IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

PFIZER INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	1:05CV39
	)	
SYNTHON HOLDINGS BV;	)	
SYNTHON BV;	)	
SYNTHON PHARMACEUTICALS, LTD.;	)	
and SYNTHON LABORATORIES, INC.,	)	
	)	
Defendants.	)	

FINDINGS OF FACT & CONCLUSIONS OF LAW

BEATY, District Judge.

This matter is before the Court to determine the ultimate question of whether Defendants Synthon Laboratories, Inc., Synthon Holding, B.V., Synthon, B.V., and Synthon Pharmaceuticals, Ltd.'s (collectively, "Synthon") are infringing on Plaintiff Pfizer, Inc.'s ("Pfizer") patent concerning the drug Norvasc®, and if so, whether Synthon has a valid defense to such an allegation. The Court heard evidence in the matter for four days, beginning on April 10, 2006, and received numerous designations of additional deposition testimony. Based upon a review of all of the evidence, including the testimony and exhibits presented during that bench trial, the Court makes the following findings of fact and conclusions of law as shown hereafter:

I. FINDINGS OF FACT

A. The Parties and General Information

1. Plaintiff Pfizer is a corporation organized and existing under the laws of the State of Delaware. Pfizer has a principal place of business at 235 East 42nd Street, New York, New York.

2. Defendant Synthon Laboratories, Inc. ("Labs") is a Virginia corporation with its sole place of business at 7130 Heritage Village Plaza, Suite 201, Gainesville, Virginia, 20155.

3. Defendants Synthon BV and Synthon Holdings BV are Netherlands companies with their headquarters at P.O. Box 7071, 6503 GN in Nijmegen, Netherlands.

4. Defendant Synthon Pharmaceuticals, Inc. is a North Carolina corporation with its principal place of business at 9000 Development Drive, P.O. Box 110486, Research Triangle Park, North Carolina, 27709.

5. Within the 45-day statutory period provided for in 21 U.S.C. § 355(j)(5)(B)(iii), Pfizer commenced this action against Synthon alleging that, pursuant to 35 U.S.C. § 271(e)(2)(A), Synthon's filing with the United States Food and Drug Administration (the "FDA") of its Abbreviated New Drug Application ("ANDA") seeking approval to commercially sell 2.5, 5, and 10 mg dosage strength amlodipine besylate tablets (the "ANDA product"), before the expiration

of the term of Pfizer's United States Patent No. 4,879,303 (the " '303 patent"), infringes claims 1 through 3 of the '303 patent.

6. Synthon's ANDA product is a generic version of Pfizer's amlodipine besylate drug product commercially sold in tablet form in the United States as Norvasc®. Norvasc® is approved by the FDA for treating hypertension and chronic stable and vasospastic angina, and is the leading cardiovascular drug in the United States and the world.

7. Claim 1 of the '303 patent states: "The besylate salt of amlodipine." The besylate salt of amlodipine is also known as "amlodipine besylate."

8. Amlodipine is the common name for the chemical compound, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine, which is a member of the class of compounds referred to as "1,4-dihydropyridines."

9. Amlodipine besylate is a chemical compound, designated as an acid addition salt, formed from the reaction of the chemical compound amlodipine and benzene sulphonic acid. (See Testimony of Bradley Anderson, Trial Transcript IV, at 7.)

10. An "acid addition salt" is a compound formed from a chemical base and an acid. A "base" such as amlodipine is a neutral (uncharged) compound which can become positively charged. The positively charged base is called a "cation." An

"acid" such as benzene sulphonic acid is a compound which can become negatively charged. The negatively charged acid is called an "anion." (See id.)

11. Acid addition salts may form as crystalline solids, which have crystalline structures that are highly ordered in lattice arrangements of the salt molecules. Acid addition salts may also form as amorphous solids, which do not have crystalline lattice arrangements, or as amorphous liquids, such as oils. Water or other solvents can be incorporated into the crystal lattice structure of some salts. (See id. at 8.)

12. A finished drug product consists of an active pharmaceutical ingredient (also known as the "API" or the "drug substance") together with inactive ingredients, known as excipients, in a dosage form, such as a tablet, capsule, or injectable solution. (See Testimony of Stephen Hoag, Trial Transcript III, at 112, 120.)

13. Active drug molecules are frequently made into pharmaceutically acceptable acid addition salts ("pharmaceutically acceptable salt"). (See Testimony of Arthur Kibbe, Trial Transcript II, at 52.)

14. A pharmaceutically acceptable salt is any salt of an active drug molecule that can be used to make a finished drug product suitable for administration of the drug to a patient. (See Testimony of Bradley Anderson, Trial Transcript IV, at 27-28.)

15. Claim 2 of the '303 patent recites: A pharmaceutical composition comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the

besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically acceptable diluent or carrier.

16. Claim 3 of the '303 patent recites: A tablet formulation comprising an anti-hypertensive, antiischaemic or angina-alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.

17. Dr. James I. Wells ("Dr. Wells") and Mr. Edward Davison ("Mr. Davison") are identified in the '303 patent as the inventors.

B. The Discovery of Amlodipine Besylate

18. Amlodipine is a pharmacologically active chemical compound that has anti-hypertensive and antiischaemic activity in the body. Anti-hypertensive activity means that amlodipine lowers the blood pressure of a patient. Antiischaemic activity means that amlodipine reduces angina, the pain associated with a lack of blood flow to the heart muscle. (See '303 patent, col. 1.)

19. Prior to 1982, Pfizer's Discovery Chemistry group located at its research center in Sandwich, England, invented the chemical compound amlodipine and discovered its anti-hypertensive and antiischaemic pharmacological properties. Pfizer's Discovery Chemistry group recommended that an effort be made to develop amlodipine into a commercial drug product.

20. Pfizer's Discovery Chemistry group designated amlodipine maleate (amlodipine base + malic acid) as the drug substance for commercial development. The

finished commercial drug product was intended to be an amlodipine maleate tablet. (See Designations of James Wells, at 7.)[1]

21. In 1982, Pfizer's Pharmaceutical Research & Development Group ("Pharm. R&D"), in Sandwich, England, was responsible for developing commercial dosage forms of pharmacologically active compounds discovered in the Pfizer Discovery Chemistry group and recommended by it for advancement to development as a commercial product. (See Designations of Edward Davison, at 8-9.)

22. Pharm. R&D did not participate in selecting the form of a pharmacologically active compound, that is, which salt form was to be developed. It specifically did not select the maleate salt form as the salt of amlodipine that would be developed. (See Designations of Edward Davison, Pfizer v. Apotex (Canada), at 4-5; see also Designations of James Wells, Pfizer v. Mylan, at 15.)

23. The head of Pharm. R&D in 1982 was Mr. J.E. Jeffries. His deputy, Dr. J.R. Davidson, assigned Dr. Wells, a manager in the group, the primary responsibility to develop a commercial dosage form of amlodipine maleate. (See Designations of James Wells, Pfizer v. Mylan, at 10-12.)

