on another peak. (*Id.* at 549-50, 552-55)

101. Dr. Munson also determined that no peaks present in the crystalline apixaban reference spectra were missing from the Sigmapharm tablet. (*Id.* at 549, 557) Five crystalline apixaban peaks were obscured by large peaks from excipients, which is "fairly typical" and did not change Dr. Munson's conclusion. (*Id.* at 556-57)

102. Artifacts in Dr. Munson's spectra, including a spinning sideband and baseline distortions (in which the baseline is not perfectly flat), were not unusual and did not impair his analysis. (*Id.* at 550-51, 557-58) Dr. Munson was able to view the peaks partially obscured by the spinning sidebands. (*Id.* at 550-51)

c. Dr. Apperley's Testing

103. After conducting SSNMR testing, Sigmapharm expert Dr. Apperley concluded that Sigmapharm's ANDA products did not contain crystalline apixaban.

104. Dr. Apperley conducted three sets of experiments. (Apperley Tr. 730-31) He conducted his first set of experiments using both a sample of crystalline apixaban ("API") and a sample of Sigmapharm's ANDA product. (*Id.* at 732) Dr. Apperley ran the crystalline material for one hour and the tableted material (which contained only 3 percent apixaban) for 16 hours. (*Id.* at 735)

105. Dr. Apperley opined that the first set of experiments were "not consistent with the presence of crystalline apixaban" in Sigmapharm's products because the NMR data for the Sigmapharm ANDA products featured broad peaks and, thus, showed amorphous material. (*Id.* at 737) He noted that although a signature peak at 121.7 ppm was present in the crystalline sample it was missing in the Sigmapharm ANDA product sample. (*Id.*) However, he also acknowledged that his first set of SSNMR experiments was "not sufficiently sensitive to definitively determine the crystallographic form of apixaban." (*Id.* at 763-64)

106. Dr. Apperley's second set of experiments used the same experimental parameters as the first, but with a larger sample size and accumulation time (both of which improved the signal-to-noise ratio) as well as a different spin rate. (*Id.* at 741-42) This second set was designed to try to detect crystalline apixaban material in the Sigmapharm ANDA product. (*Id.* at 741)

107. The second test also showed a spectrum with broader line widths than the crystalline material, which suggests amorphous material. (*Id.* at 742) The signature peak at 121.7 ppm was again missing from the Sigmapharm ANDA product spectrum. (*Id.* at 744-45) As a result of the second test, Dr. Apperley again opined that there was no evidence of crystalline apixaban in the Sigmapharm product. (*Id.* at 742)

108. Dr. Apperley's third set of experiments involved a mixture of crystalline apixaban

and a placebo. (*Id.* at 748) The purpose of these experiments was to determine how the spectrum would appear if Sigmapharm's ANDA product contained crystalline apixaban in addition to the other excipients. (*Id.*) Dr. Apperley also tested the placebo alone to confirm that there were no signals from other ingredients in the Sigmapharm ANDA product that would affect the analysis of apixaban. (*Id.* at 750; *see also* Schurko Tr. 804-07)

109. In the third set of experiments, Dr. Apperley established a LOD of ≈ 1.5 percent. (Apperley Tr. 757)

110. Dr. Apperley opined that all three sets of experiments indicated that Sigmapharm's ANDA product does not contain crystalline apixaban. The Court does not find Dr. Apperley's conclusions persuasive. Dr. Apperley did not know the limit of detection for his first and second sets of SSNMR experiments, and the limit of detection for Dr. Apperley's third set of SSNMR experiments was about 1.5 percent or higher, which he admitted means that even if half of the apixaban in the sample were crystalline his SSNMR experiment would still not detect it. (*Id.* at 761; *see also id.* at 757-58)

d. Dr. Schurko's Analysis

111. Another Sigmapharm expert, Dr. Schurko, examined NMR testing conducted by Dr. Nethercott (and interpreted by Dr. Munson) and by Dr. Apperley. (Schurko Tr. 784) Dr. Schurko concluded that all of the NMR evidence showed no indication of crystalline apixaban in Sigmapharm's ANDA products and, instead, showed amorphous apixaban. (*Id.* at 784-85, 789-91)

112. Dr. Schurko processed the data relied on by Dr. Munson using different sets of parameters to account for factors like signal-to-noise ratio and influence on line widths. (*Id.* at 838-39)

113. Dr. Schurko's decision to process Dr. Munson's data using different parameters changed the appearance of the spectra, rendering his depiction of Dr. Munson's data unreliable. (*Id.* at 838-40; *see also* Munson Tr. 558-59)

C. Sunshine Lake

i. Sunshine Lake's Manufacturing Process

114. Sunshine Lake uses the same manufacturing process for its 2.5 mg and 5 mg tablets. (Atwood Tr. 429)

115. Sunshine Lake attempts to avoid crystallization by using a process designed to make an amorphous dispersion. (Brittain Tr. 1078) Sunshine Lake uses the polymer povidone as an excipient, as povidone is a well-known nucleation and crystallization inhibitor. (*Id.* at 1078-79)

116. Sunshine Lake starts by dissolving crystalline apixaban in a solution with povidone. (Atwood Tr. 425) The solution of povidone and apixaban is then sprayed onto a bed of excipient particles on which the droplets rapidly dry. (*Id.*; Brittain Tr. 1058-59)

117. Sunshine Lake's manufacturing process limits the size of the crystalline apixaban particles that form in Sunshine Lake's ANDA products. (Atwood Tr. 426) Rapid drying leaves the apixaban uniformly distributed. (*Id.* at 426-27; Brittain Tr. 1058-59) Dr. Atwood testified that the apixaban will be "well separated" in the solution step and the rapid drying "will capture apixaban in small pockets rather uniformly distributed among the excipients." (Atwood Tr. 426-27)

118. When apixaban crystals first form, they will be on the order of a few nanometers across in size. (*Id.* at 330, 424) Even if the apixaban were to crystallize completely, the small quantity of apixaban present in the crystalline particles "places a distinct limitation on the size to

which crystals could grow." (*Id.* at 427) Crystals must convert surrounding amorphous material in order to grow. (*Id.* at 331) Dr. Atwood opined that because the small amount of apixaban is uniformly distributed, "[t]here is just not enough material in these individual pockets to support growth of crystals of 89,000 nanometers." (*Id.* at 427)

119. Povidone and other excipients keep the crystalline apixaban particles separate. (*Id.*) Dr Brittain described the apixaban as existing in "a film of povidone on the surface of the excipient particles." (Brittain Tr. 1058-59) He acknowledged that povidone is a well-known crystallization inhibitor. (*Id.* at 1097-98)

ii. Crystallization in Sunshine Lake's ANDA Products

a. Dr. Atwood's Testing

120. Plaintiffs' expert Dr. Atwood performed XRPD scans on Sunshine Lake's 2.5 mg ANDA product, using count times as long as 1,000 seconds per step. (Atwood Tr. 409, 412, 414-15; PTX 960 at 13, 21, 23)

121. Dr. Atwood's XPRD scans of Sunshine Lake's ANDA product show three characteristic peaks of crystalline apixaban, at 12.4, 16.9, and 27.1 degrees. (Atwood Tr. 409-15; PTX 960 at 21 (12.4 peak); PTX 960 at 13 (16.9 peak); PTX 960 at 23 (27.1 peak); PTX 960 at 26 (API)) A peak at 12.4 degrees is indicative of crystalline apixaban because it is within 0.1 degrees of the characteristic peak at 12.3 listed in the '945 patent; a peak of 27.1 degrees is listed in the '945 patent as characteristic of crystalline apixaban; and a peak at 16.9 degrees appears in Dr. Atwood's XRPD test of Sunshine Lake's pure crystalline apixaban API. (Atwood Tr. 411-14; Brittain Tr. 1106; '945 patent at 5:5-14 & Table 2; PTX 960 at 26)

122. Large excipient peaks between 10-11 degrees and 18-19 degrees obscure smaller

apixaban peaks at 10, 10.6, and 18.5 degrees. (Atwood Tr. 407-08; PTX 960 at 2) A large excipient peak also obscures a crystalline apixaban peak at 12.9 degrees. (Atwood Tr. 408-09; PTX 960 at 8)

123. Dr. Atwood testified he did not need to perform a limit of detection study because he was able to detect three characteristic peaks and was not quantifying how much crystalline apixaban is present in Sunshine Lake's ANDA products. (*See* Atwood Tr. 371-72)

b. Internal Sunshine Lake Evidence

124. Sunshine Lake conducted stability testing on its lab scale and exhibit batches of its ANDA product at 0, 2-months, 3-months, 6-months, and 3-years, for a total of 40 tests. (DTX 996 at 160-82) Only one out of Sunshine Lake's 40 stability tests showed crystalline conversion of apixaban; the remaining 39 tests showed that no crystalline apixaban was present. (DTX 996 at 160-62; *see also* Chen Tr. 1019)

125. Nonetheless, Sunshine Lake reported to the FDA that "it can be concluded that the polymorph conversion can consistently occur during the stability of Apixaban tablets." (PTX 846 at -1956; *see also* Chen Tr. 1013-14) Sunshine Lake's Director of the Excipient Department, Dr. Yong Chen, testified that when preparing for his deposition in the instant action, he "found out that . . . in the company ANDA application, the description of polymorph conversion has some error." (Chen Tr. 1004) After this deposition, Sunshine Lake amended its ANDA to recharacterize allegedly erroneous descriptions related to polymorph conversion. (*Id.* at 1003-04, 1022, 1016) But the conclusion that "polymorph conversion can consistently occur during the stability of Apixaban tablets," as well as the underlying XRPD data, remains in the amended ANDA submitted in August 2019. (*Id.* at 1013-14, 1017-18; PTX 948 at -394, -397)

126. Dr. Chen testified at trial that these statements were in error because they did not reflect the actual data in Sunshine Lake's ANDA. (Chen Tr. 1014, 1020)

127. Sunshine Lake determined that its 5 mg ANDA product from a larger lab-scale batch contained crystalline apixaban form N-1 based on a single peak at 17.1 in an XRPD scan. (PTX 948 at -397; Chen Tr. 1013, 1017)

128. The manufacturing method for the larger lab scale batches and the exhibit batches is the same. (Chen Tr. 1015)

129. Sunshine Lake's internal testing and analysis show that the amorphous apixaban in its ANDA product can convert to crystalline form N-1. (*Id.* at 1010-11) A 2015 internal presentation by HEC, a company affiliated with Sunshine Lake, is entitled "Discussion on the Crystalline Form of Apixaban Tablet U.S." (*Id.* at 1009; *see also* UF ¶¶ 5-7) That presentation states that "during the stability process, amorphous apixaban will partially convert to crystalline form N. The longer, the higher the conversion ratio." (Chen Tr. 1010) (discussing PTX 875[4]) The presentation further specifies that "82 percent of the amorphous form converts into crystalline form N," and "in the end, all will convert to crystalline N." (Chen Tr. 1010-11) Dr. Chen admitted at trial that amorphous apixaban "can convert" to crystalline form N-1 apixaban. (*Id.*)

c. Dr. Brittain's Testing and Analysis

130. Sunshine Lake expert Dr. Brittain obtained XRPD patterns for Sunshine Lake's 2.5 mg and 5 mg apixaban tablets, which came from Sunshine Lake's exhibit batches. (Brittain Tr. 1069-70; DTX 504 at 2, 9, 10; DTX 996 at 160, 161)

[4] PTX 875 is in Chinese and was not admitted into evidence. (*See* D.I. 713 at 4 n.3) The Court's understanding of the document is based on Dr. Chen's testimony about it. Dr. Chen testified in Chinese, with the assistance of an interpreter.

131. To produce his XRPD pattern of the 2.5 mg tablet, Dr. Brittain ground five tablets, ran five separate XRPD scans on the same day he ground the tablets, and then averaged the results, to arrive at a single scan-averaged pattern. (Brittain Tr. 1070-72; DTX 504 at 2-7) In obtaining his XRPD pattern of Sunshine Lake's 2.5 mg tablet, Dr. Brittain performed scan averaging and spent a total of 1.75 seconds counting at each step. (Brittain Tr. 1070-72, 1113-14; DTX 504 at 2, 7)

132. To produce his XRPD pattern of the 5 mg tablet, Dr. Brittain followed a comparable method: grinding multiple tablets, running multiple XRPD scans on the same day, and averaging the results, to arrive at a single scan-averaged pattern. (Brittain Tr. 1075-76; DTX 504 at 2-7) Each of Dr. Brittain's scans was run with from 0 to 41°2Θ, with a count time of 0.33 seconds per step. (Brittain Tr. 1113; DTX 504 at 2-7, 9-10)

133. Dr. Brittain's XRPD pattern for the 2.5 mg Sunshine Lake tablet showed no peaks within 0.1°2Θ of any of the six peaks identified in Table 2 of the '945 patent for crystalline form N-1. (Brittain Tr. 1068-69, 1073; DTX 504 at 9)

134. Dr. Brittain's XRPD pattern for the 5 mg Sunshine Lake tablet also showed no peaks within 0.1°2Θ of any of the six peaks identified in Table 2 of the '945 patent for crystalline form N-1. (Brittain Tr. 1075-76; DTX 504 at 10)

135. Dr. Brittain concluded that the apixaban in Sunshine Lake's ANDA product is present in an amorphous form, which is stable for at least up to three years. (Brittain Tr. 1068-69, 1071, 1073, 1075-76)

136. Dr. Brittain testified that while Dr. Atwood's XPRD tests showed a peak at 12.4 degrees – which would be characteristic of crystalline apixaban – this peak was caused by lactose monohydrate. (*Id.* at 1095-96, 1106-07) However, at trial Dr. Brittain conceded that

lactose monohydrate is not an ingredient in Sunshine Lake's ANDA products. (*Id.* at 1109) He ultimately agreed that Dr. Atwood's November 7, 2018 scan shows a peak at 12.4 degrees. (*Id.* at 1106-07, 1110-12)

