UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

SPECTRUM PHARMACEUTICALS, INC. and UNIVERSITY OF STRATHCLYDE, Plaintiffs, vs. SANDOZ INC., Defendant.	Case No.: 2:12-cv-00111-GMN-NJK **ORDER**

I. BACKGROUND

1. Plaintiffs Spectrum Pharmaceuticals, Inc. and University of Strathclyde (collectively, "Spectrum" or "Plaintiffs") filed this action under the Hatch-Waxman Act alleging patent infringement against Defendant Sandoz Inc. ("Sandoz"). Sandoz contends that the asserted patent claims are invalid.

2. The Court conducted a bench trial from January 12–20, 2015, regarding the validity of claims 1 and 2 of U.S. Patent No. 5,800,829 (the "'829 patent"). Having considered the parties' pleadings and filings, the testimony and credibility of the witnesses, the evidence, the arguments and briefs of counsel, and the applicable law, the Court enters the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

3. Congress passed the Hatch-Waxman Act in 1984 to promote the approval and marketing of lower-cost generic drugs. See Drug Price Competition and Patent Term Restoration Act, 98 Stat. 1585 (1984); PLIVA, Inc. v. Mensing, 131 S. Ct. 2567, 2574 (2011). "Under this law, 'generic drugs' can gain [U.S. Food and Drug Administration ("FDA")] approval simply by showing equivalence to a reference listed drug that has already been approved by the FDA." PLIVA, 131 S. Ct. at 2547. "This allows manufacturers to develop

generic drugs inexpensively, without duplicating the clinical trials already performed on the equivalent brand-name drug." Id.

4. Spectrum is the holder of approved New Drug Application ("NDA") No. 20-140 for formulations containing the active ingredient levoleucovorin. (Ex. 1A to Pretrial Order ¶ 5, ECF No. 331-1). Spectrum markets drug products under NDA No. 20-140 under the name Fusilev®. (Id.).

5. Pursuant to 21 U.S.C. § 355(b)(1), the '829 patent is listed in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book, with respect to Fusilev®. (Id. ¶ 11). The Orange Book is the authoritative reference source for drug products approved by FDA under the Federal Food, Drug & Cosmetic Act. Companies self-identify those patents they contend cover their products.

6. Sandoz submitted Abbreviated New Drug Application ("ANDA") No. 203563 to the FDA for approval to market generic levoleucovorin products on October 26, 2011. (Id. ¶ 12). On or about December 7, 2011, Plaintiffs received a letter from Sandoz pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) regarding the '829 patent, which asserts that the claims of the '829 patent are invalid, unenforceable, and/or will not be infringed by the manufacture, use, importation, sale or offer for sale of the Sandoz ANDA product. (Compl. ¶ 19, ECF No. 1).

7. On January 20, 2012, Plaintiffs initiated the present action by filing a complaint against Sandoz in the United States District Court for the District of Nevada alleging, inter alia, that Sandoz's submission of ANDA No. 203563 to the FDA constitutes infringement of the '829 patent. (Id. ¶ 24). The action was designated Civil No. 2:12-cv-00111-GMN-NJK.

8. This Court has subject-matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1338(a), 2201 and 2202 because this action arises under the patent laws of the United States, 35 U.S.C. § 1 et seq., and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

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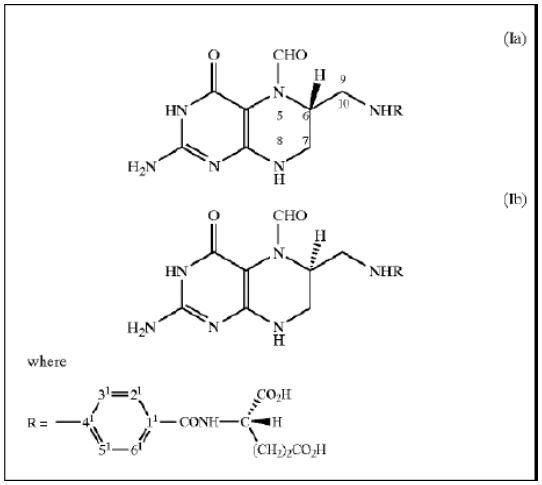
II. FINDINGS OF FACT

A. LEUCOVORIN BACKROUND

i. Leucovorin Exists as (6S) and (6R) Diastereoisomers

9. Leucovorin is a chemically synthesized compound. (PTX 14; PTX 417 at 34:20–35:6 (Machover)). Its chemical name is 5-formyl-(6R,S)-tetrahydrofolic acid. (PTX 14). As the chemical name suggests, leucovorin contains a stereocenter at the 6 carbon. (PTX 1 at 1:30–35). This stereocenter causes leucovorin to exist primarily as a 50-50 mixture of two diastereoisomers, denoted as the "(6S)" and "(6R)" isomers.[1] (Id.).

10. The chemical structures of the (6S) and (6R) leucovorin isomers are depicted below, where formula (Ia) represents the (6R) isomers and (Ib) represents the (6S) isomer:



(PTX 1 at 1:36–56).

11. Leucovorin (in the form of its calcium salt) has a long history of being used as a pharmaceutical for human beings (first sold under the trade name Wellcovorin). (PTX 1 at

[1] The 50/50 mixture of the (6S) and (6R) leucovorin isomers is sometimes called "racemic leucovorin." The term "racemic leucovorin" is technically incorrect because "racemic" refers to enantiomers and leucovorin exists as diastereoisomers, not enantiomers. (Tr. 274:19–275:6 (Martin)). This technical distinction is insignificant to the Court's decision. For the purposes of this opinion, the Court uses the term "racemic leucovorin" and "leucovorin" to refer to a 50/50 mixture of the (6S) and (6R) leucovorin isomers.

1:30–35; DX 739; Tr. 164:22–25 (Suckling); 269:3–273:14 (Martin); 475:10–15 (Moran); 503:2–6 (Krook)). Dr. Krook and Dr. Martin provided unchallenged testimony that leucovorin was first used to treat patients in the 1950s. (Tr. 289:20–22 (Martin); 503:2–6 (Krook)).

12. It has been known since the 1950s that between the leucovorin isomers, only the (6S) isomer has desired biological activity. (PTX 1 at 1:57–61, 4:67–5:9; PTX 14; PTX 15 at 1:13–23; PTX 22 at 117; PTX 241 at 687; DX 732 at 70; DX 739 at 821; Tr. 165:9–15 (Suckling); 312:25–313:6 (Martin); 475:3–20 (Moran); 515:9–516:10 (Krook)).

13. The (6S) leucovorin isomer is also known as levoleucovorin, the natural leucovorin isomer, Citrovorum factor, l-leucovorin, or (-)-folinic acid. (See, e.g., PTX 14; PTX 15; PTX 242; DX 711; DX 732).

14. The (6R) leucovorin isomer is also known as the unnatural leucovorin isomer, or d-leucovorin. (See, e.g., DX 609; DX 711).

ii. Leucovorin Has Been Used For Methotrexate Rescue Since the 1950s

15. Leucovorin has been used in human patients since the 1950s to prevent toxic side-effects of the cancer chemotherapy treatment methotrexate. (PTX 1 at 1:22–24; Tr. 164:22–25 (Suckling); 287:3–14 (Martin); 475:10–15 (Moran); 503:2–6 (Krook)). This use of leucovorin is known as "methotrexate rescue." (PTX 1 at 1:24–29).

16. Methotrexate is a chemotherapy agent that prevents the biosynthesis of DNA. (PTX 1 at 1:22–26). Methotrexate is toxic to normal cells as well as cancerous cells. (Id.). Methotrexate toxicity can be inhibited by administering leucovorin. (DX 832; DX 822; Tr. 506:5–19, 507:3–24; 509:24–510:8, 515:9–516:7 (Krook)). In this sense, leucovorin may be used as a "rescue agent," administered 12 to 24 hours after the methotrexate, to prevent methotrexate toxicity to normal cells after the methotrexate affects faster-dividing cancer cells. (PTX 1 at 1:24–29). Without leucovorin rescue, the methotrexate would cause more undesired side effects. (Id.; Tr. 506:5–19 (Krook)).

17. A typical daily dose of leucovorin used for methotrexate rescue is around 50 to 300 mg. (DX 739 at 821 ("A conventional leucovorin rescue dosage schedule is 10 mg/m^2 I.M. or I.V. followed by 10 mg/m^2 orally every six hours for seventy-two hours"); Tr. 553:24–555:10 (Krook)). As noted in the '829 patent, the dose range for levoleucovorin for methotrexate rescue is "in the range from 25 to 150 mg." (PTX 1 at 5:15–21).

18. Leucovorin has also been used for treating folate deficiency. (PTX 1 at 4:67–5:1; DX 739; Tr. 516:8–10 (Krook)). For treating folate deficiency, lower doses of leucovorin generally are administered. (PTX 1 at 5:21–22). As noted in the '829 patent, the dosed range for levoleucovorin used for treating folate deficiency is "from 2 to 25 mg." (Id. at 5:22–24).

iii. In the 1980s, Clinicians Began Using Leucovorin in Much Larger Doses in "5-FU Combination Therapy"

19. Around 1982, clinicians began using leucovorin in a different way—to enhance the effects of 5-fluorouracil ("5-FU") in the treatment of colorectal cancer. (PTX 1 at 5:1–8; PTX 417 at 20:18–21 (Machover)). This use of leucovorin is known as "5-FU combination therapy" or "5-FU modulation."