[1] The Court will, for a number of the findings of fact, cite to a specific designated testimony. Where the citation does not include a case name, the citation is to a designation for that individual in this case, that being, Pfizer v. Synthon.

24. Dr. Wells in turn was directed to develop a tablet as the preferred commercial dosage form of amlodipine maleate. (See Designations of James Wells, Pfizer v. Mylan, at 11-12.)

25. Dr. Wells assigned Mr. Davison, a member of Pharm. R&D, to assist him in developing dosage forms of amlodipine maleate. (See id.)

26. At the time Dr. Wells and Mr. Davison were given this assignment, neither scientist expected that formulating a commercial dosage form of amlodipine maleate would present any problems in terms of stability or processability. (See id. at 24, 40.)

27. Dr. Wells and Mr. Davison desired to formulate a tablet form of amlodipine maleate using the direct compression method, which was often used to make tablets when the drug substance was less than 25 percent of the total tablet weight or where water-based instability of the drug substance is a concern. (See Testimony of Stephen Hoag, Trial Transcript III, at 119.)

28. Direct compression tableting is desirable for manufacturing purposes on a commercial scale because it has fewer processing steps, reduces the potential for hydrolytic breakdown, and is more cost effective than other tablet manufacturing processes. (See id.)

29. Direct compression tableting is accomplished by blending the active drug substance with excipients called compression aids, and feeding that blend into a

tablet press. The tablet press applies force (compression) to transform the dry formulation into a tablet. Water or other liquid excipients are not used in the direct compression process. (See id.)

30. After Dr. Wells and Mr. Davison began trying to formulate a direct compression amlodipine maleate tablet, they discovered two significant problems: (a) chemical instability of amlodipine maleate alone and in tablet formulations, caused by the amlodipine ion interacting with the maleic acid ion and creating a breakdown product known as UK-57,269, among other breakdown products, and (b) the sticking of the tablet blend of amlodipine maleate to the punch faces of the tablet making press. This sticking problem would become exacerbated when tablets were made on a high speed commercial production press. (See Designations of James Wells, Pfizer v. Mylan, at 24, 37-37.)

31. Amlodipine maleate was also discovered to be very unstable in a liquid formulation, and required the addition of cosolvents in order to increase stability. (See Designations of James Wells, at 36-37; see also '303 patent, col. 2.)

32. Dr. Wells and Mr. Davison tried many different combinations of excipients with amlodipine maleate in attempting to design a tablet formulation that would overcome both the sticking and instability problems. However, the fact that the problems were interrelated – excipients that reduced sticking also increased

instability – made such a formulation difficult to discover. (See Designations of Edward Davison, 28-32.)

33. As a result of the difficulties, on or about April 24, 1984, Dr. Wells proposed to Dr. Davidson, his supervisor and the head of Pharm. R&D, that other salts of amlodipine should be considered for development. Dr. Wells identified several acids which could be used to attempt to make a new salt for testing. (See Designations of Edward Davison, 33-34.)

34. At the time that Dr. Wells made this proposal, amlodipine maleate was already being used in clinical trials by Pfizer. (See Designations of Edward Davison, at 38-40.)

35. Soon after his recommendation to make and test other amlodipine salts was approved, Dr. Wells asked Pfizer's Process Research & Development Group ("Process R&D"), to attempt to make new acid addition salts of amlodipine. Process R&D created the following salts, based upon the acids that Pfizer had on hand at the time: amlodipine besylate, amlodipine tosylate, amlodipine mesylate, amlodipine succinate, amlodipine salicylate, amlodipine acetate, amlodipine hydrochloride, and amlodipine naphthsylate. (See Designations of Robin Platt, at 24.)

36. Process R&D failed to make at least one salt because it would not form as a salt. Additionally, the methane sulphonate salt formed as an oil. (See Designations of Edward Davison, at 44; see also Designations of Alan Pettman, at 60-61.)

37. Dr. Wells also requested that Process R&D try to make other amlodipine salts that he identified in order to test their physicochemical properties and compare those properties with amlodipine maleate. (See Designations of Edward Davison, 33-34.)

38. Dr. Wells chose these candidate acids from a larger number of pharmaceutically acceptable acids that he was aware of from various sources. However, he could not predict whether any particular salt of amlodipine would form as a crystalline solid, or what the physiochemical properties of any salts that did form would be. Dr. Wells proposed a broad range of salts, including sulfonates, carboxylates, and inorganic salts. (See Designations of James Wells, Pfizer v. Mylan, at 56-57.)

39. Dr. Wells did not know prior to testing whether any salt he proposed would be an improvement over amlodipine maleate. (See id. at 116.)

40. Dr. Wells and Mr. Davison, along with other members of Pharm. R&D, tested the amlodipine salts made by Process R&D for the physicochemical properties of solubility, hygroscopicity, chemical stability in formulations, and sticking to tablet-making equipment, in order to determine the properties of the new salts

and to compare them to the newly disfavored salt of amlodipine maleate. (See Designations of Edward Davison, at 59.)

41. The solubility of each of the tested amlodipine salts was determined by a standard method. An excess of each salt was placed in distilled water at 37°C and the mixture was continuously agitated overnight. The undissolved salt was removed by centrifugation and the amount of salt dissolved was determined by ultraviolet spectroscopy. (See '303 patent, col. 2, table 1.)

42. The aqueous solubility of amlodipine besylate at 37°C was determined to be well above the 1 mg/ml threshold preferred by formulation scientists. Amlodipine besylate's solubility, which was inherently measured as the solubility of the monohydrate form of amlodipine besylate, fell in the mid-range of solubilities of the amlodipine salts tested. (See '303 patent, col. 2, table 1.)

43. The fact that amlodipine besylate would have an acceptable aqueous solubility at 37°C that is greater than 1 mg/ml could not have been predicted. To determine its aqueous solubility, the amlodipine besylate acid addition salt had to be made and tested.

44. Mr. Davison and the other members of Pharm. R&D tested all of the newly created amlodipine salts for hygroscopicity.[2] They measured hygroscopicity by

[2] Hygroscopicity is the tendency of a drug crystal to take up water. Hygroscopicity is *not* synonymous with hydrates, which are chemical compounds that include bound water, unlike

subjecting each of the amlodipine salts to controlled temperature and humidity conditions from 79°C in a vacuum, through 25°C at 75 percent relative humidity, and 30°C for three days at 95 percent relative humidity. All of the amlodipine salts that were tested, other than the besylate salt and the maleate salt, were hygroscopic at these test conditions, because they took up water to become at least a monohydrate at three days under the best set of conditions. (See Designations of Edward Davison, at 55-56.)

45. The fact that the besylate salt of amlodipine was capable of remaining nonhygroscopic through the range of conditions used in the tests could not have been predicted. (See Designations of James Wells, Pfizer v. Mylan, at 50.)