137. Dr. Brittain also contended that the apixaban in its amorphous dispersion in Sunshine Lake's ANDA products is bound to excipients and does not exist as discrete particles, a view he supported by reference to a patent application by a third party, Cadila Healthcare, Limited. (*Id.* at 1119-20; DTX 503) Dr. Brittain admitted that the Cadila patent application does not describe Sunshine Lake's manufacturing process. (Brittain Tr. 1119-20, 1122) He agreed that Sunshine Lake uses a different solvent than what is described in the patent application. (*Id.* at 1122) Sunshine Lake's manufacturing process involves spray drying apixaban and povidone on an excipient, while the patent application's process does not. (*Id.*)

D. Unichem

i. Unichem's Manufacturing Process

138. Unichem manufactures its ANDA products by a process called fluidized bed manufacturing. (Berkland Tr. 631)

139. First, dry excipients – including lactose anhydrous, microcrystalline cellulose, and croscarmellose sodium – are fed into a fluidized bed granulator and air is passaged underneath them. (*Id.* at 631-32) In parallel, the starting apixaban API is completely dissolved in volatile solvents. (*Id.* at 632) These solvents are methylene chloride and isopropyl alcohol. (PTX 1126 at -720; PTX 1127 -895) The concentration of apixaban in this solution is very dilute: 1.2 percent. (Berkland Tr. 632)

140. The apixaban solution is then sprayed onto the surface of the excipient particles

floating in the fluidized bed granulator. (*Id.*) Droplets containing apixaban impact the surface of the dry excipients. (*Id.*)

141. The volatile solvents in the droplet evaporate off, leaving behind small apixaban particles. (*Id.*) The use of volatile solvents and a high temperature in Unichem's manufacturing process ensures that the solvents evaporate quickly. (PTX 1126 at -767; PTX 1127 at -979)

142. The parameters used in Unichem's process guarantee that only very small apixaban particles are deposited on the surface of the excipient particles. (Berkland Tr. 633)

143. The final result is a granule – a composite of the excipient particle with apixaban particles deposited on the surface. (*Id.* at 632)

144. After granulation, subsequent steps are undertaken to create the final tablet. (*Id.* at 633) None of the subsequent steps has any impact on the size of the apixaban particles. (*Id.*)

145. The apixaban particle size Dr. Berkland observed in Unichem's ANDA products using SEM-EDS was consistent with the apixaban particle size a POSA would expect Unichem's manufacturing process to produce. (*Id.*) Even Defendants' expert, Dr. Genck, agreed that the crystalline apixaban sprayed onto the excipients and ultimately formulated into Unichem's ANDA products is not the same as the starting material. (Genck Tr. 1201)

146. There are no material differences between the manufacturing processes used in connection with Unichem's 2.5 mg and 5 mg tablets. (Berkland Tr. 634-35) Thus, the apixaban particle size in Unichem's 2.5 mg ANDA product will be the same as that in Unichem's 5 mg ANDA product. (*Id.* at 634)

ii. Size of Unichem's Crystalline Apixaban Particles

a. Dr. Berkland's Testing

147. Dr. Berkland tested the particle size of apixaban in Unichem's ANDA products

using SEM-EDS. (*Id.* at 604)

148. Of all the ingredients used in Unichem's tablets, only apixaban contains nitrogen. (*Id.* at 612-13) Therefore, Dr. Berkland was able to identify apixaban in Unichem's ANDA products by looking (with EDS) for the presence of nitrogen atoms. (*Id.* at 613)

149. Dr. Berkland first ran a number of controls. (*Id.* at 610) He analyzed the Unichem starting API as well as the excipients used in Unichem's manufacturing process, using SEM-EDS. (*Id.* at 610-12)

150. After analyzing Unichem's ANDA, Dr. Berkland contacted Unichem's vendors and obtained from them the exact excipients Unichem uses. (*Id.* at 611-12)

151. Dr. Berkland's SEM-EDS analysis of Unichem's starting apixaban API showed a uniform distribution of nitrogen across the entire particle. (*Id.* at 613-15) The particle size of the Unichem apixaban API was quite large: several hundred microns. (*Id.* at 615-16)

152. The size of Unichem's starting API does not have any bearing on the particle size in the final tablet because Unichem dissolves its API during its manufacturing process. (*Id.* at 611, 616)

153. Dr. Berkland's SEM-EDS analysis of the excipients used in Unichem's ANDA products demonstrated that none of them contained nitrogen while all of them had particle sizes on average of around 100 microns. (*Id.* at 616-17; PTX 1219; PTX 1220; PTX 1221)

154. To analyze the contents of Unichem's ANDA products by SEM-EDS, Dr. Berkland fractured a 5 mg tablet and gently removed some of the core material with a razor blade, creating a powder that could be placed in a sample holder and placed in the SEM microscope for analysis. (Berkland Tr. 618)

155. Because SEM-EDS only looks at the surface of samples, Dr. Berkland could not

analyze an intact tablet to determine particle size. (*Id.*)

156. Dr. Berkland concluded that his sample preparation method had no impact because the size of the granules liberated from the tablet was consistent with the size of the excipients used in the starting formulation. (*Id.* at 618-19, 668)

157. Unichem's ANDA documents show that the particle size of the common blend is a D_{50} of approximately 150 microns. (*Id. at* 654-56)

158. If a granule breaks, there would be a portion of the granule that did not look the same as the rest of the granule, when one is observing using SEM or EDS. (*Id.* at 668) In Dr. Berkland's images, there was no indication that any of the granules were broken during preparation. (*Id.*)

159. Dr. Berkland tested samples from three different batches of Unichem's ANDA Products: batch numbers GAPH1002, GAPH1003, and GAPH1004. (*Id.* at 619) He tested three different tablets from batch GAPH1004, and tested two different sites on the material from a single tablet from batch GAPH1003. (*Id.* at 619-20) He tested a single tablet from GAPH1002. (*Id.* at 619)

160. Dr. Berkland randomly selected granules for analysis from a region of powder in the sample holder. (*Id.* at 620)

161. In total, Dr. Berkland analyzed 68 granules. (*Id.*) Approximately 85 percent of the granules contained apixaban particles. (*Id.*) This finding was consistent with Unichem's manufacturing process, in which extragranular excipients are added after spray granulation in an amount equal to approximately 15 percent of the total tablet weight. (*Id.*; Genck. Tr. 1180)

162. Each granule containing apixaban had dozens to hundreds of apixaban particles on the surface of the excipient particle. (Berkland Tr. 620) In total, Dr. Berkland observed thousands of apixaban particles. (*Id.* at 660-61)

163. Dr. Berkland observed that each granule showed a continuous distribution of carbon and oxygen consistent with his expectation that the carbon and oxygen atoms would be distributed across the entire excipient particle. (*Id.* at 623)

164. Taking nitrogen as an indicator of apixaban, Dr. Berkland found that the distribution of apixaban was different from that of carbon and oxygen; the apixaban (i.e., nitrogen) appeared as small islands separated from one another. (*Id.*)

165. The distribution of nitrogen in Unichem's ANDA products was different than the distribution found in Unichem's starting API. (*Id.* at 624) While the Unichem starting API was a several-hundred-micron particle that showed a contiguous nitrogen signal over the entire particle, the nitrogen signal in the Unichem's ANDA products was much smaller. (*Id.*)

166. Dr. Berkland determined the apixaban particles in Unichem's ANDA products were all approximately 1 micron in size. (*Id.* at 623-25) In every sample Dr. Berkland tested, the apixaban particles were about 1 micron in size. (*Id.* at 623-27; PTX 1214; PTX 1215; PTX 1216; PTX 1217; PTX 1218)

167. The apixaban particles in Unichem's ANDA products were almost 100 times smaller than the claim limitation of equal to or less than 89 microns. (Berkland Tr. 625, 627)

168. Dr. Berkland did not observe a single apixaban particle in Unichem's ANDA products approaching 89 microns in size. (*Id.* at 628-29)

169. Dr. Berkland concluded his results were representative of all of Unichem's

ANDA products because "from granule to granule, tablet to tablet and batch to batch, [he] consistently saw this pattern and the size of red [nitrogen] domains which told [him] that the apixaban particle size was consistently around 1 micron." (*Id.* at 623, 628)

b. Dr. Genck's Testing

170. Unichem's noninfringement expert, Dr. Genck, relied upon particle size testing performed on Unichem's starting apixaban API, as reported in Unichem's ANDA. (Genck Tr. 1197)

171. Dr. Genck had an independent laboratory, Particle Technologies Laboratories, measure the D_{90} value of a sample of Unichem bulk apixaban. (*Id.* at 1170-71) Dr. Genck did not do any testing on the apixaban in Unichem's final ANDA products. (*Id.* at 1197)

172. Particle Technology Laboratories employed a Malvern Mastersizer 2000 instrument (liquid dispersion) to test the apixaban sample, using essentially the same parameters and conditions set forth in the Unichem ANDA. (*Id.* at 1170)

173. The D_{90} values obtained from this independent testing were approximately 321 microns, which falls well outside the scope of the D_{90} limitation recited in the asserted claims of the '945 patent. (*Id.* at 1175; DTX 546 at 2)

174. Dr. Genck testified that he did not know the particle size of the apixaban in Unichem's ANDA products. (Genck Tr. 1206-07)

175. Dr. Genck also referred to a letter Unichem has submitted to the FDA stating that the D_{90} of the apixaban tablets in its ANDA products exceed 89 microns. (*Id.* at 1164-65; DTX 942)

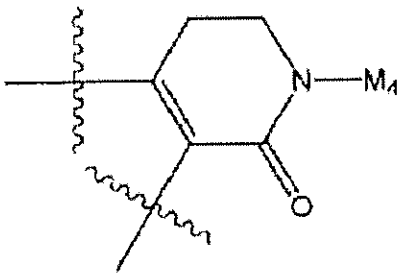
VI. Facts Related To Invalidity

A. '208 Patent

i. Improper Dependency

176. Claim 1 of the '208 patent is directed to a chemical genus. '208 patent at 237:2-242:23. Claim 1 defines the genus in two ways. First, claim 1 defines a scaffold chemical structure that the claimed compounds may have (e.g., the rings). (MacMillan Tr. 284-85) Second, claim 1 allows changes such that the scaffold structure may be "substituted with" a certain number of recited groups at each position. (*Id.* at 286)

177. For example, "ring M" is one of the scaffold components recited in claim 1: ring M, including P^1, P_2, M_1, and M_2 is substituted with 0-2 R^{1a} and is



'208 patent at 237:14-23.

178. It is undisputed that a POSA would have understood the chemical subunit recited in claim 1's ring M limitation to have four hydrogens. (MacMillan Tr. 285; Heathcock Tr. 715-16)

179. Claim 1's ring M limitation allows ring M to be "substituted with 0-2 R^{1a}" groups. R^{1a} is a *Markush* group of various chemical structures. '208 patent at 238:62-239:13.

180. To determine how many times ring M in a given compound has been "substituted with" R^{1a}, a POSA would look at the number of changes between the compound and the structure for ring M recited in claim 1. (MacMillan Tr. 300-01) If ring M in a compound is the

same as the ring M recited in claim 1 – as it is in apixaban – a POSA would understand that it has been "substituted with 0" R^{1a}, which claim 1 allows. (*Id.* at 285-86)

ii. Enablement

a. Disclosure in the '208 Patent

181. Salts are made of positively-charged cations and negatively-charged anions. (*Id.* at 1574-76) Chemists make salts by reacting compounds with acids and bases. (*Id.* at 1575-76)

182. A POSA in 2001 would have been able to look at the structure of apixaban and identify both acidic and basic sites that could form salts. (*Id.* at 1580-82)

183. Example 18 of the '208 patent explains how to make apixaban. (Orwat Tr. 246, 251-52) The '208 patent also explains how to make pharmaceutically acceptable salts of the disclosed compounds. (MacMillan Tr. 1579) Column 117 of the '208 patent explains that "[t]he pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods." '208 patent at 117:1-4. A POSA would have understood that apixaban is a parent compound that contains both basic and acidic moieties that could be used to form salts using the "conventional chemical methods" described in column 117 of the '208 patent. (MacMillan Tr. 1584-85; Jacobsen Tr. 1498-1500) Likewise, the '208 patent explains that "[g]enerally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two." '208 patent at 117:4-9. Column 116 of the '208 patent provides examples of acids and bases that can be used to prepare pharmaceutically acceptable salts. '208 patent at 116:48-67.

b. Dr. Jacobsen's Experiments

184. Plaintiffs' expert, Dr. Jacobsen, followed the disclosure of the '208 patent and, doing so, made sodium, potassium, and hydrochloride salt forms of apixaban. (Jacobsen Tr. 1494-95, 1497, 1523, 1527-28) Dr. Jacobsen and one of his students made all three salts of apixaban on the first day they tried, in less than five hours. (*Id.* at 1495, 1504) Later, when they repeated the experiments on a larger scale, they spent around 10 to 20 hours and again succeeded in making salts of apixaban. (*Id.*)

185. Dr. Jacobsen recorded a video of the experiment by which he prepared the sodium apixaban salt. (PTX 805) The video shows the formation of the sodium apixaban salt as a white solid precipitate immediately upon addition of a base to a solution of apixaban. (Jacobsen Tr. 1507-08; PTX 805)

186. Dr. Jacobsen's NMR testing confirmed that he had made sodium, potassium, and hydrochloride salts of apixaban; his chemical testing further confirmed he made sodium and potassium salts. (Jacobsen Tr. 1511-16, 1518-21)