20. 5-FU is a cytotoxic chemotherapy agent. (DX 831 at 1). 5-FU is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication). (Id.). After absorption of leucovorin, the (6S) isomer is readily converted to 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme. (Id.).

21. The development of this 5-FU combination therapy in the 1980s greatly increased the use of leucovorin in terms of the number of patients administered leucovorin, and the amount of leucovorin administered. (Tr. 451:5–452:1 (Moran); 514:2–13, 554:20–555:10 (Krook).)

22. A typical daily dose of leucovorin for 5-FU combination therapy for treating colorectal cancer is in the range from 400 mg to 4000 mg. (PTX 1 at 5:25–28). As noted in the '829 patent, the dose range for levoleucovorin for use in combination with 5-FU is "from 200 to 2000 mg." (Id.).

23. 5-FU combination therapy for treating colorectal cancer requires significantly greater quantities of leucovorin than the prior uses of methotrexate rescue and treating folate deficiency. (Tr. 554:2–555:10 (Krook)).

24. Dr. Moran testified that in the early 1980s "people were starting to use leucovorin in humans at much higher levels than they usually use for methotrexate when they were combining it with 5-FU." (Tr. 451:5–452:1 (Moran)).

25. At the high end of the dose ranges provided in the '829 patent, a typical daily dose of leucovorin for 5-FU combination therapy is about 80 times greater than for treating folate deficiency (4000 mg compared to 50 mg), and about 13.3 times greater than for methotrexate rescue (4000 mg compared to 300 mg). (See PTX 1 at 5:15–30).

26. The typical dose of leucovorin in a 5-FU combination treatment course for colorectal cancer is substantially greater than the daily dose. A typical treatment course in the 1980s was 5 days, with 3-4 weeks between repeated treatments. (See, e.g., PTX 242 at 1805 ("Treatment comprised 5-day courses followed by drug-free intervals of 21 days")). The typical dose for just one course could thus be 20,000 mg leucovorin (4000 mg daily for 5 days). (See PTX 1 at 5:15–30). And, colorectal cancer patients typically undergo numerous courses. (See, e.g., PTX 242 at 1804, Table 1 (describing number of courses at evaluation from 2 to 14)).

B. THE '829 PATENT

27. The '829 patent is titled "Substantially Pure Diastereoisomers of Tetrahydrofolate Derivatives." (PTX 1). It issued on December 31, 2002, and was assigned to the University of

Strathclyde. (Ex. 1B to Pretrial Order 1, ECF No. 331-2). Spectrum is the exclusive licensee of the '829 patent. (Id.). The '829 patent lists a September 2, 1987, earliest related U.S. application and a September 3, 1986, foreign application priority date. (Ex. 1A ¶ 10; PTX 1 at (63) "Related U.S. Application Data", (30) "Foreign Application Priority Data").

28. The '829 patent discloses a process for preparing a "substantially pure" diastereoisomer of a derivative of tetrahydrofolic acid—e.g., purified (6S) leucovorin. (PTX 1 at 2:45–67). The disclosed process involves: (1) attaching a chiral auxiliary group to precursors of the chosen diastereoisomers in a mixture so as to form a pair of new diastereoisomers; (2) partially separating the pair of new diastereoisomers and recovering the new diastereoisomer ((6R) or (6S)) so formed; and (3) converting the isolated, substantially pure new diastereoisomer into the corresponding desired diastereoisomer. (Id. at 2:45–67). However, none of the claims of the '829 patent cover this process. (Tr. 172:17–24 (Suckling); 242:6–24 (Martin); 455:8–11 (Moran)).

29. Ms. Lilias Rees was the primary person working on the project leading up to the filing of the '829 patent. (Tr. 176:1–4 (Suckling)). Ms. Rees was a lab technician and she did not have an advanced degree in life sciences prior to September 196, or at any time point. (Tr. 176:5–8 (Suckling)).

30. There is no evidence that anyone has ever used the University's method disclosed in the '829 patent to manufacture a commercial product. (Tr. 181:9–17 (Suckling)). Dr. Suckling testified that none of the companies that expressed interest in the '829 patent ever produced a commercial (6S) leucovorin using the '829 patent's chiral auxiliary method. (Tr. 181:9–17 (Suckling)). Additionally, there is no evidence that Burroughs Wellcome ever used the method to make a commercial product. (181:24–182:2 (Suckling)). Not even Spectrum or its supplier uses the method. (Tr. 181:9–20 (Suckling)). As Spectrum's senior vice president of pharmaceutical operations testified, how Spectrum's Fusilev is made is "proprietary to Merck

Eprova" and does not involve use of a chiral auxiliary, as in the '829 patent. (DX 1029 at 15:16–18, 79:19–21, 82:10–14 (Gupta)).

31. The inventors of the '829 patent also obtained U.S. Patent No. 4,959,472 (the "'472 patent"), which is directed to their chiral auxiliary process. (DX 501; Tr. 172:22–173:4 (Suckling); 261:21–262:10 (Martin)). The '472 patent has expired. (Tr. 172:25–173:4 (Suckling); 262:11–12 (Martin); 600:24–601:10 (Sullivan)).

32. Only claims 1 and 2 of the '829 patent were asserted at trial. (Am. Pre-Trial Order ¶ 14, ECF No. 334; Tr. 242:1–19 (Martin)). Claims 1 and 2 are reproduced below:

i. Claim 1

33. Claim 1 of the '829 patent is:

> 1. A pharmaceutical composition for therapeutic use which consists essentially of a therapeutically effective amount sufficient for the treatment of human beings for methotrexate rescue or folate deficiency, of a pharmaceutically acceptable compound which is a (6S) diastereoisomer selected from the group consisting of (6S) leucovorin (5-formyl-(6S)-tetrahydrofolic acid) and pharmaceutically acceptable salts and esters of (6S) leucovorin; wherein the compound consists of a mixture of (6S) and (6R) diastereoisomers and consists of at least 92% by weight of the (6S) diastereoisomer, the balance of said compound consisting of the (6R) diastereoisomer; in combination with a pharmaceutically acceptable carrier

(PTX 1 at 9:55–67).

ii. Claim 2

34. Claim 2 of the '829 patent is:

> 2. The pharmaceutical composition according to claim 1 which consists of greater than 95% by weight of the (6S) diastereoisomer.

(PTX 1 at 10:1–3).

35. Dr. Suckling testified that the goal of claims 1 and 2 was to reduce the (6R) impurities in a (6S) composition. (Tr. 173:5–16, 174:4–7 (Suckling)).

C. CLAIM CONSTRUCTION

36. On January 8, 2014, the Court issued a final Claim Construction Order. (Order, ECF No. 202). The Court construed disputed claim terms relevant to claims 1 and 2 of the '829 patent as follows:

Claim Term	Court's Construction (D.I. 202)
"mixture"	Plain and ordinary meaning
the "percentage" claim terms	Plain and ordinary meaning
"the balance of said composition consisting of the (6R) diastereoisomer"	the remaining amount of the mixture of (6S) and (6R) diastereoisomers is the (6R) diastereoisomers, and any impurities normally associated with the mixture of (6S) and (6R) diastereoisomers
"pharmaceutical composition for therapeutic use"	a pharmaceutical composition suitable for treating medical conditions
"pharmaceutical composition for preparing medicaments for therapeutic use for the treatment of human beings"	a pharmaceutical composition from which can be prepared a medicine suitable for treating medical conditions in human beings
"consists essentially of"	"the specified materials and those that do not materially affect the basic and novel characteristic(s) of the composition"
the "multiple dose" or "4,000 mg (4 grams)" claim terms	Plain and ordinary meaning; the pharmaceutical composition must contain enough of the (6S)/(6R) mixture to provide two or more doses of, at minimum, 2000 mg per dose of the mixture

(Id. at 24–26, 37).

D. CLAIMS 1 AND 2 OF THE '829 PATENT ARE INVALID AS OBVIOUS

37. The Court addresses below the level of ordinary skill in the art, the scope and content of the prior art, the difference between the claims and the prior art, and the lack of objective (also called "secondary") considerations of nonobviousness.

i. The Level of Ordinary Skill in the Art

38. Dr. Martin testified that "one of ordinary skill in the art in 1986 in the chemical aspects of the patent would have a PhD in organic chemistry with two to five years of industrial

and/or postdoctoral experience in synthetic, organic, and/or medicinal chemistry." (Tr. 238:10–15, 238:23–239:1 (Martin)).

39. Additionally, "a person of ordinary skill in the art may consult with others in the relevant field. For example, a person with a medical degree having the requisite experience in treating patients with leucovorin could work with a person of expertise in the chemical aspects of the patent." (Tr. 238:16–22 (Martin)).

40. The Court credits and applies Dr. Martin's definition of the level of ordinary skill in the art.

41. Spectrum's expert, Dr. Moran, applied a definition of a person of ordinary skill in the art that includes a person having pharmacology and formulation science expertise. (Tr. 239:11–22 (Martin)). Such a person may not have significant experience with stereoisomers, or in making them or separating them. (Id. at 239:23–240:3 (Martin)).

42. The Court disagrees with Dr. Moran's definition with respect to the chemical aspects of the '829 patent, to the extent that it includes a person without significant experience with stereoisomers, or in making them or separating them.