46. In order to test the formulation stability, Mr. Davison and other members of Pharm. R&D made multiple formulation blends of each of the newly created amlodipine salts, with different excipients, and they made tablets by compressing some of the blends. (See Designations of Robin Platt, at 23-24.)

47. The simulated tablets were exposed to a range of elevated temperatures to promote degradation for testing purposes. Using the analytical procedure known as thin-layer chromatography, a universally accepted technique for studying chemical stability of drug compounds, Dr. Platt measured the chemical stability

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the surface water that is described by hygroscopicity. (See Testimony of Bradley Anderson, Trial Transcript IV, at 8, 11.)

of multiple blends and tablets containing the amlodipine salts at multiple time intervals after they had been stored at fixed temperatures. (See id. at 27, 49.)

48. The various newly created amlodipine salts degraded at different rates and produced different kinds and amounts of degradation products when exposed to the range of temperatures and measured at different times. (See id. at 53-54.)

49. By use of thin-layer chromatography, Dr. Platt was able to evaluate the number and relative amounts of degradants produced as a function of temperature and time, and compare the number and amounts of degradants produced by each of the amlodipine salts. (See id. at 49.)

50. Dr. Platt used amlodipine maleate, which was considered to have unacceptable chemical stability in formulation, as a control in these experiments. Amlodipine maleate degraded in formulation to create the degradant UK-57,269, a reaction caused by the so-called "Michael addition reaction" of the amlodipine ion interacting with the maleic acid ion. (See id. at 23, 29.)

51. Dr. Platt compiled the results of the formulation stability testing and rank ordered the various amlodipine salts according to their formulation stability. Dr. Platt concluded that amlodipine besylate was the most stable of all of the amlodipine salts that he had tested. Dr. Platt did not rule out any particular salt after this test, but instead passed the information along to Dr. Wells and Mr. Davison. (See id. at 54-55.)

52. Dr. Platt set out his findings regarding stability testing in a memoranda that he prepared for Dr. Wells on or about October 9, 1984. (See id. at 47.)

53. In terms of stickiness, actual experience by Dr. Wells and Mr. Davison showed that amlodipine maleate was unacceptably sticky in that it adhered to tableting machinery. (See Designations of James Wells, Pfizer v. Mylan, at 24.)

54. Mr. Davison designed an experimental method to quantify the sticking of amlodipine salts to the faces of the tablet punches and to compare their sticking propensities with one another. (See id. at 72.)

55. Mr. Davison modified an experiment that was previously devised and used to access the stickiness of another Pfizer drug candidate by his Pfizer colleague, Dr. Yarwood, to quantify and compare the stickiness of the amlodipine salts with each other. (See '303 patent, col. 3.)

56. Mr. Davison tested the amlodipine salts for sticking by making tablets with blends of the salts and measuring the amount of amlodipine that adhered to the tablet punch face as a function of the number of tablets made. (See '303 patent, col. 3.)

57. Mr. Davison's testing demonstrated that amlodipine besylate was 41 percent less sticky than amlodipine maleate. It also showed that amlodipine besylate was less sticky than all but one other amlodipine salt, the amlodipine mesylate, which was 42 percent less sticky than the amlodipine maleate. (See Designations of Edward Davison, Pfizer v. Mylan, at 166; see also '303 patent, col. 4, table 2.)

58. The significant superiority of amlodipine besylate compared with amlodipine maleate with respect to sticking properties was confirmed by Mr. Davison in a head-to-head comparison between amlodipine maleate and amlodipine besylate that he carried out over an extended tablet-making run.

59. Pharm. R&D also confirmed the superiority of amlodipine besylate over the prior art amlodipine maleate salt by its successful use in scale-up studies of direct compression tableting.

60. Based on the test results of the amlodipine salts, on or about October 11, 1984, Dr. Wells recommended to Dr. J.R. Davidson, the head of Pharm. R&D, that the amlodipine besylate salt should be substituted for the amlodipine maleate salt for the commercial amlodipine product. (See Designations of James Wells, Pfizer v. Torpharm, at 106-09.)

61. At the time Dr. Wells made his recommendation to switch salts, Pfizer was conducting Phase II clinical trials of amlodipine maleate (in capsules). (See id.)

62. Dr. Wells' recommendation to switch salts so late in the development cycle was unusual and a direct result of the seriousness of the chemical instability and sticking problems that Pharm. R&D had experienced in developing amlodipine maleate in a tablet formulation. (See id.)

63. Dr. Wells' recommendation to switch to amlodipine besylate was based on its superior properties as compared with amlodipine maleate and the other amlodipine salts that were tested. (See id.)

64. Consistent with Dr. Wells' recommendation, based upon the studies of Dr. Wells and Mr. Davison and the results they reported, Pfizer's senior research and development management decided to switch from amlodipine maleate to amlodipine besylate for commercial development.

65. At the time Pfizer's senior research and development management considered the recommendation to switch salts, Pfizer had begun Phase III clinical trials of amlodipine maleate. Such a switch during Phase III clinical trials was unprecedented at Pfizer.

66. Such a late switch from amlodipine maleate to amlodipine besylate as Pfizer's commercial dosage form created the risk that the FDA might not approve the new salt without requiring Pfizer to repeat substantial testing that it had already performed on the amlodipine maleate salt. The switch could also have resulted in a substantial delay in the launch of the commercial product. (See id.)

67. However, as a result of switching from amlodipine maleate to amlodipine besylate, Pfizer formulation scientists were able to produce large commercial batches of amlodipine besylate tablets by direct compression on high speed tablet

presses without disruption, unlike its attempt to do so with the amlodipine maleate salt.

68. In addition, the amlodipine besylate tablets were significantly more chemically stable than the similarly formulated amlodipine maleate tablets.

69. In a supplement to the Investigational New Drug Application ("NDA") for amlodipine besylate tablets, Pfizer stated to the FDA that it had switched salts from the maleate to the besylate in order to increase chemical stability and decrease sticking to the processing equipment.

70. Dr. Wells and Mr. Davison did not file a patent application on amlodipine besylate until more than 18 months after Dr. Wells made his recommendation to Pfizer management.

71. In April 1985, Alan Pettman of the Pfizer Pharma. R&D group made amlodipine besylate monohydrate by using water as a solvent to make the salt. (See Designations of Alan Pettman, at 65.)

72. Mr. Davison recognized that the aqueous solubility measurements at equilibrium, as reported in the patent for amlodipine besylate, were actually measurements of the monohydrate form of the amlodipine besylate salt and he reported this in his May 15, 1986 pharmacy report. (See Designations of Edward Davison, at 101.)

C. The '303 Patent Prosecution

73. The '303 patent issued from the United States Patent Application Serial No. 256,938 (the "'938 application"), which was filed in the United States Patent and Trademark Office ("PTO") on October 13, 1988.