187. Defendants do not dispute that Dr. Jacobsen made the sodium and potassium salts of apixaban. (Scheidt Tr. 1409-10, 1458; Buckton Tr. 12, 52-54) Nor do they contest that he made at least some hydrochloride salt of apixaban. (D.I. 691 at ¶¶ 123-24)

188. Dr. Jacobsen observed that the sodium apixaban salt he prepared was stable after sitting in his lab for two days. (Jacobsen Tr. 1526-27) Dr. Jacobsen performed an experiment in which he added acetic acid to the sodium apixaban salt after two days, which showed that there had been no spontaneous reversion or decomposition of the sodium apixaban salt. (*Id.*)

c. Pharmaceutical Acceptability

189. Defendants do not dispute that apixaban itself, in its neutral form, has a favorable

benefit/risk ratio. (Buckton Tr. 71)

190. Dr. MacMillan testified that the benefits of taking a salt form of apixaban would be identical to the benefits of taking neutral apixaban because the salt immediately converts in the body into neutral apixaban and an amount of sodium, potassium, chloride, hydroxide, or hydronium ions that does not pose any risk of toxicity, irritation, or allergic response. (MacMillan Tr. 1590-94, 1596-98, 1607)

191. Plaintiffs' expert, Dr. Kowey, a clinical cardiologist who treats patients with thromboembolic disorders and has prescribed Eliquis, testified "it would be extraordinarily unlikely that there would be any harm caused to the human being using these amounts of cation," and "any risk that would be associated with using this would never come anywhere close to what the benefit of the intervention would be." (Kowey Tr. 1274, 1294)

192. While Defendants offered several internal BMS documents suggesting that apixaban was non-ionizable (*see, e.g.*, DTX 632, DTX 188), testimony at trial demonstrated that these documents were specifically discussing whether apixaban could be ionized for the purpose of improving its aqueous solubility; they were not stating that apixaban could never be ionized or never form a salt. (Buckton Tr. 28; Scheidt Tr. 1472; *see also* Knabb Tr. 214)

193. At the maximum therapeutic doses of apixaban, the sodium, potassium, and hydrochloride salts of apixaban do not pose a risk of excessive toxicity, irritation, allergic response, or other complication. (MacMillan Tr. 1593-94, 1596-98) The risks to a patient from taking a salt form of apixaban would be identical to the risks of taking neutral apixaban. (*Id.* at 1607-08) The trace amounts of additional ions formed from administering the salt form of apixaban would have no impact on the patient. (*Id.*; Kowey Tr. 1294-97)

d. pH and PK_a

194. pH is a measure of the concentration of hydronium ions in a solution of water, whereas pK_a is an intrinsic measure of the susceptibility of a molecule to act as an acid. (MacMillan Tr. 1600-01) Because pH is a measure of concentration, it can vary based on the amount of acid and the amount of water. (*Id.* at 1604-05) Thus, a compound that has a given pK_a can form a solution having a range of pH values depending on the amount of the compound and the volume of water. For example, an aqueous solution of a compound with a pK_a of 0 could have a pH of 6.9, which is near neutral. (*Id.* at 1600-02)

e. Formulating a Stable Apixaban Salt

195. Plaintiffs' expert, Dr. Myerson, testified about several methods known in the art to stabilize apixaban salts by excluding water. He testified that the dosage form (either tablets or capsules) could have been prepared using a nitrogen blanket or a dry-air blanket, techniques which were available in 2001. (Myerson Tr. 1735-36, 1740) Other options known in 2001 included packaging the salt in water-impermeable aluminum-film blister packs or in a glass or polymer bottle with a foil seal or using desiccants. (*Id.* at 1736-37)

iii. Written Description

196. The earliest provisional application to which the '208 patent claims priority is U.S. Provisional App. No. 60/324,165, filed on September 21, 2001. (PTX 331)

197. Example 18 of the '165 application describes how to synthesize apixaban. (PTX 331 at -33 to -36; MacMillan Tr. 1622) The '165 application contains the same paragraph describing how to make pharmaceutically acceptable salts of the invention that also appears in column 117 of the '208 patent. (PTX 331 at -071; MacMillan Tr. 1622-23) The '165 application also contains a claim (claim 8) to a short list of specifically-named compounds, one

of which is apixaban, and their pharmaceutically acceptable salt forms. (PTX 331 at -246--250; MacMillan Tr. 1623-24)

198. The '208 patent's specification describes apixaban by chemical name and describes how to synthesize it. ('208 patent at 174:21-175:51; MacMillan Tr. 1624-26) The '208 patent's specification also specifically identifies what "pharmaceutically acceptable salts of the present invention" are and how to make them. ('208 patent at 117:1-13; MacMillan Tr. 1624-26)

B. '945 Patent

i. Technical Background

199. The dosage form of the '945 patent is an immediate-release tablet. (Myerson Tr. 1669) An immediate-release tablet is one in which the formulator has not done anything to delay or sustain the release of the active ingredient; immediate release is commonly defined as 70% or more release in one hour. (*Id.* at 1668, 1713)

200. The Biopharmaceutical Classification System, or "BCS," classifies drugs based on two properties: solubility and permeability. (*Id.* at 1681, 1684) Each of these properties may be characterized as high or low, yielding four quadrants: high solubility and high permeability (Class I), low solubility and high permeability (Class II), high solubility and low permeability (Class III), and low solubility and low permeability (Class IV). (*Id.* at 1682; DTX 347 at -370)

201. Solubility is the maximum amount of a compound that can dissolve in a liquid at a given temperature. (Myerson Tr. 1672, 1682)

202. Absolute solubility, also known as water solubility or USP solubility, is a physical chemical property of a solid that does not consider the amount of the dose to be administered to a

patient. (*Id.* at 1672, 1683; Chambliss Tr. 1384) Absolute/USP solubility does not characterize solubility in the human physiological context. (Chambliss Tr. 1384-85)

203. By contrast, BCS solubility is a dose-solubility ratio that determines whether the highest administered dose can dissolve in 250 milliliters of solution at physiological temperature and pH. (Myerson Tr. 1682-83)

204. A drug can have low absolute solubility and still be considered highly soluble under the BCS. (Chambliss Tr. 1384) The BCS describes a drug as highly permeable if the *in vivo* absorption is greater than 90 percent. (Myerson Tr. 1684)

205. Bioavailability is the amount of drug that gets into the blood. (*Id.* at 1672)

206. Dissolution rate is the rate at which the drug's active ingredient dissolves in the body. (*Id.*)

207. As of 2010, a POSA would have known several methods for measuring particle size, including laser light scattering, microscopy, sonic methods, and electrical zone sensing, among others. (*Id.* at 1671-72; Chambliss Tr. 1352) Defendants' experts, Drs. Genck and Chambliss, further agreed that imaging techniques, such as SEM-EDS, could have been used to measure particle size. (Genck Tr. 1178, 1202-03; Chambliss Tr. 1352-53)

208. Particle size may be described according to several parameters, including volume. (Myerson Tr. 1670) The size of particles in a composition may vary, so size is typically characterized by a particle size distribution. (*Id.* at 1669-70)

209. A D_{90} is mathematically determined from a cumulative distribution plot and is defined as the size at which 90 percent of the volume is smaller than a particular value, while the remaining 10 percent of the volume is larger than that same particular value. (*Id.* at 1670-71)

ii. Subject Matter Background

210. The inventors of the '945 patent discovered that "compositions for tablets comprising up to 5 mg[] apixaban particles having a D_{90} (90% of the volume) less than 89 microns (μm) lead to consistent in vivo dissolution in humans (at physiologic pH), hence, consistent exposure and consistent Factor Xa inhibition that will lead to consistency in therapeutic effect." ('945 patent at 1:64-2:3; *see also* Myerson Tr. 1667-68, 1717) More specifically, the inventors discovered that to achieve consistent exposure – exposure from tablets that approximates exposure from a solution; that is, the highest oral exposure that can be achieved – the apixaban formulation had to have a dissolution rate of at least 77% in 30 minutes. ('945 patent at 9:14-28; Myerson Tr. 1717) They also discovered that particle size is an important factor in controlling dissolution rate, and specifically that the composition achieves consistent exposure when the crystalline apixaban particle size has a D_{90} less than 89 microns along with the requisite dissolution rate. '945 patent at 9:29-46.

211. The '945 patent describes at least one example of a manufacturing method that can be used to make the claimed pharmaceutical compositions: dry granulation. ('945 patent at 5:27-63; Myerson Tr. 1717) Dry granulation is a standard manufacturing method in the pharmaceutical industry. (Myerson Tr. 1718) The '945 patent shows in Table 6, Figures 3 and 4, and the supporting text how these methods can produce a composition meeting the dissolution rate and particle size claim limitations. '945 patent at 8:28-9:46. The specification contains an example involving measuring the D_{90} of apixaban before formulation via laser light scattering and subsequently using a dry granulation to prepare the solid pharmaceutical composition. '945 patent at 5:18-65, 6:15-18.

iii. Enablement

212. The claims cover solid pharmaceutical compositions having crystalline apixaban with the claimed particle size and claimed dissolution rate. (Myerson Tr. 1716, 1732) The '945 patent provides working examples of the claimed solid pharmaceutical composition. (*Id.* at 1717, 1732-33) As Dr. Myerson explained, the '945 patent provides substantial direction to a POSA seeking to practice the asserted claims, including describing methods for formulation and for measuring the particle size of the crystalline apixaban particles, tables demonstrating the dissolution rate of different compositions having the proper particle size, and examples of solid pharmaceutical compositions that meet the claim limitations. (*Id.* at 1732-33) Methods and ingredients for formulating solid pharmaceutical compositions were well known. (*Id.*)

213. A POSA could use routine techniques to make a composition that had the claimed D_{90} particle size and dissolution rate limitations that would result in improved properties of an apixaban formulation. (*Id.* at 1733)

214. Dr. Chambliss agreed that a POSA could make an apixaban pharmaceutical composition within the recited limitations of the asserted claims of the '945 patent. (Chambliss Tr. 1350-52)

215. The '945 patent discloses that particle size can be determined by Malvern laser light scattering. '945 patent at 6:15-16. Upon completion of the measurement, the sample cell is emptied and cleaned, and refilled with suspending medium, and then the sampling procedure is repeated for a total of three measurements. '945 patent at 6:20-23.

216. To select the conditions to measure particle size using a laser light scattering instrument, a POSA would simply follow the guidance in references like the USP. (Myerson Tr. 1730-31) ("[M]y students do it all the time.") Unichem's expert, Dr. Genck, testified

that laser light scattering was the "gold standard" being used in the pharmaceutical industry in 2010. (Genck Tr. 1145)

iv. Written Description

217. As noted already, the specification contains an example involving measuring the D_{90} of apixaban before formulation via laser light scattering and subsequently using a dry granulation to prepare the solid pharmaceutical composition. ('945 patent at 5:18-65, 6:15-18; Myerson Tr. 1719-20, 1743) Dr. Myerson explained that the particle size of the bulk crystalline apixaban will not increase using this technique because: (1) the apixaban comprises a low percentage of the final solid pharmaceutical composition and will not, therefore, be located near other apixaban particles; and (2) apixaban has a high melting point and, thus, will not fuse together. (Myerson Tr. 1720)

218. There were several methods available at the time of the invention to measure particle size in a formulated pharmaceutical composition, including SEM-EDS and methods that combine vibrational spectroscopy, such as infrared spectroscopy, Raman spectroscopy, or FTNIR spectroscopy, with imaging techniques like light or SEM microscopy. (*Id.* at 1721, 1723) Dr. Myerson had used each of these techniques before (*id.* at 1721-22) and Dr. Berkland had used SEM to measure particle size (Berkland Tr. 609). Dr. Myerson identified several studies that used these methods. (Myerson Tr. 1722-30)

v. Obviousness

a. Prior Literature on Apixaban

219. As of the priority date, prior art literature described existing apixaban formulations used in clinical trials as demonstrating rapid absorption and good bioavailability. (*Id.* at 1673)

220. Carreiro (2008) discusses apixaban preclinical studies and clinical trials. (*Id.* at 1673-74; PTX 738) It is prior art to the '945 patent under 35 U.S.C. § 102(b). (UF ¶ 103) Carreiro was the "most comprehensive" publication in the prior art about the pharmacokinetics of apixaban. (Chambliss Tr. 1360) Carreiro was, hence, a "reliable reference" and one a POSA would have looked to in informing herself about the pharmacokinetics of apixaban. (*Id.* at 1360-61) Carreiro discloses the pharmacological activity of apixaban as an antithrombotic agent and that apixaban had good oral bioavailability in animals and humans. (*Id.* at 1363; Myerson Tr. 1752-53; PTX 738 at -2538)

221. Sobieraj-Teague (2009) discloses that apixaban is rapidly absorbed, reaching peak plasma concentrations three hours post-injection. (Chambliss Tr. 1370; Myerson Tr. 1676) It also reports that apixaban had bioavailability of 80 percent, which was higher than every other drug discussed except for one, which was a subcutaneous therapy (which has 100% bioavailability, since it can be injected directly under the skin). (Chambliss Tr. 1374-75) Dr. Chambliss agreed that Sobieraj-Teague was the type of reference a POSA would have relied on in looking for information about the pharmacokinetics of apixaban. (*Id.* at 1369)

222. The information disclosed in Sobieraj-Teague would have indicated to a POSA that there was no need to improve the apixaban formulation. (Myerson Tr. 1676-77)

223. Pinto (2007) discloses apixaban's bioavailability in preclinical studies to be 58 percent. (Chambliss Tr. 1376) Pinto describes this as "good" bioavailability. (*Id.* at 1376-77)