43. However, the Court's conclusions on the invalidity of claims 1 and 2 of the '829 patent do not change whether Dr. Martin's or Dr. Moran's definition is applied.

ii. The Scope and Content of the Prior Art

44. The prior art falls into four general categories, described below:

45. **Leucovorin:** Leucovorin, the 50/50 mixture of (6R) and (6S) isomers, had been synthesized, studied and used clinically since at least the 1950s. The record is replete with undisputed evidence that a person of ordinary skill in the art would have known that the desirable properties of leucovorin (e.g. its usefulness for methotrexate rescue, folate deficiency, and 5-FU combination therapy) derive in whole from the (6S) isomer. It was equally well-established that the (6R) isomer lacked significant biological activity, and was an impurity

resulting from the way leucovorin was manufactured.

46. **Purified (6S) Leucovorin Made by Enzymatic Synthesis:** Before the priority date, more than one group of researchers had publically reported the synthesis of purified (6S) leucovorin by using an enzymatic synthesis technique.[2] This prior art technique had been used to produce nearly 1 gram of (6S) leucovorin by scientists at the University of Strathclyde. Purified (6R) isomer also had been produced by Spectrum's expert, Dr. Richard Moran, using an enzymatic synthesis technique before the critical time. And, there was no technical obstacle to preparing more of either isomer.

47. **Purified (6S) Leucovorin Made by Separation Methods:** Before the priority date, more than one group of researchers had publically reported the preparation of purified (6S) leucovorin by separating the (6S) and (6R) leucovorin isomers using techniques such as fractional crystallization and chromatography.

48. **University of Strathclyde Samples Sent to Burroughs Wellcome:** Before the priority date, the University of Strathclyde sent 500 mg samples of the two diastereoisomers of leucovorin to a pharmaceutical company, Burroughs Wellcome.

a. Prior Art: Leucovorin

49. Leucovorin, the 50/50 mixture of (6R) and (6S) isomers, has been synthesized, studied and used clinically since at least the 1950s. (PTX 1 at 1:30–35; PTX 14; PTX 15).

50. Dr. Suckling admitted that long before 1986, leucovorin was commonly used for methotrexate rescue, known to have two chiral centers, and known to contain equal parts of the (6S) and (6R) isomers. (Tr. 164:22–165:8 (Suckling); see also PTX 14; PTX 15; DX 732; DX

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[2] Although the issue was disputed during claim construction, Sandoz did not dispute at trial whether the prior art enzymatic technique also produced a small amount of the (6R) isomer, because whether or not it did does not change the obviousness analysis. The Court agrees that the claimed composition would have been just as obvious regardless of whether the prior art enzymatic technique produced a small amount of the (6R) isomer.

739).

51. Further, Dr. Suckling admitted that persons of skill in the art knew before 1986 that only the (6S) isomer was effective for methotrexate rescue, and that before 1986 leucovorin had been separated into the (6S) and (6R) isomers. (Tr. 165:9–15 (Suckling); see also PTX 14; PTX 15).

52. As admitted in the '829 patent specification, before the priority date, a group led by Dr. Donna Cosulich had separated the (6R) and (6S) leucovorin isomers by fractional crystallization, and another group led by scientist Feeney had separated the isomers by chromatography. (PTX 1 at 2:13–16; Tr. 166:9–20 (Suckling); PTX 14; PTX 15). Dr. Suckling confirmed that the fact that the (6R) and (6S) isomers had been separated before September 1986 "was true in terms of what was reported in the literature." (Tr. 167:1–7 (Suckling)).

53. A person of ordinary skill in the art would have known that the desirable properties of leucovorin (e.g. its usefulness for methotrexate rescue, folate deficiency, and 5-FU combination therapy) derive in whole from the (6S) isomer. (PTX 1 at 1:57–61, 4:67–5:1; PTX 14; PTX 15 at 1:15–21 ("The biologically active lL-isomer is designated l-leucovorin"); PTX 22 at 117 ("it has been established that the active diastereoisomer . . . has the S-configuration at position 6"); DX 732 at 70 ("the enzymatically active diastereoisomer of this compound was shown to have the S chirality at the 6-carbon"); DX 739 at 821 ("The biologically active component of the mixture is the (-)-L-isomer"); Tr. 165:9–15 (Suckling); 312:25–313:6 (Martin); 475:3–20 (Moran); Tr. 515:9–516:10 (Krook)).

54. One example of prior art knowledge about the (6R) and (6S) leucovorin isomers is the Wellcovorin entry in the Physician's Desk Reference. (DX 739). Entries for Wellcovorin Injection and Wellcovorin Tablets were published in the 1985 edition of the Physician's Desk Reference ("Wellcovorin PDR"). (DX 739; Tr. 288:15–290:10 (Martin); 514:16–516:10 (Krook)).

55. The Wellcovorin PDR discloses a pharmaceutical composition of leucovorin sold under the trade name "Wellcovorin" for treating humans for methotrexate rescue or folate deficiency. (DX 739 at 821–22; Tr. 288:15–289:2 (Martin); 514:16–516:10 (Krook)).

56. The Wellcovorin PDR also discloses that leucovorin is a mixture of the diastereoisomers of leucovorin. (DX 739; Tr. 289:12–19 (Martin)). The Wellcovorin PDR states that (6S) leucovorin is the biologically active component. (DX 739 at 821; Tr. 289:12–19 (Martin)).

57. The Wellcovorin PDR also discloses injectable solutions of leucovorin calcium and tablets of leucovorin calcium. (DX 739 at 821). The injectable formulation contains water and paraffins as preservatives. (DX 739; Tr. 289:23–290:7 (Martin)). These ingredients are examples of pharmaceutically acceptable carriers for leucovorin isomers. (Tr. 290:8–10 (Martin)).

58. The Court credits Dr. Martin's testimony that a person of ordinary skill in the art in 1986 would have understood from the Wellcovorin PDR that in leucovorin, the (6S) isomer was the active component with clinical utility, and one would understand that the isomers could be formulated easily as described in the Wellcovorin PDR. (Tr. 290:23–291:10 (Martin); 475:3–20 (Moran)).

59. Dr. Moran testified that the '829 patent inventors incorporated the knowledge of formulating a pharmaceutical product from what was already known about leucovorin drugs at the time. (Tr. 475:3–15 (Moran)). A person of ordinary skill in the art in 1986 would have known that they could change out the leucovorin for levoleucovorin in the Wellcovorin composition that was already on the market. (Tr. 475:16–20 (Moran)).

60. Indeed, the specification of the '829 patent admits that suitable pharmaceutical acceptable carriers for substantially pure (6S) leucovorin "include those known in the art for preparing pharmaceutical compositions containing leucovorin." (PTX 1 at 4:58–59).

b. Prior Art: Purified (6S) Leucovorin Prepared by Enzymatic Synthesis

61. Before the priority date, more than one group of researchers had publically reported the synthesis of purified (6S) leucovorin by using an enzymatic synthesis technique.

62. This prior art technique had been used to produce nearly 1 gram of purified (6S) leucovorin. Purified (6R) isomer also had been produced by using an enzymatic synthesis technique before the critical time. And, there was no technical obstacle to preparing even more of either isomer.

1. Rees 1986 (PTX 22)

63. Lilias Rees et al., Asymmetric Reduction of Dihydrofolate Using Dihydrofolate Reductase and Chiral Boron-Containing Compounds, 42 Tetrahedron 117-136 (1986) ("Rees 1986") was published in January 1986. (PTX 22). Rees 1986 is authored by the inventors of the '829 patent and a then graduate student at the University of Strathclyde, Edward Valente. (PTX 22; Tr. 168:20–169:1 (Suckling); 295:10–296:10 (Martin)).

64. Rees 1986 discloses the synthesis of the calcium salt of (6S) leucovorin by an enzymatic synthesis method. (PTX 22 at 118, 120, 129–30; Tr. 159:2–15 (Suckling); 261:2–4 (Martin)). Rees 1986 reports that the authors made 0.91 grams (or 910 mg) of the material. (PTX 22 at 130; 159:19–20 (Suckling);Tr. 296:11–297:17 (Martin)). Both experts Dr. Moran and Dr. Martin, and inventor Dr. Suckling, agreed that nearly 1 gram of (6S) leucovorin was produced as reported in Rees 1986. (Tr. 89:3–10, 169:2–9 (Suckling), 296:11–297:17 (Martin); 460:2–6 (Moran)).

65. Rees 1986 reports that the enzymatic method described therein "makes the possibility of synthesizing chiral 5-formyltetrahydrofolate (leucovorin) for use in cancer rescue therapy attainable." (PTX 22 at 117). Thus, Rees 1986 discloses that (6S) leucovorin created by the enzymatic method described therein would be useful in cancer rescue therapy (e.g.

methotrexate rescue therapy). (Tr. 298:19–24 (Martin)).

66. Indeed, in the specification of the ’829 patent, the applicants admitted that “[t]he (6S) diastereoisomer has been obtained by the enzyme catalyzed reduction of dihydrofolate followed-by formylation,” citing Rees 1986 for support. (PTX 1 at 2:16–19; Tr. 166:21–167:7 (Suckling); 299:4–25 (Martin)). The ’829 patent specification states that “yields are low” with the enzymatic method of Rees 1986, which is a measure of efficiency of the reaction and does not refer to how much (6S) material could be made in total. (Tr. 299:11–25 (Martin)). A person of ordinary skill in the art could have run a number of Rees 1986 reactions in parallel to get a desired amount of material. (Tr. 300:3–11 (Martin)).