74. The '938 application was a continuation of United States Patent Application Serial No. 30,658 (the "'658 application"), which was filed in the PTO on March 25, 1987.

75. The '303 patent claims priority to, and is entitled to, the April 4, 1986 filing date of British Patent Application No. 8,608,335 ("priority application").

76. The '938, '658, and the priority applications identify the amlodipine salts selected and tested by the inventors, the methods used to carry out the tests, and the results of the testing.

77. Based upon an obviousness rejection by the Patent Office Examiner of the claims in the '658 application, pursuant to 35 U.S.C. § 103, Pfizer filed the '938 application and submitted to the PTO a preliminary amendment of the claims and the Declaration of Dr. Wells dated October 3, 1988 (the "Wells Declaration") in support of the allowance of the claims in the '938 application.

78. The Wells Declaration identifies the amlodipine salts tested by the inventors to determine their physicochemical properties, the methods used to carry out the tests, and the results of the testing.

79. On November 7, 1989, although the '658 application had previously been rejected for obviousness, the Patent Office Examiner changed its earlier ruling and allowed the claims of the '938 application without stating the reason for the allowance.

80. Pursuant to 21 U.S.C. § 355(b)(1) and the regulations the FDA had promulgated pursuant thereto, Pfizer listed the '303 patent in the FDA's "Orange Book," in which all patents protecting approved drug products must be listed, as covering the drug substance, amlodipine besylate, in Norvasc®.

81. The '303 patent term, including a six-month period of pediatric exclusivity, expires on September 25, 2007.

82. The co-inventors, Dr. Wells and Mr. Davison, assigned their interests in the '303 patent to Pfizer.

83. Pfizer is the present owner of the '303 patent.

D. Prior Art to the '303 Patent

84. The prior art to the '303 patent includes (1) United States Patent No. 4,572,909 ("'909 patent), (2) an article describing acids that had previously been used to make pharmaceutically acceptable salts (Berge), (3) an article describing a drug called Xilobam and the effect of salt form on pharmaceutical properties (Walkling), and (4) three patents that mentioned benzene sulphonic acid. Internal Pfizer memoranda relating to its development work with amlodipine maleate and its testing of other amlodipine salts are not prior art to the '303 patent because

internal Pfizer memoranda would not be available to a person of ordinary skill in the art of drug formulation. The Court will describe each of the prior art references in more detail *infra*.

85. As previously stated, before the inventors on the '303 patent began the work described in that patent, the amlodipine molecule had already been invented by another group of Pfizer scientists in England. Pfizer filed a patent application on amlodipine in 1982, which ultimately led to the '909 patent. Therefore, the '909 patent is prior art to the '303 patent.

86. Claim 8 of the '909 patent is specifically directed to amlodipine and the "pharmaceutically acceptable acid addition salts" of amlodipine. However, the preferred salt in the '909 patent is amlodipine maleate.

87. The '909 patent teaches that amlodipine maleate formed a crystalline salt. It discloses no other properties of the maleate salt, such as its stability or processability.

88. The '909 patent also mentions 12 acid anions in col. 2, and one additional acid in example 1. These acid anions are primarily carboxylic acids,[3] and the rest are mineral acids.[4] More specifically, these acid addition salts are: hydrochloride,

[3] Carboxylic acids are organic acids characterized by the presence of a carboxyl group, -C(=O)-OH.

[4] Mineral acids are acids derived from inorganic minerals by a chemical reaction, such as hydrochloric acid.

hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, and oxalate. None of the acid anions mentioned are sulphonic acids,[5] of which benzene sulphonic acid is a member. (See Testimony of Bradley Anderson, Trial Transcript IV, at 29.)

89. Additionally, a publication by Berge, S.M., et al., (1977) *J. Pharm. Sci.* 66:1-19 ("Berge") is prior art to the '303 patent, because it lists all known pharmaceutically acceptable acids, including benzene sulphonic acid, and the percentage of drugs made from those acids.

90. The prior art Berge publication discloses 53 different anions that had been used in FDA-approved commercially marketed salts as of 1974.

91. Berge, however, discloses that only 4.16 percent of the drugs commercially marketed in the United States as of 1974 included sulphonic acid salts. Moreover, Berge discloses that of the sulphonic acid salts, the besylate anion was used only .25 percent of the time compared to other acids that were used to make salts.

92. In contrast, Berge discloses that the hydrochloride salt was the anion most frequently used to make salts commercially marketed in the United States as of 1974, because these salts were used 42.98 percent of the time.

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[5] Sulphonic acids are a class of organic acids with the general formula of RSO^3H, where R is usually a hydrocarbon side chain. (See Testimony of Bradley Anderson, Trial Transcript IV, at 30-31.)

93. Berge further discloses that one cannot predict the properties of a new salt, and therefore Berg teaches that acids used to form salts on other bases are not a useful guide for selecting an acid for a new base compound. Specifically, Berge itself states the following: "Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound."

94. The prior art of Walkling et al, "Xilobam: Effect of Salt Form on Pharmaceutical Properties" *Drug Development and Industrial Pharmacy*, 9(5), 809-819 (1983), is an article that addresses four salts made of the base compound Xilobam, in an effort to increase the solid state stability of Xilobam. Xilobam, however, has a very different structure than amlodipine because it is not a dihydropyridine. Walkling may teach that aryl sulphonic acids can be used to reduce hydrolytic instability. However, Walkling prefers the 1-napsylate salt, and not the besylate salt, which was never mentioned. Moreover, Walkling's theory actually provides no indication that any particular compound using benzene sulphonic acid will form. In fact, when Pfizer tried to make a mesylate salt and a besylate salt (both sulphonic acids) of the compound UK-52,831, which is another 1,4 di-hydropyridine like amlodipine, adding the mesylate salt created an oil. In addition, the use of the besylate salt with the compound UK-52,831 resulted in a rapid degrading. Thus, the addition of an aryl sulphonic acid to UK-52,831 did not result in any increased hydrolytic stability, as Pfizer may have been looking

for, as it did not result in a pharmaceutically acceptable salt. (See Testimony of Bradley Anderson, Trial Transcript IV, at 47-49.)

95. Three other prior art patents mentioned the possibility of using benzene sulphonic acid to make a salt prior to the invention of the '303 patent. These are United States Patent No. 3,970,662 ("Carabateas"), United States Patent No. 3,816,612 ("Schmidt"), and United States Patent No. 4,032,637 ("Spiegel").

96. The prior art patents of Spiegel, Carabateas, and Schmidt each describe salts of pharmacologically active compounds that also are structurally different from amlodipine. In addition, these other salts are approved or used for different medical treatments than amlodipine.