224. Eriksson (2009) describes the pharmacokinetics of apixaban in animal studies. (Myerson Tr. 1678) It states that in preclinical studies, apixaban demonstrated high oral bioavailability: 51 percent, 88 percent, and 34 percent in chimpanzees, dogs, and rats,

respectively. (*Id.*) Eriksson discloses that apixaban is rapidly absorbed in humans, reaching C_{max} approximately one to three hours after administration. (*Id.* at 1678-79)

225. Defendants' expert, Dr. Chambliss, could not identify any prior art reference that described apixaban's onset of action as slow. (Chambliss Tr. 1368)

226. Based on the prior art characterizing apixaban as having good bioavailability and rapid absorption, a POSA would have concluded that the formulations being used were satisfactory. (Myerson Tr. 1679)

b. Dissolution Rate and Bioavailability

227. As of the priority date, a POSA could have used the BCS to predict the rate-limiting step of drug absorption. (*Id.* at 1685)

228. The rate-limiting step for the absorption of a BCS Class III drug, which has high solubility and low permeability, will be permeability. (*Id.* at 1685-86, 1689) This is true even for drugs with poor absolute or USP solubility because "even a very poorly soluble drug having a sufficiently small therapeutic dose may completely dissolve under physiological conditions." (PTX 690 at -082) This means that the dissolution rate and solubility of a BCS Class III drug would not have been expected to have a significant effect on absorption. (Myerson Tr. 1690) A POSA would not have expected reducing particle size to impact the bioavailability of a drug that did not demonstrate dissolution-rate-limited absorption. (*Id.* at 1686, 1705-06)

229. Blume (1999) discloses that permeation through the intestinal membrane is the rate-limiting step for drug absorption of BCS Class III drugs. (Chambliss Tr. 1387-88) Blume further discloses that bioavailability of Class III drugs will be independent of drug dissolution properties. (*Id.* at 1388)

230. Apixaban was known in 2010 to be a BCS Class III drug. (Myerson Tr. 1686)

231. Also as of 2010, 2.5 mg and 5 mg dosages of apixaban were being used in Phase III clinical trials, as Defendants' Dr. Chambliss acknowledged. (Chambliss Tr. 1316)

232. A POSA would have known at the priority date that apixaban had low permeability, given that the absolute bioavailability of apixaban was 66 percent, which is less than the BCS 90 percent threshold for high permeability. (Myerson Tr. 1684, 1686-87; PTX 320 at -774)

233. A POSA would not have expected dissolution rate to impact apixaban's bioavailability because it is a BCS Class III drug. (Myerson Tr. 1681) Based on its BCS classification, a POSA would have expected permeability to be the rate-limiting step of apixaban absorption. (*Id.* at 1688-89)

234. A POSA seeking to formulate a drug for clinical use would have relied on a drug's BCS solubility, not absolute solubility, in predicting its bioavailability, because BCS solubility takes into account the dose of drug to be administered under physiological conditions. (*Id.* at 1682-83) Once a dose is known, a POSA would not have made any formulation decisions based on absolute solubility. (*Id.* at 1683-84)

235. Based on the disclosures in the prior art, a POSA would have understood the role of the BCS was not limited to biowaivers. (*Id.* at 1694)

236. Ku (2008), which is titled "Use of the biopharmaceutical classification system in early drug development," discloses that the BCS is a useful tool not only for obtaining biowaivers, but also for decision-making in the discovery and early development of new drugs. (*Id.* at 1693-94; Chambliss Tr. 1381-82)

237. Dahan, published in 2009 by Amidon, the developer of the BCS, states: "The BCS is one of the most significant prognostic tools created to facilitate oral drug product development in recent years." (DTX 437 at -369)

238. Dr. Chambliss agreed that the BCS had relevance in drug development beyond just issues relating to biowaivers. (Chambliss Tr. 1381-82)

239. The FDA did not provide guidance on biowaivers for Class III drugs until 2015. (*Id.* at 1379)

c. Reducing Particle Size

240. There were known disadvantages to reducing particle size. (Myerson Tr. 1694-96) Micronization can introduce impurities into a drug substance and can also induce polymorphic changes, cause degradation, and impact bulk density. (*Id.* at 1694-95) Because small hydrophobic particles such as apixaban can clump together and reduce the surface area of the drug available to the solution – causing a drug to dissolve more slowly, not faster – a POSA would have expected that reducing the particle size of apixaban would cause it to clump together and reduce surface area. (*Id.* at 1694-96)

241. A desire to achieve content uniformity, which ensures that the right amount of active ingredient is contained in every tablet by uniform dispersing, would not have motivated a POSA to reduce particle size, because the calculated D_{90} particle size necessary to ensure content uniformity – in both 2.5 and 5 mg doses – is significantly larger than 89 microns. (*Id.* at 1699-1700)

d. Prior Art References

242. Nause is a patent application that was filed on June 15, 2010. (DTX 344 at

-888) The preferred embodiment disclosed in Nause is a controlled-release amorphous dispersion with a dissolution rate of 70 percent in more than two hours. (Myerson Tr. 1710-12)

243. The immediate-release formulation disclosed in Nause is only used as a control. (*Id.* at 1710-11) The bioavailability of the immediate-release apixaban formulation in Nause tells a POSA only that it is an immediate-release formulation, not that the immediate-release apixaban tablet has a particular dissolution rate. (*Id.* at 1713-14)

244. Nause does not expressly or inherently disclose any information about the particle size of apixaban. (Chambliss Tr. 1330) Nause also does not disclose any information about: (1) the impact apixaban particle size may have on apixaban dissolution or bioavailability; (2) any reason to select an apixaban particle size of D_{90} equal to or less than 89 microns; or (3) any problems with the bioavailability of apixaban. (*Id.* at 1710-11, 1714)

245. Nause's summary discloses a continuing need to find safe, effective methods of delivering Factor Xa inhibitors; this disclosure is unrelated to apixaban bioavailability. (*Id.* at 1714)

246. Wei is 35 U.S.C. § 102(b) prior art to the '945 patent. (UF ¶ 110) It is directed to a general method of transforming one polymorph to another using a recirculation apparatus. (Myerson Tr. 1704-05) The process disclosed in Wei is not specific to apixaban. (*Id.* at 1705)

247. The process described in Wei is unrelated to improving bioavailability. (*Id.*) Rather, Wei contains only a general statement that reducing particle size often increases the bioavailability of sparingly soluble compounds. (*Id.*; DTX 359 at [0003]) Wei does not disclose any bioavailability data for apixaban, explicitly refer to a threshold of D_{90} particle size of 89 microns or less, or disclose a solid pharmaceutical formulation of apixaban. (Myerson Tr. 1706)

248. The FDA publication *Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (Aug. 1997) ("FDA Guidance") is prior art to the '945 patent under 35 U.S.C. § 102(b). (UF ¶ 102) It provides general guidance on how to perform dissolution testing for solid oral dosage forms, and discusses different apparatuses and sets of conditions that can be used. (Myerson Tr. 1707; PTX 696)

249. The FDA Guidance disclosed that, in order to ensure that the bioavailability of a drug is not limited by dissolution rate, the dissolution rate should be 85% in 15 minutes for BCS Class III drugs. (DTX 320 at -232)

250. The FDA Guidance does not provide any specific teaching for apixaban, does not specifically disclose a dissolution rate of 77 percent in 30 minutes, and does not disclose selecting a particle size distribution with a D_{90} of 89 microns or less. (Myerson Tr. 1707, 1754) A POSA would have had no reason to target a dissolution rate of apixaban of 77 percent in 30 minutes based on the FDA Guidance's disclosures. (*Id.* at 1707)

251. The '208 patent issued on November 22, 2005 and is prior art to the '945 patent under 35 U.S.C. § 102(b). (JTX 1) The '208 patent discloses (1) oral dosage forms (e.g., tablets or capsules) of apixaban along with a "pharmaceutical carrier" according to "standard pharmaceutical practice" and (2) for a tablet, the compounds of this invention generally may be present in an amount of about 1 to 100 mg, or 5 to 10 mg per dosage unit with a second anti-coagulant, and expressly discloses 2.5 and 5 mg dosages. '208 patent at 155:710, 156:23-28, 157:6-11, 24-32.

252. The '208 patent does not disclose any issues with the bioavailability of apixaban. (Myerson Tr. 1708) Nor does the '208 patent disclose any motivation to select a dissolution rate

of 77 percent in 30 minutes or provide a motivation to select a D_{90} of 89 microns or less. (*Id.* at 1708-09)

253. The '306 application is prior art to the '945 patent under 35 U.S.C. § 102(b). (UF ¶ 103) It is primarily directed to injectable formulations. (Chambliss Tr. 1232)

254. The '306 publication discloses (1) administering therapeutically effective apixaban dosages of 2.5 mg to 10 mg once daily to "prevent or treat diseases associated with Factor Xa including venous thrombosis, deep vein thrombosis and acute coronary syndrome in human patients" and that (2) these apixaban dosages may be administered in tablets, including a pharmaceutically acceptable diluent or carrier. (DTX 303 at ¶¶ [0081], [0062]-[0063], [0051])

255. The '306 application did not provide any motivation to (1) arrive at the target dissolution rate in the '945 patent or (2) select a D_{90} of 89 microns or less. (Myerson Tr. 1709-10)

LEGAL STANDARDS

I. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). 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).

Courts employ a two-step analysis in 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 to the accused infringing product. *See id.* Literal infringement (the only theory of

infringement alleged here) occurs where "every limitation set forth in a claim" is "found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995).

If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Id.* at 1552 n.9.

In the specific context of a patent infringement action brought pursuant to 35 U.S.C. § 271(e)(2)(A) – the statutory provision under which Plaintiffs have sued Defendants – the infringement inquiry is "whether, if a particular drug were put on the market, it would infringe the relevant patent." *Acorda Therapeutics Inc. v. Mylan Pharm. Inc.*, 817 F.3d 755, 760 (Fed. Cir. 2016).

II. Presumption of Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). 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. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original). A defendant's burden to prove invalidity based on prior art (e.g., anticipation or obviousness) is "especially difficult when the prior art [on which it relies] was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

A. Enablement

"The enablement requirement asks whether the specification teaches those in the art to make and use the invention without undue experimentation." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1345 (Fed. Cir. 2019) (internal quotations omitted). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012) (internal quotation marks omitted).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors may include: "(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." *Id.* Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). A patent "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

B. Written Description

Whether a specification satisfies the written description requirement is a question of fact. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 729 (Fed. Cir. 2014); *see also Alcon, Inc. v. Teva Pharms. USA, Inc.*, 664 F. Supp. 2d 443, 468 (D. Del.

2009) ("Satisfaction of the written description requirement is a fact-based inquiry, depending on 'the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed.'") (quoting *Carnegie Mellon Univ. v. Hoffmann–La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)).

To comply with the written description requirement, a patent's specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (internal brackets and quotation marks omitted). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "[T]he hallmark of written description is disclosure. Thus, 'possession as shown in the disclosure' is a more complete formulation" of the written description requirement. *Id.* "[T]he test requires an objective inquiry into the four comers of the specification from the perspective of a person of ordinary skill in the art." *Id.* "[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Id.* at 1352. However, "a description that merely renders the invention obvious does not satisfy the requirement." *Id.*

C. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on

underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. *See Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal citation and quotation marks omitted); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007).

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon ex post reasoning"). To protect against the improper use of hindsight in a determination that an invention would have been obvious, the Court is required to consider objective (or "secondary") considerations of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g., Leo Pharm. Prods., Ltd v. Rea*, 726 F.3d 1346, 1357-58 (Fed. Cir. 2013). Objective considerations "may often be the most probative and cogent evidence in the record"

relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

DISCUSSION

I. Infringement

A. Sigmapharm's ANDA Product Infringes The '208 Patent

BMS alleges that Sigmapharm's ANDA product infringes claims 13 and 104 of the '208 patent. (Findings of Fact ("FF") ¶ 8) According to Sigmapharm, however, (1) BMS failed to prove that claim 1 of the '208 patent – from which claims 13 and 104 depend – covers apixaban; (2) BMS failed to prove infringement of claim 104 also because Sigmapharm's ANDA product does not contain crystalline apixaban; and (3) BMS failed even to state a claim for infringement of claim 104. (D.I. 705 at 18-25) As explained below, the Court finds that BMS has met its burden to prove Sigmapharm's product infringes.

1. Claim 1 of the '208 Patent Covers Apixaban

Sigmapharm concedes its ANDA product contains apixaban (FF ¶ 14) but disputes infringement of the '208 patent. Its first defense to infringement is that the asserted claims do not cover apixaban. Sigmapharm argues that independent claim 1 of the '208 patent does not claim apixaban; hence, Sigmapharm continues, asserted claims 13 and 104 – which depend from claim 1 – cannot as a matter of law cover apixaban. In the Court's view, BMS has proven, by a preponderance of the evidence, that claims 1, 13, and 104 do claim apixaban.

Claim 1 recites that rings M, E, A, and Q are "substituted with" a certain number of R groups: M with 0-2 R^{1a}, E with 1-2 R, A with 0-2 R^{4}, and Q with 0-2 R^{4a}. (FF ¶¶ 83, 85, 87, 89) Sigmapharm contends each of these limitations specifies how many hydrogen atom "substituents" can be included in each ring. For example, to Sigmapharm, claim 1 requires that

ring M contain no more than two hydrogen "substituents." (D.I. 705 at 19) To Sigmapharm, because it is undisputed that (for example) in apixaban ring M contains more hydrogen atoms than the claim allows, apixaban does not meet the ring M limitation and, it follows, ring M is not covered by claim 1.

BMS counters that these ring limitations specify how many R groups can be replaced in the rings of the claimed chemical structure. For example, to BMS, claim 1 requires that ring M contain 0-2 R^{1a}; so a compound that (in addition to meeting all other claim limitations) contains 0, 1, or 2 R^{1a} groups is within the scope of claim 1. BMS has proven that a POSA would understand claim 1 (and dependent claims 13 and 104) in the manner BMS articulates.