67. During the prosecution of the ’829 patent, the applicant submitted a declaration from their consultant Dr. Stanley Michael Roberts, “a professor of organic chemistry who had expertise in the field of enzymes and organic synthesis.” (DX 503; DX 752; Tr. 169:20–170:11 (Suckling); Tr. 301:2–21 (Martin)). Dr. Roberts’s declaration states that the Rees 1986 reaction that made about 0.9 grams could be scaled up and, doing a rough calculation, determined that one could get about 500 grams of the material in a year. (DX 752 ¶ 11; Tr. 171:1–10 (Suckling); 302:3–19 (Martin)). Dr. Roberts did not include the fact that one could also have run the reaction in parallel, which could greatly increase the amount of product prepared in a very short time. (Tr. 302:3–19 (Martin)).

68. Dr. Suckling did not disagree with Dr. Roberts that the enzymatic process potentially could make 500 grams of purified (6S) leucovorin in a year. (Tr. 171:1–10 (Suckling)). He testified that as a practical matter they could have made 10 grams and, theoretically, could have made 500 grams in a year. (Tr. 171:1–10, 171:22–172:12 (Suckling)).

69. Mr. Valente, the graduate student who performed much of the work described in Rees 1986 and an author of the publication, also testified that the Rees 1986 process could have been repeated to produce more than 1 gram of (6S) leucovorin. (DX 1030 at 33:4–7, 99:2–10

(Valente)). Dr. Suckling testified that Mr. Valente did all of the lab work on the enzymatic process along with Ms. Rees. (Tr. 168:20–169:1 (Suckling)).

70. Thus, Rees 1986 discloses an operable prior art method for generating purified (6S) leucovorin. (Tr. 261:2–4 (Martin)). Furthermore, the Rees 1986 method easily made more than the "therapeutically effective amount sufficient for the treatment of human beings for methotrexate rescue or folate deficiency" claimed in the '829 patent. As described in the background section above, the typical daily doses of (6S) leucovorin range from 2 to 25 mg for folate deficiency, and from 25 to 150 mg for methotrexate rescue. (See PTX 1 5:15–25). The 910 mg reported in Rees 1986 would have been more than the claimed amount "sufficient" for methotrexate rescue or folate deficiency treatment.

2. Moran (1982) (DX 732)

71. Richard Moran & Paul Colman, A Simple Procedure for the Synthesis of High Specific Activity Tritiated (6S)-5-Formyltetrahydrofolate, 122 Analytical Biochemistry 70-78 1982) ("Moran"), was published in 1982. (DX 732; Tr. 305:10–25 (Martin); Tr. 445:3–11 (Moran)). Dr. Moran was Spectrum's technical expert at trial.

72. Moran also discloses the preparation of (6S) leucovorin by the enzymatic reduction of dihydrofolic acid followed by formylation, which is the basically same method described in Rees 1986. (DX 732; Tr. 306:1–14 (Martin); Tr. 445:12–446:3 (Moran)).

73. Moran describes the (6S) leucovorin isomer as an active pharmaceutical ingredient, and described using calcium leucovorin to treat human beings for methotrexate rescue. (DX 732 at 70–71). Moran proposes using (6S) leucovorin to study the mechanism of reversal of methotrexate toxicity. (Id.). Moran reports a bioassay showing that its (6S) leucovorin composition was about twice as active as the (6R,S) mixture composition. (Id. at 75).

74. Rees 1986 and Moran taught that pure (6S) leucovorin could be readily made before the priority date for the '829 patent. (PTX 22; DX 732; Tr. 307:4–12 (Martin); Tr.

445:12–446:3 (Moran)).

75. The (6S) leucovorin compositions prepared by enzymatic synthesis techniques described in Rees 1986 and Moran contained impurities other than the (6R) isomer impurity. Rees 1986 and Moran employed basically the same method, and Moran discloses the synthesis of (6S) leucovorin resulted in a purity "in excess of 95%"—in other words, less than 5% impurities. (DX 732 at 74, Figure 1B; Tr. 448:9–19 (Moran)).

c. Prior Art: Purified (6S) Leucovorin Made by Separation Methods

76. As admitted in the '829 patent, separation of the two leucovorin isomers had been carried out by fractional crystallization and by chromatography prior to the priority date. (PTX 1 at 2:13–21).

1. Cosulich 1952 (PTX 14)

77. "Cosulich 1952" is an article published in the peer-reviewed Journal of the American Chemical Society in 1952, titled "Diastereoisomers of Leucovorin." (PTX 14; Tr. 276:14–21 (Martin)).

78. The Court accepts Dr. Martin's uncontested testimony that the Journal of the American Chemical Society is "one of the most prestigious journals in chemistry in the world" today and certainly was in 1952. (Tr. 276:14–277:16 (Martin)).

79. Cosulich 1952 discloses that leucovorin is a mixture of diastereoisomers, the dL and lL isomers, which are the (6R) and (6S) isomers of leucovorin, respectively. (PTX 14; Tr. 277:17–25 (Martin)). It teaches that the (6S) isomer is the biologically active component of the mixture, and that (6S) leucovorin is about twice as active as the mixture itself. (PTX 14; Tr. 278:9–18).

80. Cosulich 1952 reports the separation of (6S) and (6R) leucovorin isomers utilizing the difference in solubility of the calcium salts. (PTX 14). As Dr. Martin explained,

diastereoisomers have different physical properties, and one manifestation of a physical property is solubility. (Tr. 280:17–281:2 (Martin)).

81. Cosulich 1952 reports the isolation of (6S) leucovorin having an optical rotation of -15.1°. (PTX 14; Tr. 281:21–282:8 (Martin); Tr. 473:12–20 (Moran)). Due to the nature of the separation method described in Cosulich, (6S) leucovorin isolated by the method would have invariably existed as a mixture also containing (6R) leucovorin as an impurity. (Tr. 295:3–9 (Martin)). A person of ordinary skill would have understood this fact. (Id.).

82. The reported optical rotation of the (6S) isomer in Cosulich 1952 is consistent with what scientists later confirmed—namely, that the optical rotation of (6S) leucovorin is about -15°. (Tr. 283:6–16 (Martin); Tr. 473:12–20 (Moran)). Dr. Martin testified that the optical rotation reported in Cosulich 1952 for the (6S) isomer is "right on the money" for (6S) leucovorin. (Tr. 283:6–16 (Martin)). Dr. Moran testified that the data "is compatible with it being the (6S) diastereomer" and "within the range of what's commonly accepted now as the correct thing." (Tr. 473:12–20 (Moran)).

83. Furthermore, Cosulich 1952 reported that the isolated (6S) isomer had nearly twice the activity as the mixture of isomers using a Leuconostoc citrovorum assay and by examining PGA activity—exactly what would be expected for the (6S) isomer. (PTX 14; Tr. 278:19–279:6 (Martin)).

84. The Court credits Dr. Martin's opinion that "[i]n 1986, a person of ordinary skill would read this article and understand that leucovorin was a mixture of two stereoisomers; that one of the isomers had all of the activity, and that that isomer was the (6S) isomer." (Tr. 279:7–280:9 (Martin)). This knowledge would have motivated a person of ordinary skill in the art to make the purified (6S) leucovorin isomer. (Tr. 280:11–14 (Martin)).

85. The data from the optical rotation and biological activity analyses reported in Cosulich 1952 demonstrate that Dr. Cosulich generated purified (6S) leucovorin. All trial

witnesses agreed or did not dispute this fact.

86. For example, Dr. Suckling testified that he did not doubt that Dr. Cosulich obtained purified (6S) leucovorin, noting that the article was peer reviewed and that "[a] scientist would normally attribute veracity to somebody else's results." (Tr. 167:8–23 (Suckling)).

87. Moreover, Dr. Martin said that the publication data "indicates to me. . . that she has the pure (6S) isomer." (Tr. 283:6–16 (Martin)).

88. Additionally, Dr. Moran testified "if I were a betting man . . . I would say she got it." (Tr. 474:13–15 (Moran)).

89. Indeed, in the specification of the '829 patent, the inventors admitted that "[s]eparation of the two diastereoisomers of leucovorin has been carried out by fractional crystallisation," citing Cosulich 1952 to support this statement. (PTX 1 at 2:13–15).

90. Thus, Cosulich would have provided motivation to a person of skill in the art to make a substantially pure (6S) leucovorin pharmaceutical product as recited in the claim 1 and 2 of the '829 patent. (Tr. 279:7–10, 280:5–14 (Martin); 450:25–451:7 (Moran)).

2. Cosulich '018 Patent (PTX 15)

91. U.S. Patent No. 2,688,018 (the "'018 patent") issued on August 31, 1954. (PTX 15; Tr. 286:2–287:2 (Martin)). The '018 patent is titled "Method of Preparing Alkaline Earth Metal Salts of l-Leucovorin." (PTX 15). The inventor of the '018 patent is Dr. Cosulich. (Id.).

92. The '018 patent discloses and claims a method for isolating calcium l-leucovorin, which is (6S) leucovorin. (Id.; Tr. 286:2–287:2 (Martin)). It discloses the isolation of (6S) leucovorin having an optical rotation of -15.2°. (PTX 15 at 1:52–2:8; 2:21–42; Tr. 288:5–14 (Martin)). As Dr. Martin explained about the optical rotation data, the fact that Dr. Cosulich obtained a constant rotation "supports the fact that she had pure (6S)." (Tr. 288:11–14 (Martin)).

93. The '018 patent also discloses that calcium leucovorin was known for treating

humans for methotrexate rescue. (PTX 15 at 1:10–36). It teaches that the isolated (6S) isomer is about twice as active for Leuconostoc citrovorum 8081 as the mixture of (6S) and (6R) isomers. (Id. at 2:5–8).