97. For instance, the Spiegel patent, issued on June 28, 1977, states that the preferred salt for the drug compound mesoridazine is the besylate. The compound mesoridazine has anti-psychotic activity and is useful in treating humans. However, mesoridazine has a very different structure than amlodipine, and it would not be possible to extrapolate the effects of the besylate on amlodipine based upon the Spiegel prior art. Moreover, the Spiegel prior art does not teach anything about the properties of the resulting salt that would suggest whether, or how, it would be useful to pair it with amlodipine. (See Testimony of Bradley Anderson, Trial Transcript IV, at 46-47.)

98. Considering the Carabateas patent, which was also issued on July 20, 1976, it shows only how to produce a particular compound, referred to as formula VII. The patent also refers to a number of intermediates in the process of forming formula VII. One intermediate compound, referred to as formula IV, is a di-hydropyridine (the same class as amlodipine). However, Carabeteas does not give any specific examples of any salt of the di-hydropyridine, and in fact states that the entire class of mineral acids and the entire class of organic acids would be appropriate for use (including benzene sulphonate). Thus, the Carabeteas patent does not suggest how it would be useful to specifically pair benzene sulphonic acid with amlodipine. (See Testimony of Bradley Anderson, Trial Transcript IV, at 43-44.)

99. With respect to the Schmidt patent, issued on June 11, 1974, it includes, in a general sense, benzene sulphonic acid among a long list of acids that one might experiment with along with an undefined group of bases for use in aerosol sprays with organic solvents. It states that the group of aryl sulfonic acid salts are preferred over other salts, and indicates that sulphonic acids can be used to improve solubility. However, the Schmidt patent contains no examples of a besylate salt, and it does not provide a reason why a person of ordinary skill would particularly select besylate from the list of acids, including the list of sulphonic acids. In addition, the proposed use of amlodipine was for tablets, and

not for aerosols, as was involved in the Schmidt patent. (See Testimony of Bradley Anderson, Trial Transcript IV, at 45-46.)

100. Accordingly, based upon all of these prior art references, a person of ordinary skill in the art would not have been motivated to make amlodipine besylate, nor would one have a reasonable expectation that amlodipine besylate would be successful based on the knowledge that besylate salts of different pharmaceutical compounds than amlodipine, such as the compounds described in Berge, Walkling, Spiegel, Carabateas, or Schmidt had been made or suggested. (See Testimony of Bradley Anderson, Trial Transcript IV, at 49.)

101. Neither in 1986, nor today, is it possible to predict any of the physicochemical properties of the salt that might result from the reaction of a newly discovered chemical base and an acid pairing. (See Testimony of Bradley Anderson, Trial Transcript IV, at 36-37.)

102. To discover the physiochemical properties of a new salt candidate, the salt must be made and tested. (See Testimony of Bradley Anderson, Trial Transcript IV, at 36.)

103. One of ordinary skill in the art could not have predicted that amlodipine besylate would exhibit good solubility, nonhygroscopicity, good stability, and good processing capabilities. (See id.)

104. It is significant to the Court on the question of obviousness that the besylate salt of amlodipine has superior properties as compared to the prior art, those being good stability, good processability, nonhygroscopicity, and good solubility.

105. The superior properties of amlodipine besylate, individually and in combination, were unexpected at the time of the invention of the '303 patent.

E. Properties of Amlodipine Besylate Monohydrate as Compared to Amlodipine Besylate Anhydrous

106. The measurement of aqueous stability at equilibrium of amlodipine besylate necessarily measures the solubility of the monohydrate form. The monohydrate form of amlodipine besylate has the solubility reported in the '303 patent for amlodipine besylate. (See Designations of Edward Davison, at 73.)

107. Based upon all the evidence before the Court, the amlodipine besylate used in Synthon's ANDA product does not take up significant amounts of water during the normal manufacturing and processing conditions. Therefore, amlodipine besylate monohydrate is not hygroscopic. (Cf. Designations of Peter Brewer at 89, 101.)

108. Synthon has not informed the FDA in its ANDA of any hygroscopicity of its amlodipine besylate.

109. Synthon has not informed the FDA of any problems with the stability of its ANDA product. Therefore, amlodipine besylate monohydrate is not

substantially unstable in order to make it unacceptable for pharmaceutical development. (Cf. Designations of Peter Brewer at 89, 101.)

110. In addition, Synthon has not informed the FDA of any problems in the processability of its ANDA active ingredient, and in fact, Synthon's amlodipine besylate monohydrate uses a lesser amount of the excipients used to reduce sticking than Pfizer's besylate salt of amlodipine.[6]

111. Pfizer has shown based upon its own research that amlodipine besylate in its anhydrous form has at least one property that is superior to the prior art sufficiently to give it a practical advantage and such superior property was unexpected. These qualities include good stability, good processability, nonhygroscopicity, and good solubility.

112. Pfizer has shown based upon its own research that amlodipine besylate in the monohydrate form has at least one property that is superior to the prior art sufficiently to give it a practical advantage and such superior property was

[6] This factual finding by the Court regarding the monohydrate's processability includes the Court's consideration of the study done by Gert Jan Ettema, solely for this litigation, comparing amlodipine besylate monohydrate to amlodipine besylate anhydrous. The Court notes that Mr. Ettema, an inexperienced operator on the tablet press, completed his study in four days, did not ensure that his starting materials actually consisted of the compounds he thought he was testing, and that, in fact, he was actually measuring cohesion of the compound to the tablet press instead of adhesion, thus his results are uninterpretable. (See Testimony of Stephen Hoag, Trial Transcript III, at 134-37.)

unexpected. This quality is good solubility. (See Designations of Edward Davison, at 73.)

II. CONCLUSIONS OF LAW

A. Standard of Review - Infringement

1. The filing of an ANDA under 21 U.S.C. § 505(j)(2) seeking approval of a generic drug claimed in a patent with the purpose of marketing the drug before the patent expires is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

2. Pfizer's '303 patent is listed in the FDA "Orange Book," with respect to Norvasc®, and the filing of an ANDA seeking approval to market amlodipine besylate tablets prior to the expiration of the '303 patent is an act of infringement of that patent. 35 U.S.C. § 271(e)(2)(A).

3. The factual inquiry on infringement in this case under § 271(e)(2)(A) is "whether the patent in question will be infringed by the manufacture, use, or sale of the generic drug for which the ANDA was submitted." 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

4. A patent claim is literally infringed when each element of the claim is literally found in the accused product. Markman v. Westview Instruments, Inc., 517 U.S. 370, 384-391 (1996).

5. This Court conducted a claim construction hearing as to the phrase "the besylate salt of amlodipine." The Court, thereafter, in a March 7, 2006 Order construed

the phrase to mean "any salt that contains the positively charged amlodipine cation and the negatively charged besylate anion, without limitation to any particular physical form of the salt."

6. Based upon this claim construction, Synthon's monohydrate form of amlodipine besylate falls literally within claim 1 of the '303 patent because Synthon's monohydrate form of amlodipine besylate contains a positively charged amlodipine cation and a negatively charged besylate anion.