The plain and ordinary meaning to a POSA of "substituted with [N] R" is "replaced with [N] R," where N is a number; it is not "must include [N] hydrogen substituents." The plain and ordinary meaning of "substituted" is "replaced with." The claim language, which does not refer to "substituents," provides no grounds to ignore this plain and ordinary meaning. (FF ¶¶ 13, 83-90) This conclusion is further supported by the '208 patent specification, which states that "the term 'substituted' . . . means that any one or more of hydrogens on the designated atom is replaced." '208 patent at 113:66-114:3.

Sigmapharm criticizes this interpretation on the ground that it would allow a ring to be "substituted" with an R group even when no hydrogens are replaced. (D.I. 705 at 21-23) However, the claim language expressly provides that the M, A, and Q rings can be "substituted with" ***zero*** R groups. This plainly means that the claim language covers situations in which zero hydrogens are replaced with R groups. As BMS expert Dr. MacMillan persuasively explained, a POSA would have understood that "substitut[ing]" a ring with zero R groups means ***not*** replacing it with any R groups. (MacMillan Tr. 301) ("To a person of skill in the art, to a

chemist, when you say we're using zero R, we're going to substitute it with zero R groups, that's the same as saying, I'm going to subject it to no change. It's exactly the same thing.")

Sigmapharm insists that BMS's "theory of infringement relies on a novel claim construction, never advanced during *Markman* proceedings, which rests entirely on extrinsic evidence, is contrary to the intrinsic evidence, and further requires the Court to accept that 'substituted' here means 'unsubstituted' and that zero (0) means 'one or more.'" (D.I. 705 at 3) The Court rejects each premise of Sigmapharm's analysis. Instead, the Court agrees with BMS's summary of this aspect of the parties' dispute:

> Sigmapharm's only basis for disputing infringement is that apixaban, in Sigmapharm's view, has more "substituents" attached to rings M, E, A, and Q than claim 1 allows. To arrive at that conclusion, Sigmapharm's chemistry expert Dr. Clayton Heathcock counted ***every*** hydrogen atom bonded to the M, E, A, and Q rings in apixaban as a "substituent," because a "substituent" is simply something that is bonded to some particular position . . . .
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> . . . . While Dr. Heathcock counted ***every*** hydrogen atom attached to the claimed ring structures as a "substituent" simply because they are "bonded to some particular position," the actual claim language of "substituted with" refers only to the number of ***changes*** from the chemical structure recited in the claim . . . .
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> . . . . A POSA would . . . have understood that Ring E in apixaban is "substituted with" 1 R group because the only difference between the Ring E "phenyl" structure recited in claim 1 and Ring E in apixaban is a single methoxy (-OCH3) group.

(D.I. 718 at 6-7) (internal citations omitted) As BMS further writes, "Sigmapharm's argument appears to boil down to a single proposition: claim language allowing the recited scaffolds to be 'substituted with 0' groups does not allow the scaffolds to remain unchanged. This makes no sense." (D.I. 712 at 3)

It follows that Sigmapharm's assertion that BMS is effectively ignoring hydrogen as a member of the Markush groups of the claims (*see, e.g.*, D.I. 705 at 21) also lacks merit. "As Dr.

MacMillan testified, if there is already a hydrogen present in the scaffold recited in claim 1, the claimed compounds are not 'substituted with' anything when that same hydrogen appears in the same place." (D.I. 702 at 6) (citing MacMillan Tr. 300-02, 309) BMS correctly concludes, thus, that "[h]ydrogen is no different in that regard from any other member of the *Markush* group." (*Id.*)

Accepting Sigmapharm's contrary view of the "substituted with" claim limitations would be in tension with well-established Federal Circuit precedent that discourages claim interpretation which results in preferred embodiments being excluded from the scope of the claims. *See, e.g., Eko Brands, LLC v. Adrian Rivera Maynez Enters., Inc.*, 946 F.3d 1367, 1373 (Fed. Cir. 2020) ("A claim construction that excludes the preferred embodiment is rarely, if ever, correct and would require highly persuasive evidentiary support.") (internal quotation marks omitted). The result Sigmapharm argues for here is even more extreme: its view of the patent is that claim 1 captures ***no embodiments at all.*** Sigmapharm's expert, Dr. Heathcock, was explicit on this point. He agreed that under his (i.e., Sigmapharm's) interpretation, ***none*** of the compounds specifically disclosed in the '208 patent would fall within the scope of claim 1 – and, in fact, that it would be impossible for ***any*** compound to come within the scope of claim 1. (FF ¶ 91)

Sigmapharm does not dispute that under the interpretation proposed by BMS (and agreed to by the Court), a POSA would have understood that Rings M, A, and Q in apixaban are "substituted with" zero R^{1a}, R^4, and R^{4a} groups, respectively, because these rings appear in apixaban exactly as claim 1 depicts them, and claim 1 permits the number of R replacements at Rings M, A, and Q to be zero. (FF ¶¶ 83, 87, 89) Sigmapharm also does not dispute that a POSA applying this interpretation would have understood that Ring E in apixaban is "substituted

with" one R group because the only difference between this ring and the Ring E of claim 1 is one methoxy (-OCH_3) group, and claim 1 allows the number of R replacements at Ring E to be one. (FF ¶ 85) Thus, the Court finds that claim 1 covers apixaban.

2. Sigmapharm's ANDA Product Infringes Claim 13

Claim 13 of the '208 patent, which indirectly depends from claim 1, claims the compound apixaban. (FF ¶¶ 9-11) Because Sigmapharm's ANDA product undisputedly contains apixaban (FF ¶ 14), Sigmapharm's ANDA product infringes claim 13.

3. Sigmapharm's ANDA Product Infringes Claim 104

Claim 104 of the '208 patent depends from claim 13 and adds that the compound must be crystalline. (FF ¶ 12) For the reasons discussed below in connection with infringement of the '945 patent, the Court is persuaded that Sigmapharm's ANDA products contain crystalline apixaban. *See infra* Section I.B.1.a. Thus, the Court concludes that Sigmapharm's ANDA products infringe claim 104 of the '208 patent.

As an independent and adequate theory of infringement of claim 104, BMS points to undisputed evidence that Sigmapharm's manufacturing process begins by using crystalline apixaban, and performs that process in Pennsylvania. (*See, e.g.*, D.I. 718 at 1, 9-10; *see also* Spireas Tr. 262; PTX 1068 at 13820) "Plaintiffs are seeking a declaratory judgment and injunction based on Sigmapharm's future use of crystalline apixaban starting material in the United States to manufacture its ANDA products, which will infringe claim 104 under 35 U.S.C. § 271(a)." (D.I. 712 at 4-5) (citing D.I. 1 at ¶ 7 & Prayer ¶¶ 1, 3) Sigmapharm counters that this theory of infringement is inconsistent with the Hatch-Waxman Act, which provides a remedy only with respect to Sigmapharm's proposed final product and protects through its safe harbor provision activities undertaken in support of submitting its ANDA application. (*See* D.I. 705 at

24-25) (citing 35 U.S.C. § 271(e)(1) and (e)(2)) Under the circumstances present here – including the post-trial status of the case and the lack of any indication that Sigmapharm will delay its launch after FDA approval – the Court may properly exercise declaratory judgment jurisdiction. *See, e.g., Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1571 (Fed. Cir. 1997); *Cephalon, Inc. v. Watson Pharm., Inc.*, 629 F. Supp.2d 338, 351 (D. Del. 2009) ("Defendants have filed the ANDA and have declared their intent to manufacture, market, and sell potentially infringing products in the event that the FDA approves the ANDA.").

Therefore, BMS has met its burden to prove, by a preponderance of the evidence, that Sigmapharm's ANDA product infringes claim 104 of the '208 patent.

B. Sigmapharm's, Sunshine Lake's, And Unichem's Products Infringe The '945 Patent

BMS asserts claims 21 and 22 of the '945 patent against Sigmapharm, Sunshine Lake, and Unichem. (FF ¶ 17) Sigmapharm and Sunshine Lake argue that BMS failed to prove their ANDA products contain crystalline apixaban. Additionally, all three Defendants argue that BMS failed to prove that their ANDA products meet the particle size limitation of the claims. For the following reasons, the Court finds that all three Defendants' accused products infringe the asserted claims of the '945 patent.

1. Sigmapharm's ANDA Product Infringes the '945 Patent Claims

a. Sigmapharm's ANDA Product Contains Crystalline Apixaban Particles

BMS proved by a preponderance of the evidence that Sigmapharm's ANDA product contains crystalline apixaban particles. In particular, BMS offered persuasive testimony from two experts who identified crystalline apixaban particles in Sigmapharm's ANDA product.

Sigmapharm's experts did not successfully rebut these conclusions and Sigmapharm's attacks on Plaintiffs' evidence fail.

BMS expert Dr. Atwood used XRPD testing to analyze Sigmapharm's 5 mg ANDA product.[5] (FF ¶ 93) After performing XRPD scans with a range of sensitivities, including scans with count times of 30 to 100 seconds, he identified four characteristic crystalline apixaban peaks at 12.3, 12.9, 27.1, and 22.1 degrees. (FF ¶¶ 93-94) Dr. Atwood's conclusion that Sigmapharm's ANDA product contains crystalline apixaban was credible and persuasive. (FF ¶ 95)

In defense, Sigmapharm points to the testimony of its expert, Dr. Zaworotko, who opined that XRPD testing by Catalent revealed no evidence of crystalline apixaban. (D.I. 705 at 13-14) Catalent's testing, however, is less reliable than Dr. Atwood's because Catalent used count times of one second while Dr. Atwood used count times of between 30 and 100 seconds, making Dr. Atwood's tests more sensitive and better able to detect material in small amounts. (FF ¶¶ 61-62, 93, 97)

The results of the SSNMR testing by BMS expert Dr. Munson provide further support for the conclusion that Sigmapharm's ANDA products contain crystalline apixaban. Dr. Munson compared Sigmapharm's 5 mg ANDA product to BMS's crystalline apixaban API and observed 12 twelve peaks in Sigmapharm's product that corresponded to peaks in the spectra from the reference crystalline API. (FF ¶ 100) Six of the peaks were well-resolved while the other six were partially-resolved.

[5] Because the manufacturing processes for the Sigmapharm 5 mg and 2.5 mg tablet are the same (FF ¶ 92), Dr. Atwood's (and the Court's) conclusions regarding infringement of the '945 patent by the 5 mg tablet apply equally to the 2.5 mg tablet.

Sigmapharm's non-infringement defense with respect to the '945 patent largely relies on attacking the empirical evidence developed by BMS's experts in experiments.[6] For instance, Sigmapharm repeatedly critiques Dr. Atwood for "not establish[ing] that apixaban (which is present only at 3% in Sigmapharm's products) is even detectable by his tests." (D.I. 705 at 1) While BMS, as the patentee, has the burden to prove infringement, there is no requirement that it do so in the precise manner an accused infringer demands. The Court is persuaded that Dr. Atwood's methodology is reliable and his conclusions – particularly, that Sigmapharm's ANDA product contains crystalline apixaban particles meeting all the limitations of the asserted claims of the '945 patent – are sound.

Dr. Atwood explained why he did not need to know the limit of detection of his tests and why the peaks he measured were characteristic of crystalline apixaban, and not mere noise. Because an LOD analysis merely identifies the amount of crystalline apixaban that must be present for XRPD testing to detect it, Dr. Atwood's successful identification of crystalline apixaban in Sigmapharm's ANDA product meant he did not need also to assess how much smaller an amount of crystalline apixaban he could have detected (had he wanted to).[7] (FF ¶¶ 97-98; D.I. 712 at 8 ("Dr. Atwood did not need to determine a limit of detection for his tests because he ***detected*** crystalline apixaban particles, and he did not need to quantify the amount of the particles because any amount infringes.") (internal citations omitted))

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[6] *See, e.g.*, D.I. 705 at 4 ("Dr. Atwood's testing is also replete with methodological errors that render his results meaningless."); *id.* at n.1 ("[W]hat Dr. Atwood identifies at 22° is merely noise, lacking the height and width to be a peak."); *id.* at 12 ("Dr. Atwood did not: (1) retain a laboratory notebook or keep sufficient records of how he conducted his tests or handled his samples; (2) follow USP recommendations concerning the testing he conducted; (3) determine a LOD; (4) compare his test results to a reliable reference; or (5) consider that Sigmapharm's Amporhous Apixaban (aka "Drug Product Intermediate") was an amorphous solid dispersion, and ***not*** a neat amorphous solid.").

Sigmapharm argues that none of the patterns Dr. Atwood identified with XRPD "have the required height and width to be considered a peak," insisting that the signals on which Dr. Atwood relied were merely "noise." (D.I. 705 at 13) But the peaks were present for multiple steps, strongly suggesting the observed patterns were true crystalline peaks and not mere noise. (Atwood Tr. 364-66; *see also* 712 at 9)

Sigmapharm challenges BMS's empirical findings as being inconsistent with scientific theory. For instance, Sigmapharm asserts that BMS has "no explanation for why the amorphous solid dispersion in Sigmapharm's ANDA Products, which is both thermodynamically and kinetically stable, would convert to the crystalline form despite the unchallenged scientific literature that teaches such conversion will not occur." (D.I. 705 at 11) The Court finds no basis to conclude that BMS's experts are unaware of theoretical criticisms of their approaches and opinions. The Court found the evidence from Plaintiffs' experts to be persuasive – notwithstanding how surprising or inexplicable any other witness or party may have found the evidence which the Court has been persuaded to credit.