94. The data from the optical rotation and biological activity analyses reported in the '018 patent demonstrate that Dr. Cosulich's method generated highly pure (6S) leucovorin.

95. The Court credits Dr. Martin's testimony that a person of ordinary skill in the art in 1986 would have understood from the '018 patent that there is a clinically useful drug called leucovorin, which is a mixture of stereoisomers, and that the (6S) isomer has the desired biological activity. (Tr. 287:15–24 (Martin)). This understanding would have motivated a person of skill in the art in 1986 to make purified (6S) leucovorin. (Tr. 287:25–288:4 (Martin)).

96. Plaintiffs offered the trial testimony of Dr. Bannister who found that Cosulich was not repeatable by him. (Tr. 400:3–14 (Bannister)). But, Dr. Bannister did not offer any opinion one way or the other on whether Dr. Cosulich made highly pure (6S) leucovorin in the 1950s. (Tr. 425:16–20 (Bannister)).

97. Dr. Bannister admitted that he was not aware of any scientific literature stating that Dr. Cosulich and her team did not make purified (6S) leucovorin as described in Cosulich. (Tr. 424:11–15 (Bannister)).

98. Plaintiffs also offered statements made by various patent applicants that the method of Cosulich was not repeatable. (PTX 18; PTX 159; PTX 236; Tr. 407:22–25, 409:11–17, 411:10–14 (Bannister)).

99. However, no witness testified that Dr. Cosulich did not obtain highly pure (6S) leucovorin, and in fact Drs. Martin, Suckling and Moran all testified that they believed Dr. Cosulich did so. (Tr. 167:8–18 (Suckling); 283:6–16 (Martin); 474:13–15 (Moran)). And, as Dr. Moran testified, the Journal of the American Chemical Society has "never retracted this paper [Cosulich]" even though "they had a long time to do it." (Tr. 470:20–471:9 (Moran)).

100. Cosulich 1952 and the ’018 patent qualify as prior art for purposes of the obviousness analysis.

d. Prior Art: University of Strathclyde Samples Sent to Burroughs Wellcome

101. Although the parties introduced evidence relating to samples sent to Burroughs Wellcome, the Court does not make any factual findings on this evidence because such findings are not necessary to the Court’s conclusions of law.

iii. There Was a Strong Motivation Prior to September 1986 to Produce “Substantially Pure” (6S) Leucovorin

a. Skilled Persons Knew (6S) Leucovorin Had Desired Biological Properties

102. A person of ordinary skill in the art of the ’829 patent would have known that leucovorin’s usefulness for methotrexate rescue, folate deficiency, and 5-FU combination therapy derived wholly from the (6S) isomer, whereas the (6R) isomer was an undesired impurity. (PTX 1 at 1:57–61, 4:67–5:1; PTX 14; PTX 15 at 1:13–22; PTX 22 at 117; PTX 241 at 687; DX 732 at 70; DX 739 at 821; Tr. 165:9–15 (Suckling); 312:25–313:6 (Martin); 475:3–20 (Moran); 515:9–516:10 (Krook)). Therefore, as Dr. Martin testified, the skilled person would have “very definitely” been motivated to make purified (6S) leucovorin. (Tr. 312:25–313:9, 331:15–332:24 (Martin)). Drs. Moran and Suckling agreed. (Tr. 116:2–7 (Suckling); 450:25–451:7 (Moran)). Dr. Suckling explained that “clearly, if one were able to obtain the (6S) isomer in high degree of purity, potentially at least, that might lead to an enhanced product.” (Tr. 85:21–86:5 (Suckling)).

b. Scientists Hypothesized that the (6R) Isomer Could Have a Deleterious Effect in 5-FU Combination Therapy

103. Dr. Moran testified that in the early 1980s “people were starting to use leucovorin

in humans at much higher levels than they usually use for methotrexate when they were combining it with 5-FU." (Tr. 451:5–452:1 (Moran)).

104. A person skilled in the art would have known that only the (6S) isomer is the effective agent for 5-FU combination therapy. (PTX 417 at 21:8–22:13, 23:3–16 (Machover); DX 831 at 1 ("The d-isomer of racemic [leucovorin] has no biologic activity"); PTX 241 at 695 ("At this time, it is not known whether the D-isomer can interact with TS and FdUMP to form a ternary complex"); DX 739 at 821 ("The biologically active component of the mixture is the (-)-L-isomer"); Tr. 312:25–313:6 (Martin); 450:25–451:7 (Moran)).

105. However, preclinical studies from the 1970s and 1980s raised a research hypothesis that the presence of large amounts of the (6R) isomer in the body could have some deleterious effect on the modulation of 5-FU by the (6S) isomer. (See, e.g., DX 609 at 908 (explaining that "the possibility of a deleterious effect of the unnatural [(6R)] isomer on the modulation of FU cannot be ruled out"); PTX 417 at 45:4–24 (Machover)).

106. Dr. David Machover, a clinician experienced with 5-FU combination therapy testified that "we made the hypothesis that the D-form was, the D-form was deleterious . . . for the modulation of the fluorinated pyrimidine . . . ." (PTX 417 at 45:4–24 (Machover)). He explained that a large excess of the (6R) isomer in the plasma could compete with (6S) for entry into the cell, and if it enters the cell, could compete with the enzyme for polyglutamation of the folate species that are required for 5-FU modulation. (Id. at 38:11–39:19 (Machover)). By the mid-1980s it was a "hypothesis" that the (6R) isomer could be lowering the intracellular concentration of the folate species (derived from the (6S) isomer), preventing optimal inhibition of the thymidylate synthase enzyme, which is wanted for 5-FU modulation. (Id. at 40:19–41:13 (Machover)).

107. Dr. Suckling testified that, when the University started researching leucovorin in the early 1980s, "nobody knew whether the (6R) was a good thing or a bad thing" and the "jury

was out" since it had not been "investigated to say what the situation was." (Tr. 84:3–4, 84:15–16, 86:6–9, 173:19–174:3 (Suckling)).

108. This research hypothesis provided a rationale for investigating a purified (6S) leucovorin pharmaceutical product, meaning one with significantly less of the (6R) isomer impurity compared to leucovorin. (DX 831 at 1).

109. The concern about the (6R) in connection with 5-FU modulation did not exist with regard to methotrexate rescue, because of the different mechanisms involved, and because leucovorin could be given orally for methotrexate rescue and it was known that when leucovorin is given orally, only the (6S) isomer is absorbed in significant amounts. (DX 739 (disclosing Wellcovorin tablets for oral administration); PTX 417 at 106:21–107:11 (Machover) ("Orally, the D-form is not absorbed. It is not absorbed by the intestine, or just in very low amounts."); Tr. 521:4–7 (Krook) ("giving [leucovorin] orally stereoselects out the (6S). In other words, more (6S) is absorbed through the gut than the (6R).")).

c. Near-Simultaneous Developments of "Substantially Pure" (6S) Leucovorin Evidences the Strong Motivation

110. Besides the University of Strathclyde, numerous other research groups had responded to the motivation and were pursuing purified (6S) leucovorin prior to the priority date for the '829 patent. (Tr. 450:25–451:7 (Moran)). In short time, many succeeded. (DX 788; DX 791; DX 793; Tr. 337:18–338:4, 339:3–15, 340:2–341:4 (Martin)).

111. For example, researchers including Dr. Eguchi and others at the Kyowa Hakko Kogyo Company in Japan obtained a patent titled "Process For Producing L(-)-Tetrahydrofolic Acid" with a priority date of August 30, 1988. (DX 788; Tr. 337:18–338:4 (Martin)).

112. Researchers including Dr. Mueller and others at Eprova A.G. in Switzerland (Merck Eprova) obtained a patent titled "Process for Separating Folinic Acid" with a priority date of May 15, 1987. (DX 791; Tr. 338:13–19 (Martin)). Dr. Suckling testified that Merck

Eprova's process was different than the process described in the '829 patent. (PTX 404; Tr. 190:21–191:3 (Suckling)).

113. Researchers including Dr. Schlingmann and another at American Cyanamid Company in New Jersey obtained a patent titled "Process for the Preparation of Optically Pure Diastereoisomers of Tetrahydrofolate Compounds Using 10-Formyltetrahydrofolate Synthetase from Clostridium" with a priority date of Dec. 11, 1989. (DX 793; Tr. 339:3–15 (Martin)).

114. These patents to Drs. Eguchi, Mueller and Schlingmann teach different methods for making purified (6S) leucovorin, or precursors of (6S) leucovorin. (Tr. 340:2–341:4 (Martin)).

115. The work leading to these patents would have been done well before their priority dates. (Tr. 340:2–341:4 (Martin)). The patents evidence that numerous companies responded to the motivation for new methods for making highly pure (6S) leucovorin, and quickly succeeded. (Id.).

iv. A Skilled Person Could Have Easily Made the Claimed "Substantially Pure" (6S) Leucovorin

116. The asserted claims do not require that the claimed composition be made through any particular process, let alone by a singular process described in the prior art. (Tr. at 242:23–24 (Martin)). As Dr. Martin explained, "any process that you could come up with to make [the claimed composition] would be fine." (Id.).

117. By the priority date, the purified (6S) leucovorin isomer could have been made, and had been made in ample quantity, by at least the enzymatic techniques in Rees 1986 and Moran. Dr. Moran testified that there was no technical or scientific obstacle to making more of the enzyme in Rees 1986 so as to be able to produce more purified (6S) leucovorin. (Tr. 465:6–11 (Moran)).