7. Therefore, the Court finds that Synthon's ANDA filing infringes Pfizer's '303 patent. However, because Synthon has asserted a number of defenses to infringement, thereby asserting that Pfizer's '303 patent is invalid, the Court will first discuss the standard of review, and then look specifically at those defenses, that is, obviousness, written description, and obviousness-type double patenting.

B. Standard of Review - Invalidity

8. A patent is presumed to be valid. 35 U.S.C. § 282; Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 935 (Fed. Cir. 1990) ("While invalidity is a question of law, the party asserting invalidity must by clear and convincing evidence establish facts supporting a conclusion of invalidity, and asserted inferences of fact must similarly be supported to meet this standard.").

9. The party challenging the validity of the patent has the burden to prove each element of invalidity by clear and convincing evidence. See Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1326 (Fed. Cir. 2004).

10. Clear and convincing evidence is evidence that places in the fact finder "an abiding conviction that the truth of [the] factual contentions are [sic] highly probable." Intel Corp. v. U.S. Int'l Trade Comm'n, 946 F.2d 821, 830 (Fed. Cir. 1991) (quoting Colorado v. New Mexico, 467 U.S. 310, 316, 104 S.Ct. 2433, 2438 (1984)).

11. The party who asserts the patent claim invalidity, in this case, Synthon, bears the burden of proof by clear and convincing evidence that Pfizer's patent claim fails for obviousness. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1375 (Fed. Cir. 1986).

C. Invalidity – Defense of Obviousness

12. "Obviousness is a question of law based on underlying facts." Group One, Ltd. v. Hallmark Cards, Inc., 407 F.3d 1297, 1303 (Fed. Cir. 2005). A patent claim is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a).

13. In addressing the question of obviousness, the Court must consider a number of factors including the fact that an invention of a chemical compound includes both the chemical structure and all the properties of the chemical compound. See In re Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

14. In addition, the Court acknowledges that the relevant time to assess whether an invention is obvious is the time the invention was made, not the time of the litigation. See Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323 (Fed. Cir. 1999).

15. Likewise, the Court accepts the understanding that conclusions made by a patent examiner during the prosecution of a later-filed, unrelated patent application are irrelevant to the scope and validity of an earlier filed patent. See Abbott Labs. v. Dey, L.P., 287 F.3d 1097, 1104-05 (Fed. Cir. 2002). Therefore, the Court will not consider the conclusions of the Patent Examiner concerning Synthon's later-filed and unrelated patent concerning amlodipine besylate monohydrate.

(a.) Prima Facie Obviousness

16. A party challenging a patent claim as obvious must provide clear and convincing evidence sufficient to establish a *prima facie* case of obviousness. If the evidence of the challenging party is not sufficient to establish a *prima facie* case of obviousness, the patentee is entitled to judgment as a matter of law dismissing the obviousness challenge. See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.,

231 F.3d 1339, 1343 (Fed. Cir. 2000). Where a patent challenger successfully makes a case for *prima facie* obviousness, the patentee must then come forward with evidence to rebut that finding by showing an unexpected superior property as compared with the prior art. Id. at 1345.

17. When evidence to rebut a case of *prima facie* obviousness is provided to the Patent Examiner, the original ruling of *prima facie* obviousness must be re-evaluated in light of all the evidence. In re Rinehart, 531 F.2d 1048, 1052 (C.C.P.A. 1976). Therefore, the Court finds that the Patent Examiner's prior rejection of the '303 patent for obviousness before the Patent Examiner's eventual approval of the same patent without explanation for the reversal in judgment does not automatically indicate that the '303 patent was *prima facie* obvious.

18. In order to establish a *prima facie* case of obviousness, the party challenging the patent must prove by clear and convincing evidence that: (a) there was a suggestion or motivation in the prior art that would motivate one of ordinary skill in the art to make the claimed invention; and (b) that a person of ordinary skill in the art would have had a reasonable expectation that the invention would be successful at the time the invention was made. See In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991). Thus, this Court must first define who a person of ordinary skill in the art would be in this case, and then determine whether that

hypothetical person would be both motivated to make, and have a reasonable expectation of success, regarding the besylate salt of amlodipine.

19. A person of ordinary skill in the art is a hypothetical person who "thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985).

20. In this case, the Court finds that a person of "ordinary skill in the art" is a person with at least a bachelor's degree, or the equivalent, in pharmacy or a related field such as chemistry, and two to three years of industry experience making pharmaceutical formulations. (See Testimony of Bradley Anderson, Trial Transcript IV, at 7.)

21. The party challenging the patent claim as obvious based on a combination of prior art references must provide clear and convincing evidence in the prior art of a *motivation* to combine the references to make the claimed invention. See Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957 (Fed. Cir. 1997).

22. In the context of determining motivation, a finding that a prior art reference "teaches away" from combining references can alone defeat an obviousness claim, see Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000), because this would defeat motivation. A prior art "teaches away": "when a person

of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (internal quotations omitted).

23. However, that a particular combination is not the *most preferred* combination in a prior art reference does not defeat either obviousness or suggest a lack of motivation for the current invention. See In re Fulton, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

24. In this case, as previously discussed in another section, the Court finds that the prior art references do not suggest the combination of amlodipine and benzene sulphonic acid, because, in particular, the '909 patent teaches toward the maleate and other carboxylates. However, the Court also finds that the prior art references do not specifically teach away from the combination, either. The '909 patent does not teach toward the sulphonate salts, but, likewise, it does not teach away from them, either, because the '909 patent simply does not mention any sulphonic salts. Therefore, Pfizer cannot defeat an obviousness inquiry simply by showing that the prior art "teaches away" from the besylate, specifically where there has been no mention of it.

25. But, the Court notes that a prior art disclosure of a genus that includes the species claimed in the patent does not make *prima facie* obvious every member that falls within the genus. See In re Baird, 16 F.3d 380, 883 (Fed. Cir. 1994). The prior art disclosure of a genus which includes a claimed species must still provide the suggestion and motivation to make the particular species claimed as the invention in order for the motivation element of *prima facie* obviousness to be established. Id.

26. The Court concludes that Synthon has failed to show by clear and convincing evidence a motivation to make the besylate salt of amlodipine as contained in the prior art. The '909 patent specifically directed that the maleate salt was the preferred salt, and it listed a number of other classes of acids to try, none of which were sulphonates, of which benzene sulphonic acid is a member. None of the other prior art references provide a suggestion to combine amlodipine and benzene sulphonic acid in particular. Moreover, the prior art does not teach a reason for one skilled in the art to even try to improve upon the maleate salt. It was not until Pfizer scientists started trying to formulate the maleate salt for commercial development that they discovered any problems with the maleate, those being stickiness and stability issues. Pfizer scientists' difficulties with the maleate salt were not public knowledge and were not available to one of ordinary skill in the art.