Sigmapharm's remaining arguments about Dr. Atwood's purported methodological errors are persuasively addressed in BMS's Reply Brief and the Court rejects Sigmapharm's contentions for the reasons stated by BMS. (*See* D.I. 712 at 7-9) The Court is free as the factfinder to credit BMS's reasoning (and reject Sigmapharm's contrary view that it is "nonsensical" (D.I. 705 at 12)), and it does.[8]

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[8] One of the weakest elements of Sigmapharm's attack is its effort to convince the Court that because Dr. Atwood has been criticized by other courts in other cases for other analyses, this Court, too, should decide he is unreliable. (*See, e.g.*, D.I. 705 at 6-7) ("It is exactly the type of baseless, unsupported testimony ***from this very expert*** that other courts have properly rejected.") (citing cases) Sigmapharm's approach is no more effective than would have been a contention from BMS (which BMS did not make) that the Court ***must*** credit Dr. Atwood's analysis here because the undersigned Judge has done so in a previous (entirely unrelated) case. *See Bristol-*

Sigmapharm's critiques of Dr. Munson fare no better. Sigmapharm argues that Dr. Munson's SSNMR testing suffers from "problem baseline distortions" such as a "spinning sideband," which is a signal that "may mask a portion of the NMR spectrum" and, thus, lead to inaccurate results. (D.I. 705 at 14-15) Dr. Munson was aware of spinning sidebands, which are normal distortions in SSNMR, and he was able to observe the peaks that were partially obscured by the spinning sidebands. (FF ¶ 102)

Sigmapharm faults Dr. Munson for failing to determine the width of the peaks he observed. (D.I. 705 at 15) The evidence showed that measuring line widths is unnecessary where, as here, a POSA can simply compare the line widths of the observed peaks to those in the reference API, just as Dr. Munson did. (FF ¶¶ 64, 100)

Sigmapharm points out that Dr. Munson (like Dr. Atwood) did not determine an LOD. (D.I. 705 at 15-16) But Dr. Munson did not need to do so because his testing confirmed the presence of crystalline apixaban. Again, the LOD would have allowed Dr. Munson to determine how small of an amount of crystalline apixaban could have been present and still detected, but this was unnecessary given his findings. (FF ¶¶ 98, 123)

To counter Dr. Munson, Sigmapharm presented testimony from Dr. Apperley, who conducted his own SSNMR testing and concluded there was no evidence of crystalline apixaban in Sigmapharm's ANDA product. (D.I. 705 at 16-17) The Court agrees with BMS that "Dr. Apperley's SSNMR testing, the only testing relied on by Dr. Schurko, was not sufficiently sensitive to rule out the presence of crystalline apixaban in Sigmapharm's ANDA products." (D.I. 718 at 2) As BMS correctly explains: "The limit of detection for Sigmapharm's XRPD

Myers Squibb Co. v. Mylan Pharm. Inc., 2013 WL 12322088, at *15 (D. Del. Oct. 17, 2013) (finding Dr. Atwood offered credible testimony on several subjects).

method is 5%, but the tablets contain only 3.125% apixaban. Even if the apixaban in Sigmapharm's ANDA products was entirely crystalline, Sigmapharm's XRPD test would not detect it." (D.I. 718 at 18) (internal citations omitted)[9] Dr. Apperley admitted that his third set of tests – the only set for which he knew the limit of detection – could not have detected crystalline apixaban even if half of the apixaban in Sigmapharm's tablet was crystalline. (Apperley Tr. 759-61; *see also* FF ¶¶ 98, 110)[10]

Finally, Sigmapharm contends: "Having distinguished solid amorphous dispersions (even containing some crystalline material) to overcome Nause, Plaintiffs cannot now prove infringement merely by showing something crystalline." (D.I. 705 at 8-9) As BMS responds, however, Sigmapharm points to no clear and unambiguous prosecution history disclaimer, but instead "relies on portions of the prosecution history that do not relate to the asserted claims, which were never rejected over Nause" (and, in fact, were added after the rejection). (D.I. 712 at 14) (citing JTX 004) Sigmapharm's argument does not defeat BMS's infringement claim.

Sigmapharm argues that even if some of the apixaban in its ANDA product is crystallized, there is no "apixaban particle" but rather, at most, a "composite particle consisting of PVP-apixaban bonded together." (D.I. 705 at 9) However, Sigmapharm has not shown that

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[9] The lack of an LOD analysis as part of Sigmapharm's testing is a problem for Sigmapharm, which is trying to prove a negative (i.e., that its product does not contain any crystalline apixaban), even though the absence of an LOD analysis from BMS's experts is not (since their opinions are made reliable once they find crystalline apixaban in a sample, making it irrelevant whether they could also have found such in a sample containing even less crystalline apixaban).

[10] The Court was not persuaded by Dr. Schurko's opinion that Dr. Apperley's testing "produced better, more reliable data" than Dr. Munson's testing. (D.I. 705 at 17) (citing Schurko Tr. 803) Dr. Schurko reprocessed Dr. Munson's data and presented it using different parameters, which changed the appearance of the spectra detected by Dr. Munson's testing. (FF ¶ 113) The Court was more persuaded by Dr. Munson.

such composite participles do not contain crystalline apixaban particles; Sigmapharm has shown only that they contain crystalline apixaban ***in addition to*** other substances. In any event, the Court finds persuasive – and unrebutted – Dr. Munson's opinion that "all crystals are particles." (FF ¶ 46; *see also* D.I. 712 at 13-14)[11] Thus, the Court concludes that any crystalline apixaban in Sigmapharm's ANDA product consists of crystalline apixaban particles.

Accordingly, the Court finds that BMS has proven by a preponderance of the evidence that Sigmapharm's ANDA product contains crystalline apixaban particles.[12]

b. Sigmapharm's ANDA Product Has Crystalline Apixaban Particles Having a D_{90} Equal to or Less than 89μm

Sigmapharm contends that even if, as the Court has found, its ANDA product meets the crystalline apixaban limitation, it does not meet the particle size limitation. That is, Sigmapharm argues that BMS failed to prove the crystalline apixaban particles in Sigmapharm's ANDA product have a D_{90} equal to or less than 89μm. Sigmapharm's principal contention in this regard is that BMS has not met its burden of proof because it did not measure any crystalline apixaban particles. BMS counters that it did not need to measure or calculate precise D_{90} values because Sigmapharm's manufacturing process makes it impossible for any crystalline apixaban particles in Sigmapharm's product to have a D_{90} greater than 89μm. On this dispute, the Court is persuaded by the evidence presented by BMS and finds that BMS met its burden of proof.

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[11] The Court's factual findings on this point (and Sigmapharm's failure to cite contrary evidence) renders unavailing Sigmapharm's arguments about claim language. (*See* D.I. 705 at 9-10; *see also* D.I. 712 at 13)

[12] Because Dr. Munson and Dr. Atwood found crystalline apixaban in Sigmapharm's ANDA product, Sigmapharm's contention (based on theory and assertion) that apixaban in the form of "amorphous solid dispersion" cannot crystallize is irrelevant. (D.I. 705 at 10-11; *see also* D.I. 707 at 6-7 (Sunshine Lake making same argument))

"A patentee may prove infringement by any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek v. Biosciences Corp.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (internal quotation marks and citations omitted). There is no "general rule requiring one who alleges infringement of a claim containing functional limitations to perform actual tests or experiments on the accused product or method." *Id.* at 1374.

Here, while BMS's expert, Dr. Atwood, did not perform particle size measurements for Sigmapharm's ANDA product, he concluded that the product satisfies the particle size limitation after analyzing Sigmapharm's manufacturing process and applying well-known principles of crystallization. Dr. Atwood demonstrated that in Sigmapharm's process, (1) apixaban is dried at a rapid rate, thereby dispersing apixaban throughout the polymer and preventing it from coalescing into large crystalline particles; (2) apixaban is a relatively small percentage of the composition; and (3) apixaban is kept in position in small pockets by the formulation's polymer and other excipients. (FF ¶¶ 78-81; Atwood Tr. 383) Dr. Atwood further explained that crystalline apixaban particles are only a few nanometers in size when they first form, and the various constraints in the compound (noted just above) preclude the particles from reaching or exceeding 89 microns – a size that is 400-500% of their original size. (FF ¶¶ 48, 81)

Sigmapharm faults BMS for relying on "speculative theory" rather than "objective, replicable testing." (D.I. 705 at 6) In fact, Dr. Atwood's analysis is based on Sigmapharm's internal documents and scientific principles, and Federal Circuit caselaw establishes that testing is not always required to prove infringement.[13] Moreover, Sigmapharm and its witnesses have

[13] Sigmapharm argues that BMS's theory of inhibited crystalline growth supports Sigmapharm's argument that the apixaban in its ANDA product does not form crystals at all. (D.I. 705 at 6) The Court is not persuaded by Sigmapharm's logic. Just because crystal growth is ***limited*** (such

not explained how the crystalline particles in Sigmapharm's ANDA product could exceed the claimed size limitations given their original size and the constraints imposed by the manufacturing process.

Accordingly, BMS has proven that Sigmapharm's ANDA product has crystalline apixaban particles with a D_{90} equal to or less than 89μm and, thus, that Sigmapharm's product infringes the '945 patent.

2. Sunshine Lake's ANDA Product Infringes the '945 Patent Claims

a. Sunshine Lake's ANDA Product Has Crystalline Apixaban Particles

BMS proved by a preponderance of the evidence that Sunshine Lake's ANDA product contains crystalline apixaban particles. As he did for Sigmapharm's product, Dr. Atwood used XPRD testing to analyze Sunshine Lake's 2.5 mg ANDA product.[14] After scanning with count times of up to 1,000 steps, Dr. Atwood identified crystalline apixaban peaks at 12.3 and 27.1 degrees, which are listed in the '945 patent as characteristic peaks of crystalline apixaban, and one peak at 16.9 degrees, which matched a peak in his analysis of Sunshine Lake's apixaban starting crystalline API. (FF ¶¶ 120-21) Sunshine Lake's expert, Dr. Brittan, agreed that Dr. Atwood's testing showed a peak at 12.4 degrees; he admitted this peak was within the margin of error of the characteristic crystalline peak at 12.3 degrees. (FF ¶¶ 136)

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that its size never approaches 89 microns), it does not follow that growth of any crystals is ***impossible***.

[14] Because the manufacturing processes for Sunshine Lake's 5 mg and 2.5 mg tablets are the same (FF ¶ 114), Dr. Atwood's conclusions regarding infringement of the '945 patent apply equally to the 5 mg tablet.

Sunshine Lake attempts to discredit Dr. Atwood's findings by arguing that he was unable to identify four of the six characteristic peaks disclosed in the '945 patent. (*See* D.I. 707 at 15-16) It is undisputed, however, that Dr. Atwood identified a peak at 12.3 degrees. (FF ¶ ¶ 54, 136) That single peak can (and, here, does) provide a sufficient basis from which to find the presence of crystalline apixaban. (FF ¶ 55) Likewise, Sunshine Lake argues that Dr. Atwood failed to follow the "industry standard" of "matching 10 peaks" (D.I. 707 at 16), but this standard applies only when one must identify an ***unknown*** sample (Atwood Tr. 336-40). Here, the parties know the composition of Sunshine Lake's ANDA product and, crucially, know that the active ingredient is (without dispute) apixaban.

Sunshine Lake's expert, Dr. Brittain, acknowledged there genuinely is a peak at 12.4 degrees in the scan of Sunshine Lake's ANDA product. (*See, e.g.*, D.I. 707 at 19-20) (Sunshine Lake agreeing Dr. Brittain admitted existence of genuine peak at 12.4, though also suggesting he believed this "indisputable" peak is not attributable to crystalline apixaban) Sunshine Lake tries to diminish the evidentiary weight of this acknowledgement by attributing this peak to "lactose monohydrate contamination of the anhydrous lactose excipient." (D.I. 707 at 19-20) This is unavailing because, as Dr. Brittain conceded, Sunshine Lake's products do not contain lactose monohydrate; further, there is no evidence that lactose anhydrous (which is an excipient in Sunshine Lake's product) would have converted to lactose monohydrate within a week, which is how quickly Dr. Atwood tested Sunshine Lake's sample product. (FF ¶ 136; *see also* D.I. 686 at 13) Sunshine Lake also argues it is unlikely that the peak at 12.4 degrees is crystalline because Dr. Atwood failed to identify peaks at 16.9 and 27.1 degrees, which Sunshine Lake characterizes as the "two most intense peaks." (D.I. 707 at 20) Yet Dr. Atwood did identify these peaks. (FF

¶¶ 120-21) Dr. Atwood also explained why these peaks were not "more apparent" in the scan, given that they were partially obscured by excipient peaks. (Atwood Tr. 412, 414-15)

Sunshine Lake's own testing evidence does not undermine Dr. Atwood's results and conclusion. Although Sunshine Lake's Dr. Brittain conducted XPRD testing and found no evidence of crystalline apixaban (*see* D.I. 707 at 13-14), Dr. Brittan's testing was less sensitive than Dr. Atwood's and, under the circumstances, less persuasive. Dr. Brittain used scan times of 1.75 seconds per step (FF ¶ 131), whereas Dr. Atwood used scan times of up to 1,000 seconds per step (FF ¶ 120). Dr. Brittain acknowledged his testing was not as sensitive as Dr. Atwood's, even accounting for Dr. Brittain's use of scan averaging, a step Dr. Atwood did not undertake. (Brittain Tr. 1114) Sunshine Lake also emphasizes that only one lab scale test out of the 39 lab scale and exhibit batch tests it performed revealed any crystalline apixaban. (D.I. 707 at 11-12) While true, the import of this evidence is that it confirms that Sunshine Lake's ANDA product ***can*** contain crystalline apixaban (particularly given that the manufacturing methods for the larger lab scale batches and the exhibit batches are identical).[15] (FF ¶ 128)