118. Dr. Moran had even published how to successfully make the purified (6R)

leucovorin isomer. (Tr. 467:7–20 (Moran)). When asked whether he could have made more, Dr. Moran testified "Certainly. I mean, it just is a question of how much time do you have to do what." (Tr. 469:9–17 (Moran)).

119. It would have been very easy for a person of ordinary skill to make the claimed compositions by combining the prior art compositions. (Tr. 361:6–15 (Martin)). For example, the purified (6S) and (6R) leucovorin isomers could have been combined (Tr. 469:9–17). Dr. Moran testified "[n]obody would debate" that it could have been done. (Id.).

120. The only quantity-related limitation in claims 1 and 2 is "a therapeutically effective amount sufficient for the treatment of human beings for methotrexate rescue or folate deficiency." (PTX 1 at claim 1; Tr. 177:2–6 (Suckling); 329:15–25 (Martin)). As stated in the '829 patent specification, and confirmed by Dr. Suckling, the therapeutically effective amount is on the scale of about 2 to 25 mg for folate deficiency, and 25 to 150 mg for methotrexate rescue. (PTX 1 at 5:15–25; Tr. 178:17–24 (Suckling)).

121. The Rees 1986 enzyme method produced 910 mg of purified (6S) leucovorin, and there was no technical problem making more. (Tr. 171:22–172:12 (Suckling); 300:8–11 (Martin); 469:9–12 (Moran)).

122. The 910 mg of purified (6S) leucovorin produced in Rees 1986 was significantly more than the amount required by claims 1 and 2 of the '829 patent. (Tr. 461:13–19, 465:13–18 (Moran)). Furthermore, Dr. Moran himself had produced and published how to produce more than the claimed therapeutically effective amount of purified (6S) leucovorin in his Moran publication. (DX 732; Tr. 465:19–23 (Moran)).

v. A Skilled Person Would Have Expected the Claimed Compositions to Have the Same Properties as Pure (6S) Leucovorin

123. Dr. Suckling testified that the chiral auxiliary process of the '829 patent could produce 99 or even 99.99 pure (6S) leucovorin. (Tr. 109:5–14, 162:17–163:4; 174:25–175:10

(Suckling)). Assuming that Rees 1986 and Moran produced 100% pure (6S) leucovorin, the difference between that and a 99.99 pure (6S) leucovorin composition prepared according to the '829 patent would be meaningless because such composition would have the identical properties. (See DX 1031 at 289:4–294:15 (Reider)).

124. A person of ordinary skill in the art would not have expected there to be any differences in the biological properties between purified (6S) leucovorin with or without a small amount of (6R) impurity. (DX 1031 at 289:4–294:15 (Reider); Tr. 179:5–14 (Suckling); 328:22–329:1 (Martin)). This is because small amounts of the inactive isomer would not be noticeable in terms of therapeutic effects. (DX 1031 at 289:4–294:15 (Reider); Tr. 329:2–8 (Martin)). Plaintiffs' expert Dr. Reider testified that for leucovorin, "once you get above, you know, 92%, 90% . . ." (6S) leucovorin isomeric purity, "I don't think any biological system can tell the difference." (DX 1031 at 289:4–294:15 (Reider)).

125. Furthermore, clinical trials have established that purified (6S) leucovorin and leucovorin are clinically interchangeable. (DX 607, DX 609, DX 711, DX 823, DX 831; Tr. 524:4–12, 540:20–25 (Krook)).

126. Dr. Moran agreed that minor difference between the prior art and the claims offers no meaningful difference from the prior art. (Tr. 460:7–13 (Moran)). Dr. Moran testified that the "only advantage" of the composition in claims 1 and 2 over the Rees 1986 prior art is that it was possible to make more of the composition in the claims. (Id.).

127. Dr. Suckling agreed, too. He also testified that the "only advantage" of the composition made by the '829 patent process over the composition in Rees 1986 is that more could be made with the process in the '829 patent. (Tr. 202:18–203:5 (Suckling)).

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vi. Secondary Considerations Do Not Support Nonobviousness

a. The Claimed Composition Did Not Satisfy Any Long-Felt But Unsolved Need

128. Dr. Krook, Sandoz's expert in oncology, hematology, and clinical research provided unrebutted testimony that, by 1986, leucovorin had been used in smaller doses for methotrexate rescue or folate deficiency for decades, with no clinical concern about the (6R) isomer. (Tr. 503:2–6; 556:1–4 (Krook); DX 832; DX 822; DX 739). Dr. Krook testified that there has never been a clinical problem with leucovorin, and that there has never been a clinical need for purified (6S) leucovorin. (Tr. 504:16–22 (Krook)).

129. Clinical trials from as early as 1967 and 1970 reported the effectiveness of leucovorin for methotrexate rescues and made no mention of any problem with the (6R) isomer. (Tr. 507:25–508:3, 510:19–22 (Krook); DX 832; DX 822). Likewise, the Wellcovorin PDR in 1985, which has information about the indications for methotrexate rescue and folate deficiency, does not mention any concern about (6R) isomer. (Tr. 516:1–13 (Krook); DX 739).

130. Thus, there was no long-felt unmet need for a purified (6S) leucovorin product for the methotrexate rescue and folate deficiency uses, which are the only uses recited in claims 1 and 2 of the '819 patent.

131. Dr. Machover's 1982 publication describing one of the first clinical investigations of leucovorin in 5-FU combination therapy ("Machover 1982") expresses no concern about the (6R) isomer expressed. (PTX 242; Tr. 513:15–514:1 (Krook)). To the contrary, Machover 1982 encouraged clinicians to continue to use leucovorin in this way. (Tr. 514:2–13 (Krook)).

132. In addition, Claims 1 and 2 define the need being addressed by the '829 patent—"[a] pharmaceutical composition for therapeutic use," which the Court construed to mean "a pharmaceutical composition suitable for treating medical conditions." (Order, ECF No. 202). In other words, a composition for treatment of patients. The need identified in the patent is not

for research.

133. The research hypothesis identified by Spectrum to investigate purified (6S) leucovorin in relation to 5-FU combination therapy never developed into a pharmaceutical need, which is the relevant need in the ’829 patent.

134. Dr. Krook’s unchallenged testimony was that, before and after 1986, cancer doctors have considered leucovorin and levoleucovorin to be interchangeable. (Tr. 524:4–12, 540:20–25 (Krook)).

135. Dr. Suckling testified that he is not aware of any information in the art that the (6S) isomer of his invention is more therapeutically effective than the prior art commercially available leucovorin. (Tr. 179:5–14 (Suckling)).

1. Goldberg (DX 711)

136. Dr. Krook’s clinical research study was among the first major studies comparing the clinical safety and efficacy of leucovorin and levoleucovorin (“Goldberg”). (DX 711; Tr. 517:10–518:11 (Krook)). Goldberg reported a large clinical study, ultimately enrolling 926 patients with advanced colorectal cancer. (DX 711 at 3320; Tr. 519:18–522:23 (Krook)). Patients received one of three treatment regimens, generally: (A) 5-FU plus intravenous levoleucovorin; (B) 5-FU plus oral leucovorin; or (C) 5-FU plus intravenous leucovorin. (DX 711; Tr. 519:18–522:23 (Krook)).

137. Goldberg reported no difference in response, survival, or toxicity between the three different treatment regimens. (DX 711 at 3320, 3323–3326; Tr. 522:24–523:18 (Krook)). The conclusions of the clinical trial was that “there is no compelling reason to use either the purified l-isomer form of leucovorin or the oral administration of the (d,l) form of the drug” as there was equivalent toxicity and outcome with leucovorin and levoleucovorin. (DX 711 at 3328; Tr. 523:12–18 (Krook)).

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2. Scheithauer (DX 609)

138. Another clinical research study published in 1997 by Werner Scheithauer et al., Fluorouracil Plus Racemic Leucovorin Versus Fluorouracil Combined with the Pure l-Isomer of Leucovorin for the Treatment of Advanced Colorectal Cancer: A Randomized Phase III Study, 15 Journal of Clinical Oncology 908-914 (March 1997) ("Scheithauer"). (DX 609; Tr. 526:3–24 (Krook)).

139. Scheithauer was a smaller study with 248 patients diagnosed with advanced colorectal cancer. (DX 609 at 908; Tr. 527:3–20 (Krook)). Patients in the study were assigned to one of two treatment arms, generally (A) 5-FU and leucovorin or (B) 5-FU and levoleucovorin. (DX 609 at 908–909; Tr. 527:3–20 (Krook)). The researchers reported that both treatment regimens produced similar response rates, response durations, and survival times. (DX 609 at 908, 910–912; Tr. 527:22–528:5 (Krook)).

140. Both Scheithauer and Goldberg reached the same conclusion that leucovorin and levoleucovorin were clinically interchangeable. Taken together, these two significant clinical investigations around the same time give high confidence to their conclusion that leucovorin and levoleucovorin are clinically interchangeable in 5-FU combination therapy. (Tr. 528:6–530:13 (Krook)).

3. Kovoor (DX 831)

141. Dr. Krook testified that he agreed with the conclusions of a 2009 study by Philip A. Kovoor et al., titled "Is Levoleucovorin an Alternative to Racemic Leucovorin? A Literature Review" ("Kovoor"). (DX 831 at 200; Tr. 533:13–22, 535:18–21 (Krook)).