In response to this position, Synthon has pointed to the case of Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804 (Fed. Cir. 1989) for the proposition that selecting a known specific compound or "species" from a known "genus" of compounds is *prima facie* obvious when the prior art taught the use of the genus. However, the Court finds that Synthon's argument is an overstatement of what the Federal Circuit actually determined in Merck. In Merck, the prior art patent taught a genus that included about 1,200 species combinations of diuretics, one of which *was* the patentee's claimed combination. Id. at 806-07. Thus, in Merck, the Federal Circuit found the patentee's combination to be *prima facie* obvious, even though neither of the diuretics were identified as *preferred* in the patent, because the prior art *specifically taught* that each combination, including the patentee's combination, would work. See id. at 807-08. Thus, the Court finds that Merck is not on point with the instant matter, because in Merck the combination of amiloride hydrochloride and hydrochlorothiazide were both specifically mentioned in the prior art as a potential combination. Id. at 807. In this case, in no prior art, described by the Court or suggested by Synthon, was benzene sulphonic acid suggested for amlodipine, nor was it mentioned as a potential for a compound chemically similar to amlodipine. Moreover, the experts in this case agree that, based upon the uncertain nature of salt formulation, it was not until

the besylate salt of amlodipine was actually made that it could be determined to be a "pharmaceutically acceptable salt" as claimed by the prior art '909 patent.

Similarly, this Court rejects Synthon's related argument based upon the case of In re Corkill, 771 F.2d 1496, 1500 (Fed. Cir. 1985). In Corkill, the Federal Circuit also affirmed an obvious rejection in light of prior art that taught that all "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims [in the challenged patent] from among 'thousands' of compounds." The Court finds that none of the prior art in this case suggests that a combination of amlodipine and benzene sulphuric acids would work as a *pharmaceutically acceptable* salt, given the unpredictable nature of determining the properties a particular salt will have. The prior art Berge article, as previously stated, acknowledges this by stating that "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." Thus, even though the benzene sulphuric acid had been used before to make other pharmaceutically acceptable salts, there was no reasonable expectation during the relevant time period in 1984 that a besylate salt of amlodipine could even be made, much less that it would be pharmaceutically acceptable, as well as commercially developable. (For instance, the hydrochloride salt, so often used in other pharmaceutically acceptable drug products, failed in Pfizer's testing when paired with amlodipine.) This last determination, that there

was no reasonable expectation that the besylate salt of amlodipine would even form as a pharmaceutically acceptable salt, leads the Court to a discussion of what is meant by "success" under a *prima facie* obviousness determination.

27. Regardless of whether it is suggested by the prior art, an invention is not *prima facie* obvious unless a person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success. See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000).

28. Patent claims are not obvious if the prior art does not provide a reasonable expectation of success, but instead merely suggests that they are "obvious-to-try." In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

29. Claims are merely "obvious-to-try" where: (a) there is a teaching to try each of numerous possible choices until reaching a successful result, but no teaching as to which of many possible choices is likely to be successful; or (b) there is a teaching to explore a new technology or a general approach that seems to be a promising field of experimentation, but the prior art gives only general guidance as to the claimed invention. See id.

30. Stated differently, "[a]n 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be

obtained if certain directions were pursued." In re Eli Lilly & Co., 902 F.2d 943, 945 (Fed. Cir. 1990).

31. In this case, the Court defines a "reasonable expectation of success" as more than the ability of one of ordinary skill in the art to create a salt from amlodipine and benzene sulphonic acid. Instead, the Court looks to the '909 patent, which claimed the "pharmaceutically acceptable acid addition salts of amlodipine." A "pharmaceutically acceptable salt," is, as the Court previously defined it, a "salt of an active drug molecule that can be used to make a finished drug product suitable for administration of the drug to a patient." Salts that are unstable, that fail solubility tests, that create unwanted and potentially toxic degradants, or that are hygroscopic may not be suitable for administration to a patient, because such salts may have difficulty being approved by the FDA, among other reasons. (See Testimony of Bradley Anderson, Trial Transcript IV, at 27-28 ("[W]e have to consider that to be successful or to be pharmaceutically acceptable a salt not only must form, must prove to be nontoxic, but a pharmaceutically acceptable salt has to be, from a practical matter, a salt which can be formed in a characterizable composition with a defined stoichiometry that can be made reproducibly and characterized since it is compounds that are being claimed. And in addition to that . . . the salt formed must enable one to administer the composition to a patient."); see also Testimony of Walter Chambliss, Trial Transcript III, at 99 ("Q:

And if a salt does not have good stability, it can't be used as a pharmaceutical salt; is that correct? A: It depends on how you're planning on using it. Q: But would a person of ordinary skill in the art have believed when the patent was filed that unless a pharmaceutical salt had good stability it could not be used as a pharmaceutical salt? A: Yes").) In this case, the Court heard evidence about a number of salts of amlodipine that failed to make pharmaceutically acceptable salts (such as the hydrochloride salt (suffered extensive breakdown in stability testing), other acids that would not form a salt when combined with amlodipine, and UK-52,831 (rapidly degraded)), as well as a number of salts that performed adequately (such as the mesylate salt), but not as well as the besylate salt.

32. Therefore, the Court finds that Synthon has failed to show, by clear and convincing evidence, that one skilled in the art would have been motivated to create, or would have had a reasonable expectation of success in creating, the pharmaceutically acceptable salt of amlodipine besylate, solely based upon a reading of the prior art. This is because it was completely unpredictable as to whether a salt would even form, much less whether it would form a pharmaceutically acceptable acid addition salt.

33. Therefore, the Court finds that the besylate salt of amlodipine is not *prima facie* obvious. As such, Synthon's defense of obviousness would fail and this matter

would be resolved based upon the Court's prior finding of infringement by Synthon.

(b.) Objective Indicia of Nonobviousness

34. However, even if this Court were to find the claim to "the besylate salt of amlodipine" to be *prima facie* obvious, which it has not, the Court would nevertheless conclude that Pfizer has come forward with evidence to rebut Synthon's claim of obviousness by showing to the Court an unexpected, superior property of the patent as compared with the prior art.

35. A result is unexpected for the purpose of showing non-obviousness when the result could not have been predicted by a person of ordinary skill in the art at the time of the invention. See In re May, 574 F.2d 1082, 1094 (C.C.P.A. 1978) ("Thus, merely because those skilled in the art would have expected the compound of claim 11 to have analgesic activity, [that] does not mean, as the board apparently suggests, that an irrebuttable presumption of obviousness has been established. Those properties which would have been expected must be balanced against the unexpected properties.").

36. Only one unexpected superior property that has some practical advantage is needed to overcome a *prima facie* case of obviousness. Not all embodiments of the invention nor all uses of the invention must have all of the superior properties.

See In re Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987); In re Ackermann, 444 F.2d 1172, 1176 (C.C.P.A. 1971).