Dr. Atwood's opinions are persuasive. Sunshine Lake's efforts to rebut them lack merit. Hence, the Court finds BMS has proven that Sunshine Lake's ANDA product contains crystalline apixaban particles.

b. Sunshine Lake's ANDA Product Has Crystalline Apixaban Particles Having a D_{90} Equal to or Less than 89μm

BMS has also proven that Sunshine Lake's ANDA product meets the particle size limitation of the '945 patent. Just as he did with respect to Sigmapharm, Dr. Atwood analyzed

[15] Accordingly, this lab batch evidence – along with Dr. Atwood's testing results – renders irrelevant Sunshine Lake's suggestion that that a POSA with "knowledge in the art" regarding PVP would not believe it was possible for Sigmapharm's ANDA products to contain crystalline apixaban. (D.I. 707 at 9-10)

Sunshine Lake's manufacturing process and concluded that the crystalline apixaban in Sunshine Lake's ANDA product cannot reach or exceed 89 microns because this apixaban is (1) rapidly dried; (2) very small in amount relative to the polymer and other excipients; (3) only a few nanometers in size when first crystallized; and (4) constrained from growing by povidone and other excipients. (FF ¶¶ 115-19) As BMS correctly summarizes: "the manufacturing steps Sunshine Lake uses to make its ANDA products, while insufficient to avoid the formation of crystalline apixaban particles altogether, ensure that the apixaban particles will not come close to approaching the D_{90} particle size threshold in the asserted claims." (D.I. 686 at 14)

Sunshine Lake asks the Court to reject Dr. Atwood's opinions, for essentially the same reasons the Court has already found to be unpersuasive when offered by Sigmapharm. Sunshine Lake faults Dr. Atwood for not measuring the size of any crystalline apixaban particles (D.I. 707 at 23) but, as explained above, Dr. Atwood was not obligated to "perform actual tests or experiments on the accused product." *Martek*, 579 F.3d at 1374; *see also supra* Section I.B.1.b. Sunshine Lake recognizes that the Court's claim construction "does not limit the measurement technique for apixaban particle size to any one particular method," but vaguely insists nonetheless that the Court "***implied*** that ***some*** form of physical measurement is necessary." (D.I. 707 at 3 (first emphasis added, second emphasis in original); *see also id.* at 23-25) For this contention, Sunshine Lake cites to two pages of the Court's claim construction opinion (*see* D.I. 380 at 10-11), but nowhere there (or elsewhere) did the Court require physical measurement, and the Court does not impose such a requirement now. The claim limitation is satisfied if the required particle size is present, and BMS has proven – through circumstantial evidence and theory – that the required particle size is present in Sunshine Lake's ANDA product (even without direct physical measurement). It might be "an odd result," as Sunshine Lake contends,

"if a claim limitation that was particularly important to patentability did not need to be rigorously established." (D.I. 707 at 23) But that is not the result here. Instead, the Court has found that BMS has "rigorously" and sufficiently established that Sunshine Lake's product meets the particle size limitation, through circumstantial evidence, as the law allows.[16]

Sunshine Lake argues that Dr. Atwood's testimony relies on "models [] not applicable to amorphous solid dispersions" (D.I. 707 at 23) but, as BMS correctly notes, Sunshine Lake's own evidence – in addition to Dr. Atwood's testing – shows that Sunshine Lake's products contain crystalline apixaban particles (D.I. 713 at 2-3), so contentions about amorphous solid dispersions are neither dispositive (nor, in context, persuasive). Ultimately, the Court agrees with BMS's assessment: "Sunshine Lake attempted to design around the asserted claims by making a so-called 'amorphous dispersion,' but as evidenced by the presence of crystalline apixaban particles in Sunshine Lake's ANDA products, this design-around effort was unsuccessful." (D.I. 686 at 2)

Thus, the Court finds that Sunshine Lake's ANDA product satisfies the particle size limitation. BMS has proven that Sunshine Lake's ANDA product infringes the asserted claims of the '945 patent. (*See generally* D.I. 713 at 2) ("[I]f, as Plaintiffs have shown, there is crystalline apixaban in Sunshine Lake's ANDA products, the evidence was unrebutted that these particles must be smaller than 89 microns.")

[16] Sunshine Lake's attempt to analogize the situation here with what the Court confronted in *Reckitt Benckiser LLC v. Aurobindo Pharma LLC*, 239 F. Supp. 3d 822, 829-33 (D. Del. 2017), falls flat. Just because a party in an entirely unrelated patent case failed to adduce adequate and persuasive circumstantial evidence to prove infringement has no implication for whether BMS has met its evidentiary burden in the instant case.

3. Unichem's ANDA Product Infringes the '945 Patent Claims

The only limitation Unichem disputes is the particle size limitation. BMS has proven that Unichem's ANDA product meets the particle size limitation.

BMS's expert, Dr. Berkland, analyzed the particle size of Unichem's 5 mg ANDA product using SEM-EDS, a technique disclosed in the prior art for imaging pharmaceutical compositions and identifying their elements. (FF ¶¶ 70-73, 154) After observing 68 granules containing thousands of apixaban particles, he determined that all of the particles were 1 micron in size. (FF ¶¶ 161-62, 166) Dr. Berkland then concluded that the crystalline apixaban in Unichem's ANDA products had a D_{90} of much less than 89 microns. (FF ¶¶ 166-69) Dr. Berkland opined that his conclusions were consistent with Unichem's manufacturing process, which (1) creates a solution consisting of volatile solvents and highly dilute apixaban and (2) evaporates out the solvent, thereby "leaving behind small apixaban particles." (Berkland Tr. 632-33; FF ¶¶ 139-44)

Unichem attempts to defeat BMS's infringement case but ultimately fails. Unichem argues that BMS lacks "direct evidence" – such as D_{90} measurements – that Unichem's ANDA products satisfy the particle size limitation (D.I. 709 at 5-6), but, as has already been explained, a patentee may prove infringement through circumstantial evidence, and here BMS was not obligated to provide precise measurements of apixaban particles. *See Martek*, 579 F.3d at 1372; *supra* at Section I.B.1.b. Unichem tries to discredit Dr. Berkland's technique by emphasizing that SEM-EDS has never been used to determine the D_{90} value of tableted API particles and is not suitable for this purpose. (D.I. 709 at 6-7, 10-13) But Dr. Berkland did not use SEM-EDS to obtain precise D_{90} measurements; rather, he used it to develop circumstantial evidence that Unichem's ANDA product satisfies the particle size limitation, and he did so in a manner

consistent with prior art disclosures of appropriate uses of SEM-EDS: for example, the capture of an image of a pharmaceutical sample allowing identification of its elements. (FF ¶¶ 70-73; Berkland Tr. 606-07; PTX 362 at -116)

Unichem also argues that Dr. Berkland failed to show that the 68 granules he observed constituted a statistically significant sample. (*See* D.I. 709 at 8-10) While Dr. Berkland's analysis would have been ***more*** persuasive had he shown that the sample he used was representative of the relevant population of granules at a statistically significant level, nothing in the patent or the Court's claim construction required him to do so. (*See* D.I. 714 at 6) The publications cited by Unichem suggest only that Dr. Berkland was required to measure a "sufficient number of particles," not a statistically significant number. (PTX 394 at 1805; *see also* D.I. 709 at 8) Unichem provides no basis to conclude that the thousands of apixaban particles Dr. Berkland viewed were an insufficient number.[17]

Finally, the Court is not persuaded by Unichem's affirmative evidence of non-infringement, specifically, (1) statements in the Unichem ANDA requiring the apixaban particles to have a D_{90} value between 150-1000 microns and (2) testing from Dr. Genck showing a D_{90} of around 321 microns. (*See* D.I. 709 at 19-22) This evidence is based on Unichem's starting apixaban API, not the apixaban in Unichem's ***ANDA product***, which has a different form. (FF

[17] Unichem's arguments about Dr. Berkland's purportedly deficient lack of "controls" are unavailing for the same reasons. (*Compare* D.I. 709 at 16-19 *with* D.I. 714 at 10) Moreover, many of Unichem's methodological criticisms of Dr. Berkland and what Unichem (alone) calls the "Berkland Method" were considered and rejected by the Court in its Daubert ruling. (*See* D.I. 675 at 4-5) Unichem's arguments remain unpersuasive as either a basis for excluding Dr. Berkland's opinions as a gatekeeper or rejecting them as a factfinder.

¶¶ 145, 152, 171) In fact, Dr. Genck conceded he did not know the particle size of the apixaban in Unichem's ANDA product. (FF ¶ 174)[18]

BMS's evidence that Unichem's ANDA product satisfies the particle size limitation is persuasive and not persuasively rebutted by Unichem or its evidence. Because this is the only limitation Unichem disputes, the Court finds that BMS has proven that Unichem's ANDA product infringes the asserted claims of the '945 patent.

III. Defendants Have Failed To Prove The '208 And '945 Patents Are Invalid

A. '208 Patent

Defendants contend that the asserted claims of the '208 patent are invalid because (1) claims 13 and 104 claim subject matter not claimed by claim 1, from which they depend; (2) the patent fails to enable the full scope of claim 13, which claims "pharmaceutically acceptable" salts of apixaban; and (3) both asserted claims lack an adequate written description. (D.I. 716 at 2-21) For the following reasons, the Court finds that Defendants have failed to meet their burden to prove, by clear and convincing evidence, that either claim 13 or 104 of the '208 is invalid.

1. Claims 13 And 104 Are Not Invalid For Improper Dependency

Defendants argue that claims 13 and 104 are invalid because they claim apixaban but a claim from which they depend, claim 1, does not. "It is axiomatic that a dependent claim cannot

[18] Unichem is wrong when it charges that BMS contradicted the Court's claim construction and that BMS's interpretation excludes a preferred embodiment. (*See* D.I. 709 at 22-23) BMS has been consistent in contending that the size of Unichem's starting apixaban API is unrelated to the size of the apixaban in Unichem's final ANDA product. But BMS has not contended that it is always improper for purposes of evaluating infringement of the particle size limitation to measure an accused product's starting apixaban API with laser light scattering. (*See* D.I. 714 at 12-13)

be broader than the claim from which it depends." *Alcon Research Ltd. v. Apotex, Inc.*, 687 F.2d 1362, 1367 (Fed. Cir. 2012).

For this defense, Defendants present the same arguments Sigmapharm did in contending it does not infringe claims 13 and 104 of the '208 patent: that the claim language of "substituted with" requires counting hydrogen as a substituent, and that the ring structures in apixaban contain more hydrogen atoms than are permitted in the claimed ring structures. These arguments are no more persuasive in the context of invalidity (where Defendants bear the burden of proof, and it is by clear and convincing evidence) than they were in connection with non-infringement (where Plaintiffs bore the burden of proof). Thus, for all the reasons already given above, *see supra* I.A.1, Defendants have not proven that claims 13 and 104 are invalid due to improper dependency.

2. Claim 13 Is Not Invalid for Lack of Enablement

Claim 13 requires a "pharmaceutically acceptable salt form" of apixaban; that is, a salt form which is, "within the scope of sound medical judgment, suitable for use in contact with the tissues of human begins and animals." (D.I. 381) Defendants contend that claim 13 is invalid for lack of enablement because (1) the '208 patent does not disclose apixaban salts; (2) pharmaceutically acceptable salts are not enabled; and (3) apixaban cannot be made into a salt suitable for use in contact with human or animal tissue. Defendants have failed to persuade the Court on each of these prongs of their argument.

The '208 patent does disclose apixaban salts. As BMS showed, the '208 patent describes a conventional method for making salts and identifies specific reaction conditions and chemicals that can be used to prepare an apixaban salt. (*See* D.I. 702 at 8) (discussing '208 patent at 116:48-117:13) Persuasive evidence establishes that a POSA with the '208 patent in hand could

make apixaban salts without undue experimentation.[19] BMS's expert, Dr. Jacobsen, was able to prepare sodium, potassium, and hydrochloride salts of apixaban in under five hours by following the guidance of the '208 patent – and Defendants' experts agreed that Dr. Jacobsen did so. (FF ¶¶ 184, 187) Given Dr. Jacobsen's experiments, Defendants are simply wrong when they assert that "there are no apixaban salts in existence" and "apixaban is not ionizable." (D.I. 716 at 11)[20] Notably, Defendants and their experts did not perform any experiments attempting to make or study apixaban salts.