142. The authors performed an extensive review of the literature of levoleucovorin use in patients with colorectal cancer and other cancers of the gastrointestinal tract, which encompassed "125 citations with abstracts in the English language, including 16 randomized, controlled trials; 69 nonrandomized, controlled trials (including 6 pharmacokinetic

[PK]/pharmacodynamic studies and 1 population PK study); and 40 case studies," including the Goldberg and Scheithauer articles discussed above. (DX 831 at 201; Tr. 533:23–534:15 (Krook)). Kovoor concludes, "There seems to be no difference in efficacy or side effects between the 2 formulations of LV [i.e., levoleucovorin and leucovorin], whether they are used in combination with other chemotherapeutic agents" or alone. (DX 831 at 200, 205; Tr. 534:19–535:21 (Krook)). Kovoor also concludes that given a shortage in racemic leucovorin, levoleucovorin would be a clinically interchangeable alternative, but more expensive. (DX 831 at 205; Tr. 534:19–535:21 (Krook)).

4. Chuang (DX 823)

143. Dr. Krook also testified that he agreed with the conclusions of a 2012 report by Victor Tuan Giam Chuang & Manabu Suno, titled "Levoleucovorin as Replacement for Leucovorin in Cancer Treatment" ("Chuang"). (DX 823 at 1349; Tr. 530:22–531:14, 533:4–5 (Krook)).

144. After a search of articles published between January 1980 and April 2012, the authors analyzed articles "evaluating the efficacy, interchangeability, and safety of levoleucovorin." (DX 823 at 1349; Tr. 531:7–532:11 (Krook)). With respect to efficacy, the authors conclude that "the use of levoleucovorin as a biochemical modulator of fluorouracil or in high-dose methotrexate therapy rescue demonstrate that levoleucovorin is as efficacious as leucovorin and that no clear increase in the percentage of grade 3 or 4 toxicity profiles when patients were given levoleucovorin." (DX 823 at 1353; Tr. 532:12–18 (Krook)). The authors also found "no significant differences between levoleucovorin and leucovorin with respect to adverse events." (DX 823 at 1353; Tr. 532:12–18 (Krook)).

145. Chuang also concluded that the "current shortage of the supply of leucovorin centered in North America renders levoleucovorin a reasonable alternative in terms of efficacy and toxicity profile, but from the perspective of cost, leucovorin remains the drug of choice."

(DX 823 at 1349; Tr. 532:12–25 (Krook)).

5. Han (DX 607)

146. Dr. Krook also testified that he agreed with the conclusions of a report by David Han and others, titled "Phase I, Open-Label, Single Dose, Two-Way Crossover Bioequivalence Study of Levoleucovorin and d,l-Leucovorin in Healthy Volunteers" ("Han"). (DX 607; Tr. 536:4–23, 539:14–20 (Krook)).

147. Notably, one of the authors is a Vice President of Spectrum. (DX 607 at SPPI_SANDOZ0017979; Tr. 540:1–6 (Krook)). The study was also funded by Spectrum. (DX 607 at SPPI_SANDOZ0017980; Tr. 539:21–25 (Krook)). The study was never published. (Tr. 540:7–8 (Krook)).

148. The primary purpose of the study was to evaluate the bioequivalence of levoleucovorin and leucovorin in healthy volunteers. (DX 607 at SPPI_SANDOZ0017981; Tr. 536:24–537:11 (Krook)). Forty-three patients were randomly assigned to one of two treatment sequences: a 2-hour IV infusion of levoleucovorin 200 mg/m^2 or leucovorin 400 mg/m^2 on Day 1 (Period 1) followed by crossover to infusion of the alternative treatment on Day 8 (Period 2), separated by a one-week washout period. (DX 607 at SPPI_SANDOZ0017981; Tr. 537:17–538:14 (Krook)).

149. The authors concluded that levoleucovorin and leucovorin were bioequivalent, and that levoleucovorin and leucovorin "may be used interchangeably in clinical practice," mentioning the many clinical applications of leucovorin. (DX 607 at SPPI_SANDOZ0017992, SPPI_SANDOZ0017981; Tr. 538:15–539:13 (Krook)).

150. Accordingly, there is no evidence of a pharmaceutical need for purified (6S) leucovorin. Purified (6S) leucovorin and leucovorin are clinically interchangeable and, therefore, the claimed subject matter could not have satisfied any unmet clinical need since it is interchangeable with the prior art.

b. Spectrum's Leucovorin Product Is Not a Commercial Success

151. At trial, Spectrum argued that the licensing of the '829 patent evidences the value of the invention.

152. The Court finds no nexus between Spectrum's evidence on licensing and the claims.

153. Spectrum presented evidence on an exclusive option agreement in 1987 for rights to the '829 patent between the University and Burroughs Wellcome. (Tr. 130:3–5 (Suckling); PTX 7). Burroughs Wellcome, however, never exercised its option. (Tr. 131:9–10, 182:15–17 (Suckling); Tr. 568:15–22 (Sullivan)). Dr. Suckling admitted that Burroughs Wellcome was having a racemization problem with the '829 patent process as late as 1989, which is over two years after Dr. Wood disclosed the process to them. (DX 526; DX 533; Tr. 182:15–23, 184:12–25, 187:13–24; 189:4–15 (Suckling)). In August 1988, Burroughs Wellcome resorted to separating the leucovorin isomers by chromatography because the '829 process was not working. (DX 526; Tr. 185:16–22, 188:17–20 (Suckling)).

154. The fact that an option was not exercised and no license agreement was entered into is not evidence of commercial success. (Tr. 569:13–24 (Sullivan)).

155. Spectrum introduced evidence of other organizations reaching out to the University regarding the '829 patent, but the University did not enter into any licensing agreements with these organizations. (Tr. 132:15–134:23 (Suckling); PTX 8; PTX 9). After the lapse of the option agreement with Burroughs Wellcome, the University had the ability to license the '829 patent to other parties but no companies besides American Cyanamid and Spectrum ever took a license to the '829 patent. (Tr. 201:20–202:8 (Suckling); Tr. 571:17–572:1 (Sullivan)).

156. Expressing interest without actually entering into a license agreement is not probative of commercial success. (Tr. 569:13–15 (Sullivan)).

157. The only companies to take a license to the ’829 patent are American Cyanamid (Lederle) and Spectrum. (Tr. 201:16–202:8 (Suckling)).

158. Spectrum presented evidence of the University’s license with American Cyanamid and royalties under this license. (Tr. 141:8–10 (Suckling); PTX 12). The license was not exclusive. (Tr. 200:15–18 (Suckling); PTX 12).

159. The license with American Cyanamid included not only the application that became the ’829 patent but also patent applications in several other countries including Canada, Japan, and countries in Europe. (Tr. 199:17–21 (Suckling); PTX 12).

160. Dr. Suckling admitted he could not “subdivide” the amount received specifically for the license for the ’829 patent from the total income received for the whole leucovorin project from American Cyanamid. (Tr. 197:20–198:13 (Suckling)).

161. Spectrum also presented evidence on the University’s current license of the ’829 patent to Spectrum. (Tr. 141:13–14 (Suckling)). Dr. Suckling conceded that “not a lot of money” was made by the University from this license. (Tr. 197:23–198:1 (Suckling)).

162. For the license that Spectrum ultimately acquired, the University received a onetime, up-front payment of $50,000 and a running royalty of one percent of sales for the use of methotrexate therapy. (Tr. 581:10–582:16 (Sullivan); DX 611).

163. Dr. Suckling did not know how much money the University has been paid by Spectrum for the license to the ’829 patent for the sale of Fusilev products in the United States. (Tr. 202:17–22 (Suckling)).

164. In contrast, Spectrum paid royalties ranging from 4.5 percent to 7 percent for rights to Merck’s process patents for levoleucovorin and related know-how and technology. (Tr. 583:4–584:2 (Sullivan); DX 854).

165. In the fourth quarter of 2011, Spectrum paid approximately $28,000 in royalties to the University compared to approximately $2.4 million in royalties to Merck, about an 85-

fold difference. (Tr. 584:13–23 (Sullivan)).

166. This 85-fold difference demonstrates the relative value of the technologies as well as how the market viewed the relative values of the technologies. (Tr. 584:22–585:2 (Sullivan)).

167. The licensing fees and revenues for the technology in the '829 patent are substantially lower than the revenues of licenses for other technology that is utilized in levoleucovorin products. (Tr. 562:19–24 (Sullivan)).

168. Plaintiffs put forth no evidence of commercial success.

c. The Claimed Composition Produced No Unexpected Results

169. Plaintiffs put forth no evidence of alleged unexpected results or properties of the compositions in claims 1 and 2 of the '829 patent.

III. CONCLUSIONS OF LAW

A. RELEVANT LEGAL PRINCIPLES

i. Burden of Proof and Presumption of Validity

170. Obviousness must be shown by clear and convincing evidence. Microsoft Corp. v. *i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011).

171. Following i4i, the Federal Circuit repeatedly has held that there is no enhanced burden or heightened standard of proof for an obviousness inquiry involving prior art previously considered by the PTO. See, e.g., Osram Sylvania, Inc. v. Am. Induction Techs., Inc., 701 F.3d 698, 705 (Fed. Cir. 2012) ("the burden to prove invalidity does not change; at all times, it remains a showing 'by clear and convincing evidence.'") (citation omitted); Sciele Pharma, Inc. v. Lupin Ltd., 684 F.3d 1253, 1260 (Fed. Cir. 2012) (rejecting argument of heightened burden in Hatch-Waxman litigation).