37. Thus, the Court rejects Synthon argument that Pfizer's patent must fail because Pfizer has not specifically shown that all possible forms of amlodipine besylate have the four properties of good stability, good processability, nonhygroscopicity, and good solubility. While the Court acknowledges that a patent applicant using unexpected results to show non-obviousness must provide data commensurate in scope with the claims which the evidence is offered to support, see In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983), the Court notes that the Federal Circuit has also held that "claims allowed based on 'surprising results' may be construed more broadly than the [test] results themselves." McNeil-PPC, Inc. v. Perrigo Company, No. 05 CIV. 1321(WHP), 2006 WL 2092474, at *10 (S.D.N.Y. July 27, 2006) (citing to Purdue Pharma L.P. v. Endo Pharms., Inc., 438 F.3d 1123, 1135-37 (Fed. Cir. 2006)). Moreover, the Court finds that Pfizer has shown unexpected results, because of testimony by the inventors of the '303 patent that the solubility test of amlodipine besylate anhydrous actually measured the solubility of the monohydrate form, and even that solubility was better than the prior art salt, the maleate.

38. Furthermore, the Court finds that Synthon has failed to make a persuasive case that the monohydrate form of amlodipine besylate actually constitutes a

problematic combination, given the fact that Synthon is set to produce the monohydrate with a smaller ratio of excipients than Pfizer uses for the anhydrous form, and given the fact that Synthon has reported no hygroscopicity or stability problems with the monohydrate to the FDA.[7] (See Synthon's U.S. Patent No. 6,828,339 ("It should be noted that the amlodipine besylate hydrates, particularly the monohydrate, are surprisingly equivalent to the known prior art amlodipine besylate anhydrate form as far as stability in solid state and in solution are concerned.")

39. In this case, the Court finds that the unexpected properties of the besylate salt of amlodipine compared to the prior art salt of amlodipine, the maleate, are sufficient to overcome any potential case of *prima facie* obviousness. See Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1349 (Fed. Cir. 2004) (finding that

[7] The Court notes that Synthon repeatedly points out in its briefs that Pfizer told the FDA in its NDA that the monohydrate form was not a "suitable form for development" because it "is dehydrated by moderate conditions of relative humidity and temperature." (See Deposition of Peter Brewer, p. 80.) However, the actual depositions in this case show that Pfizer did not, in fact, specifically test that statement for its validity prior to asserting it to the FDA. Instead, Pfizer's statement was "based on theoretical consideration at the time, limited to theoretical understanding at that time, which subsequently proved incorrect . . . as I recall, there were no tests to carry out to underpin that statement." (Id.) Thus, the Court finds that Pfizer has shown that its unexpected results span the claim construction, and that Synthon has failed to show that they do not.

The Court also notes at this time that it has already precluded Synthon from asserting a defense of inequitable conduct before the PTO because Synthon decided to officially assert such a defense only a month before trial in this matter, despite knowing about the potential for such a defense three months prior to that time. (See Order of April 4, 2006, Document #142, at 5.)

patented invention of highly pure amorphous cefuroxime axetil product would have better bioavailability and stability than a crystalline form was a surprising discovery and not obvious).

D. Invalidity - Defense of Written Description

40. A patent must contain a written description of the claimed invention sufficient to demonstrate to those of ordinary skill in the art that the inventor was in the possession of the invention. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

41. However, a patent need not describe every version or embodiment of an invention. See Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003) ("As our case law makes clear . . . 'an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.'").

42. A genus claim – a claim that may include more than one species or member – may be supported for written description by a description of the genus without the need to describe every species or member of the genus. See Utter v. Hiraga, 845 F.2d 993, 998 (Fed. Cir. 1988).

43. Pfizer's '303 patent contains an adequate written description, because it demonstrates to those of ordinary skill in the art that the inventor was in the possession of the invention, that is, amlodipine besylate, in three physical forms

of the anhydrate (crystalline, salt in solution, and melt), and also potentially in the monohydrate form given that the solubility tests actually showed the solubility of the monohydrate, and given that the patent allowed for the formulation of the besylate salt of amlodipine from any inert solvent, which would include water. The Court notes that the monohydrate form of the besylate salt of amlodipine is formed from water, and that a person of ordinary skill in the art who desired to form a monohydrate form of any salt would likely begin by trying to precipitate the salt from water. (See Testimony of Bradley Anderson, Trial Transcript IV, at 50-51; see also Testimony of Walter Chambliss, Trial Transcript III, at 96.)

44. Accordingly, the Court finds that Synthon has failed to prove by clear and convincing evidence that the '303 patent lacks a written description.

E. Invalidity - Defense of Double Patenting

45. Synthon has also argued that the '303 patent is invalid because of obviousness-type double patenting.

46. Obviousness-type double patenting is a judicially-created doctrine to "prevent *improper* timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not 'patentably distinct' from the claims of the first patent." See In re Braat, F.2d 589, 592 (Fed. Cir. 1991) (emphasis in original).

47. While Synthon argues that obviousness-type double patenting does not require consideration of motive to make an invention or other objective indicia, and cites to a footnote in Geneva Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373 (Fed. Cir. 2003) for this proposition, the Court finds that that case does not apply because the Geneva case dealt with § 102 defense of anticipation, and not § 103 obviousness. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F. Supp. 2d 820, 911 (S.D. Ind. 2005).

48. Moreover, the Court finds that the '303 patent is not an obviousness-type double patent, because the claims in '303 are 'patentably distinct' from the claims of the first patent, the '909. The '909 patent claims "amlodipine and its pharmaceutically acceptable salts." The '303 patent claims amlodipine besylate. When the '909 patent expires, other individuals will theoretically be free to make other salts of amlodipine other than the besylate, such as the maleate or the fumarate.[8] Where a second patent covers matter included in the first patent, there is no double patenting problem, where there is a patentable distinction between the claims. See In re Braat, 937 F.2d 589, 594 (Fed. Cir. 1991).

49. Therefore, the Court rejects Synthon's obviousness-type double patenting defense.

III. CONCLUSION

[8] The fumarate, the Court notes, has in fact been patented by Synthon in United States Patent No. 6,518,288, which was issued on February 11, 2003.

The Court has now made a number of findings of fact and conclusions of law relevant to the issue before the Court based upon Synthon's assertion of defenses to its infringement of Pfizer's '303 patent. As previously noted, the Court has determined that Synthon's ANDA filing does, in fact, infringe upon Pfizer's '303 patent, because Synthon's product literally infringes Claims 1-3 of the '303 patent, as construed by the Court. The Court has also determined that Synthon's defenses to infringement, those being obviousness, written description, and obviousness-type double patenting, are rejected for reasons set out above. Accordingly, the Court will enter Judgment in this matter in favor of Pfizer, and an injunction will issue preventing Synthon from marketing its ANDA product until after the '303 patent and its period of pediatric exclusivity awarded to the patent have expired.

An Order and Judgment consistent with these Findings of Fact and Conclusions of Law will be filed contemporaneously herewith.

This, the 31st day of August, 2006.

United States District Judge