Defendants try to discredit Dr. Jacobsen's findings by arguing that the p*K*a values of apixaban will cause an apixaban salt to be unstable and quickly disproportionate when that salt encounters moisture, as it inevitably will. (*See, e.g.*, D.I. 716 at 8) ("Because apixaban is not ionizable, any salt formed would be unstable and would immediately disproportionate upon its inevitable exposure to moisture.") Defendants failed to present clear and convincing evidence in support of these contentions. The testimony of Dr. Buckton does not suffice. He admitted he "ha[d]n't done an independent analysis of the data" but instead relied on the opinions of Dr. Scheidt, who himself offered no evidence about apixaban's instability or tendency to disproportionate. (Buckton Tr. 39-40; *see also* D.I. 702 at 20-21) Dr. Jacobsen's testimony that the sodium apixaban salt he created was stable for two days was essentially unrebutted. (FF ¶ 188)

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[19] Dr. Orwat, an inventor of the '208 patent, testified credibly and persuasively that he considered making an apixaban salt and believed he could make a pharmaceutically acceptable one. (Orwat Tr. 243-44) He never did so partly because apixaban had sufficient solubility even without being made into a salt form. (*Id.* at 244)

[20] Defendants observe that no expert was aware of "any pharmaceutical product made from a compound with [a] p*Ka* value similar to apixaban." (D.I. 716 at 12-13) This point does not undermine the Court's conclusions, for reasons including that "[e]nablement does not require an inventor to meet lofty standards for success in the commercial marketplace." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

Nor is the Court persuaded that an apixaban salt would be "impermissibly toxic" and, thus, not "pharmaceutically acceptable." Defendants presented testimony from Drs. Buckton and Scheidt that a disproportionated apixaban salt would generate a damaging "localized pH" (*see* D.I. 716 at 15-16), but they did not rebut the testimony of BMS's experts that the ***therapeutic dose*** of an apixaban salt would not affect – let alone harmfully impact – a patient's internal pH. Instead, as Plaintiffs' experts demonstrated, the pH would be diffused before a harmful biochemical reaction occurred. (MacMillan Tr. 1593-94, 1596-98, 1605-07; *see also* D.I. 702 at 12-13)

BMS's expert, Dr. Kowey, a clinical cardiologist and expert in clinical medicine including thromboembolic disorders, persuasively opined that, in his "sound medical judgment," a POSA would view an apixaban salt as "suitable for use . . . commensurate with a reasonable benefit/risk ratio." (Kowey Tr. 1281, 1293-94) Dr. Kowey further explained that an apixaban salt would offer tremendous benefits to patients suffering from atrial fibrillation without "any risk of excessive toxicity, irritation, or other complications." (*Id.* at 1297) In the Court's view, then, an apixaban salt "suitable for use in contact with the tissues of human beings" is enabled.[21]

[21] Contrary to Defendants' suggestion (*see* D.I. 716 at 22), Dr. MacMillan's testimony that that the apixaban salt "can't get to the tissue to do that damage" does not suggest undermine BMS's case. Dr. MacMillan meant that an apixaban salt would not have harmful effects once ingested because, in the human body, it would convert to neutral apixaban. (MacMillan Tr. 1650-52) To the extent Defendants are arguing that the claim limitation is not satisfied because it would be ***neutral apixaban*** that is coming into contact with human tissue – and would not be the apixaban salt doing so – they are wrong. Nothing in the Court's claim construction requires the apixaban salt to remain a salt after ingestion or when it comes into contact with human tissue. As Defendants' own expert confirmed, salt forms of drugs typically convert to neutral forms after ingestion. (*See* D.I. 702 at 22-23) Moreover, as BMS writes: "[i]f ingesting the salt is not 'use in contact with the tissues of human beings,' it is not clear what is." (D.I. 702 at 22; *see also* D.I. 245 at 5 (Defendants' claim construction brief equating "administration" with "contact"))

Given the disclosure of the '208 patent, Dr. Jacobsen's success in creating stable apixaban salts, and Dr. Kowey's testimony that an apixaban salt would be pharmaceutically acceptable under the Court's claim construction, the Court disagrees with Defendants that the *Wands* factors[22] "confirm[]" the lack of enablement. (*See* D.I. 716 at 16-17) Instead, the Court concludes that Defendants have failed to prove that the asserted claims lack enablement.

3. Claims 13 And 104 Are Not Invalid For Lack Of Written Description

Defendants argue that the '208 patent includes only a "general description of salt formation" and a list of 80 compounds, "some of which have [salts] and some of which do not." (D.I. 716 at 18-19) In fact, however, the '208 patent specifically recites apixaban, outlines "pharmaceutically acceptable salts of the present invention," and describes how to make these salts. '208 patent at 63:16-18; 116:40-117:13; 174:21-175:51; FF ¶ 11. BMS's expert, Dr. McMillan, persuasively testified that these disclosures would allow a POSA to identify pharmaceutically acceptable salt forms of apixaban and to recognize that the inventors possessed them. (MacMillan Tr. 1612, 1620-27)

It is true, as Defendants emphasize, that the inventors did not themselves ever make pharmaceutically acceptable apixaban salts. This fact does not alter the Court's conclusion. To assess the adequacy of written description, the Court must evaluate "the four corners of the specification from the perspective of a [POSA]."[23] *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019); *see also Endo Pharms., Inc. v. Mylan Pharms., Inc.*, 2014 WL

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[22] 858 F.2d at 737.

[23] Because the Court has concluded that the asserted claims of the '208 patent are not invalid, it need not address BMS's additional response that claim 104 does not cover pharmaceutically acceptable salt forms of apixaban (and therefore does not have to enable or provide written description for such salts). (*See* D.I. 702 at 23-24)

334178, at *28 (D. Del. Jan. 28, 2014). For the reasons already explained, the Court is persuaded that a POSA would understand from the four corners of the '208 patent that the inventors possessed pharmaceutically acceptable apixaban salts, notwithstanding that the inventors did not themselves practice these embodiments of their claims.

B. '945 Patent

Defendants contend that the '945 patent is invalid because the asserted claims (1) fail to meet the enablement requirement, (2) fail to meet the written description, and (3) are obvious in light of the prior art. (D.I. 716 at 22-39) Defendants have failed to prove any of these contentions by the required clear and convincing evidence.

1. The Asserted Claims of the '945 Patent Are Not Invalid for Lack Of Enablement

Defendants have not proven by clear and convincing evidence that the asserted claims of the '945 patent are invalid for lack of enablement. Applying the *Wands* factors, Defendants argue that the '945 patent does not provide "examples or other guidance for determining the D_{90} of apixaban after formulation," the prior art does not disclose any measurements of post-formulation D_{90}, and Dr. Berkland failed to conduct any such measurements. (D.I. 716 at 32-33) As discussed above, however, Defendants have not shown that the claims require measuring the D_{90} of any apixaban particles, particularly after tableting. *See supra* Section II.B.1; *see also* D.I. 381 (claim construction order adopting plain and ordinary meaning of "apixaban particles have a D_{90}"). Instead, the particle size limitation states a characteristic of the claimed crystalline apixaban, not a procedural (measurement) requirement. Furthermore, because the '945 patent specification discloses the use of laser light scattering to determine whether a pre-formulation D_{90} is within the claimed threshold, and because the record evidence shows that apixaban particles will not grow during the formulation process, a POSA who uses laser light scattering

can determine whether the crystalline apixaban in the formulated tablet is within the claimed threshold. *See infra* Section II.B.2.

Defendants argue that the '945 patent does not even enable determining the D_{90} of pre-formulation, bulk apixaban using laser light scattering. (D.I. 716 at 34) The Court disagrees. BMS presented unrebutted evidence that laser light scattering is routinely used to measure particle size and that a POSA could use standard references to understand how to perform laser light scattering. (FF ¶¶ 215-16)

Defendants, therefore, have failed to prove that the asserted claims of the '945 patent are invalid for lack of enablement.

2. The Asserted Claims of the '945 Patent Are Not Invalid for Lack Of Written Description

Defendants argue that the asserted claims of the '945 patent do not satisfy the written description requirement because the '945 patent "simply does not describe nor contemplate determining the D_{90} of the apixaban particles once formulated." (D.I. 716 at 23) Defendants' contention is unavailing as it is based on the inaccurate premise that the claims' scope "includes ***determining*** the apixaban D_{90} value before or after tableting." (D.I. 715 at 10) (emphasis added) Defendants do not point to anything in '945 patent that makes such a determination at both times a ***requirement*** for practicing the particle size limitation. Moreover, because the term "apixaban particles have a D_{90}" was construed as having its plain and ordinary meaning (D.I. 381), the Court understands the particle size limitation to describe a feature of the claimed invention, not a measurement requirement.

Even if Defendants were correct that the claims include a measurement requirement, the Court is persuaded that a POSA would have believed the inventors possessed a means of measuring the particle size of post-tableted apixaban. The '945 patent discloses measuring the

D_{90} of pre-formulation crystalline apixaban with laser light scattering. ('945 patent at 5:18-65, 6:15-18) As BMS's expert, Dr. Myerson, testified, after formulation the crystalline apixaban particles will not increase in size, given the low concentration of apixaban in the formulation as well as apixaban's high melting point, both of which prevent apixaban particles from bonding and growing. (Myerson Tr. 1720) Thus, as BMS correctly states, "by measuring the D_{90} of the crystalline apixaban before formulation (and ensuring it was within the claimed particle size distribution), a POSA would have known that the crystalline apixaban in the final composition would be within the claimed D_{90} threshold." (D.I. 702 at 29)

Defendants insist that the "evidence shows that the apixaban value ***could*** increase" during the process of tableting. (D.I. 715 at 12) (emphasis added) The evidence on which they rely is not specific to apixaban and does not account for the unique features of apixaban that prevent post-formulation growth. (*See* D.I. 702 at 29 n.16) Additionally, the Court agrees with BMS that Defendants' "heavy reliance" on *Eli Lilly v. Teva Pharms., USA, Inc.*, 619 F.3d 1329, 1345 (Fed. Cir. 2010), is misplaced, as there, unlike here, the patentee conceded that a POSA would not know whether the particle size of the API would increase or decrease during formulation. (*See* D.I. 716 at 23-24; D.I. 702 at 28) As BMS correctly states: "here, Plaintiffs have established that a POSA ***would not expect the particle size distribution of apixaban to increase*** using the manufacturing techniques exemplified in the specification." (D.I. 702 at 28)

Hence, the Court concludes that the asserted claims of the '945 patent are not invalid due to lack of written description.[24]

[24] Because the Court concludes that the '945 patent is not invalid for lack of written description, the Court need not and will not address the parties' further dispute over whether any prior art determined the D_{90} of an API in a finished dosage form. (*See* D.I. 702 at 30-32)

3. The Asserted Claims of the '945 Patent Are Not Invalid As Obvious

Finally, Defendants have also failed to prove, by the required clear and convincing evidence, that the asserted claims of the '945 patent are invalid as obvious.

Defendants failed to prove that a POSA would have been motivated to reduce the particle size of crystalline apixaban. While Defendants insist that a POSA would have been motivated by a desire to improve content uniformity (*see, e.g.*, D.I. 716 at 35), they point to no record evidence demonstrating that apixaban's content uniformity was a concern in the prior art. Defendants' suggestion that a POSA would have been motivated to improve apixaban's bioavailability is also unpersuasive. As BMS showed, the prior art explicitly taught that apixaban had good bioavailability; even Defendants' expert, Dr. Chambliss, was unable to identify any prior art describing apixaban's bioavailability as slow. (FF ¶¶ 219-25) Defendants' evidence about POSAs' generalized concerns about pharmaceutical development – such as the high failure rate of clinical trials and the desire to overcome certain regulatory hurdles – is inadequate to satisfy Defendants' high burden to show the necessary motivation, in light of the overall record, including the strength of BMS's evidence. *See generally Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019) (stating that generalized motivation to enhance bioavailability is insufficient).

Nor have Defendants persuaded the Court that a POSA would have had a reasonable expectation of success that she could improve apixaban's bioavailability by increasing its dissolution rate. Defendants' theory is that (1) apixaban was known in the literature to have poor water solubility and (2) reducing particle size was generally known as a method for speeding up dissolution and improving bioavailability. (*See* D.I. 716 at 36; D.I. 715 at 14-15) The evidence presented at trial did not support this theory. Instead, the literature on which Defendants rely

relating to apixaban's solubility discusses its USP solubility, a measurement which does not consider physiological conditions and, thus, has limited relevance in the context of pharmaceutical drug development. (FF ¶¶ 202-03; *see also* D.I. 702 at 36-37) The more relevant measurement is BCS solubility, which measures solubility at physiological temperature and pH – and the evidence shows that apixaban was known as highly BCS soluble. (FF ¶¶ 228, 230, 233-34) BMS also presented unrebutted evidence that the dissolution rate of BCS Class III drugs, such as apixaban, did not affect their bioavailability. (FF ¶¶ 228-232)

More particularly, Defendants have failed to show that the asserted claims of the '945 patent would have been obvious to a POSA in view of Defendants' prior art combinations. A POSA would not have been motivated to combine Carreiro and Wei in view of the FDA Guidance 1997 at least because Carreiro teaches that apixaban has good bioavailability, Wei does not teach improving the bioavailability of ***apixaban*** by reducing its particle size, and the FDA Guidance does not teach the recited dissolution rate of 77% within 30 minutes (disclosing instead the qualitatively different rate of 88% within 15 minutes). (FF ¶¶ 223, 246-50) The claims would also not have been obvious over the '306 publication and Wei in view of the FDA Guidance 1997, or over the '208 patent and Wei in view of the FDA Guidance 1997, because neither the '306 publication nor the '208 patent teaches the claimed particle size or dissolution rate limitations that are missing in Wei and the FDA Guidance. (FF ¶¶ 251-53) Likewise, the claims are not obvious over Nause in view of the FDA Guidance 1997 because Nause does not teach the particle size or dissolution rate limitations missing in the FDA Guidance. (FF ¶¶ 242-45)

Thus, Defendants have failed to prove that the asserted claims of the '945 patent are invalid as obvious.[25]

CONCLUSION

For the foregoing reasons, the Court finds that (1) Sigmapharm's ANDA products infringe the asserted claims of the '208 patent; (2) Sigmapharm's, Sunshine Lake's, and Unichem's ANDA products infringe the asserted claims of the '945 patent; and (3) the asserted claims of the '208 and '945 patents are not invalid. An appropriate order follows.

[25] The parties devote a combined two paragraphs in their briefing to the objective indicia of nonobviousness. (*See* D.I. 702 at 40; D.I. 714 at 15) Despite their lack of attention to the issue, it is clear that disputes relating to this evidence do not (and cannot) alter the Court's conclusion of nonobviousness. The Court finds that BMS has proven, by a preponderance of the evidence, that a POSA would have found it "unexpected that a BCS Class III drug like apixaban would show dissolution rate limited absorption and that dissolution rate would impact bioavailability." (D.I. 702 at 40; *see also* Myerson Tr. 1715; FF ¶¶ 232-34) This evidence, then, further supports the Court's conclusion that Defendants have failed to prove the asserted claims of the '945 patent are invalid as obvious.