172. The statutory presumption of validity merely assumes the PTO properly did its job by considering all prior art or other evidence material to patentability. Lannom Mfg. Co. v.

U.S. *Int'l Trade Comm'n*, 799 F.2d 1572, 1575 (Fed. Cir. 1986).

173. No decision of the Supreme Court or the Federal Circuit has ever suggested that there is an added burden to overcome PTO findings in district court infringement proceedings, and the presence or absence of PTO findings on particular issues does not affect the basic presumption of validity. Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd, 719 F.3d 1346, 1357 (Fed. Cir. 2013).

174. Thus, "[t]he courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the rulings of the patent examiner." Quad Envtl. Techs. Corp. v. Union Sanitary Dist., 946 F.2d 870, 876 (Fed. Cir. 1991).

ii. 35 U.S.C. § 103(a)—Obviousness

175. Under 35 U.S.C. § 103(a), "[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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 to which said subject matter pertains." 35 U.S.C. § 103(a) (2011).

176. Obviousness is a question of law, based upon underlying facts, that takes into account: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claims and the prior art; and (4) objective, also called "secondary," considerations of nonobviousness. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

177. "'Obviousness does not require absolute predictability of success . . . . [A]ll that is required is a reasonable expectation of success.'" Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)).

The "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007).

178. Moreover, a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR, 550 U.S. at 416.

179. More specifically, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Id. at 417.

180. The Supreme Court has held that market demands and pressures are critical to obviousness and "it will be necessary for a court to look to . . . the effects of demands known to the design community or present in the marketplace" because "it often may be the case that market demand, rather than scientific literature, will drive design trends." Id. at 418-19.

181. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." Id. at 421.

182. Furthermore, admissions about the prior art in the '829 patent specification are binding. Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342, 1362 (Fed. Cir. 2007); see also Sjolund v. Musland, 847 F.2d 1573, 1577-79 (Fed. Cir. 1988) (patent specification admitted that certain matter was prior art, and thus "the jury was not free to disregard [that matter]" and "must have accepted [it] as prior art, as a matter of law").

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B. CLAIMS 1 AND 2 OF THE '829 PATENT WOULD HAVE BEEN OBVIOUS OVER THE PRIOR ART

183. The Federal Circuit has held patent claims directed to a compound from a prior art mixture in a purified form to be prima facie obvious over the mixture if a person of ordinary skill in the art would know or have reason to believe the compound has some desirable property:

> However, if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.

Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007).

184. In Aventis, the asserted patent claimed 5(S) ramipril "being substantially free of other isomers." Id. at 1300. The prior art disclosed a mixture containing the 5(S) ramipril isomer with another isomer. Id. The prior art however only suggested that the 5(S) isomer contained the biological activity. The prior art disclosed a similar molecule, which had fewer stereocenters than ramipril, and disclosed that the isomer of this molecule with each stereocenter in the (S) configuration had enhanced biological activity. Id. at 1302.

185. The Federal Circuit explained that, "[i]n the chemical arts, we have long held that 'structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness.'" Id. at 1301 (citations omitted); see also In re Adamson, 275 F.2d 952, 954 (C.C.P.A. 1960) (a patent on a purified isomer was obvious when the mixture of isomers was known in the art, even though the art did not specify a method for purifying the isomer). Expectation that the new compound will have "similar properties" to the old provides such motivation. Aventis, 499 F.3d at 1301 (citing In re Dillon,

919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

186. Applying this standard, the Federal Circuit found that because the claimed 5(S) isomer was reasonably thought to be therapeutically active and that creating the purified isomer was not outside the capability of an ordinarily skilled artisan, the claimed compound was prima facie obvious. Id. at 1302. And because the potency of the purified 5(S) was consistent with the suggestions in the art, the plaintiff patentee had "failed to show unexpected results" to rebut the prima facie obviousness case. Id. The Federal Circuit thus found the asserted claims were obvious. Id.; see also In Re Merz, 97 F.2d 599, 601 (C.C.P.A. 1938) (an applicant is not entitled to a patent on a purified product unless it has different properties than the known product).

187. Here, a person of ordinary skill knew in September 1986 that leucovorin existed as a mixture of desired (6S) and undesired (6R) isomers, and that its therapeutic usefulness derives wholly from the (6S) isomer. (PTX 1 at 1:57–61, 4:67–5:9; PTX 14; PTX 15 at 1:15–21; PTX 22 at 117; PTX 241 at 687; DX 732 at 70; DX 739 at 821–22; Tr. 164:22–165:15 (Suckling); Tr. 312:25–313:6 (Martin); Tr. 475:3–20 (Moran); Tr. 515:9–516:10 (Krook)). These facts alone make the composition of claims 1 and 2 of the '829 patent "prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified." Aventis, 499 F.3d at 1301.

188. Additionally, there was an explicit prior art teaching to purify (6S) leucovorin. In about 1982, clinicians started using leucovorin in 5-FU combination therapy, which involves much larger doses of leucovorin than for the prior uses of methotrexate rescue and treating folate deficiency. (PTX 242; Tr. 451:16–19 (Moran); 514:2–13, 554:20–555:10 (Krook)). Preclinical studies raised a research "hypothesis" that high levels of the (6R) isomer in the body could have a deleterious effect on 5-FU modulation by the (6S) isomer. (See PTX 241 at 695 ("The slow disappearance of the D-isomer from plasma should be considered in future studies because there is competition between the diastereoisomers for carrier-mediated membrane

transport.")). This new use and hypothesis provided an explicit teaching to purify the (6S) isomer.[3]

189. Moreover, the desired (6S) isomer previously had been isolated and was in the prior art. The '829 patent specification admits that the state of the art was such that pure (6S) leucovorin had been produced by fractional crystallization, chromatography and enzymatic synthesis. (PTX 1 at 2:13–23). Spectrum admits that Rees 1986 and Moran made 100% pure (6S) leucovorin. Thus, a person of skill in September 1986 knew that the pure (6S) isomer and (6R) isomer were available. It would have thus been very easy for a person of ordinary skill to make the claimed compositions by combining the prior art compositions. (Tr. 361:6–15 (Martin)). Such a process would have been so easy that Dr. Moran testified "nobody would debate" that it could have been done. (Tr. 469:9–17 (Moran)). In addition, the '829 patent also taught that the racemic leucovorin could be separated using standard techniques such as crystallization and chromatography. (PTX 1 at 2:13–16).

190. Aventis controls this case and provides a basis for rendering claims 1 and 2 of the '829 patent prima facie obvious.

C. SECONDARY CONSIDERATIONS DO NOT REBUT SANDOZ'S PRIMA FACIE CASE OF OBVIOUSNESS AND RENDER THE ASSERTED CLAIMS NONOBVIOUS

191. "Once such a prima facie case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties." Aventis, 499 F.3d at 1301. See also Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007) (finding that evidence demonstrating the difficulty to separate

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[3] The '829 patent specification also identifies "a potential clinical requirement for the natural (6S) diastereoisomer of leucovorin" based on prior art preclinical studies suggesting that the (6R) isomer may inhibit the therapeutic function of (6S) and possibly have negative effects in the body. (PTX 1 at 2:10-12).

enantiomers and unexpected results rebutted prima facie case of obviousness).

192. Relevant secondary considerations that may rebut a prima facie case of obviousness may include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. KSR, 550 U.S. at 406; In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995); see also Merck & Co., Inc. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

193. Evidence of copying in the ANDA context where a showing of bioequivalence is required for FDA approval is not persuasive evidence of nonobviousness. Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 377 F. App'x 978, 983 (Fed. Cir. 2010); see also Santarus, Inc. v. Par Pharm. Inc., 720 F. Supp. 2d 427, 458 (D. Del. 2010) (evidence of copying is not compelling evidence of nonobviousness in a Hatch-Waxman case), *aff'd in part, denied in part*, 694 F.3d 1344 (Fed. Cir. 2012).

194. The only secondary considerations Spectrum asserted at trial were long-felt need and commercial licensing or interest in licensing.

i. Spectrum Failed to Prove the Required "Nexus" for Any Secondary Consideration

195. In order to give any evidence of secondary considerations "substantial weight in the calculus of obviousness/nonobviousness," there must be a "nexus" between the merits of the claimed invention and the proffered secondary consideration evidence. Ashland Oil v. Delta Resins & Refractories, Inc., 776 F.2d 281, 306 n.42 (Fed. Cir. 1985); see also Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311–12 (Fed. Cir. 2006).

196. In other words, evidence of a secondary consideration is "relevant in the obviousness context only if there is proof that . . . [it was] a direct result of the unique characteristics of the claimed invention." In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996); see also Ormco Corp, 463 F.3d at 1312 ("if the feature that creates the commercial success was known in the prior art, the success is not pertinent").

197. The patentee must produce evidence of a nexus. W. Union Co. v. MoneyGram Payment Sys., 626 F.3d 1361, 1372 (Fed. Cir. 2010).

198. "The commercial success of a product is relevant to the non-obviousness of a claim only insofar as the success of the product is due to the claimed invention." Geo M. Martin *Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010); see also Galderma, 737 F.3d ay 740 ("Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success.") (internal quotation marks and citation omitted). For example, commercial success has not been shown when features present in the prior art are the basis for the success or demand of the commercial embodiment. Ormco Corp., 463 F.3d at 1312; J.T. Eaton & Co. v. Atl. Paste & Glue Co., 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art.") (citation omitted); Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1580 (Fed. Cir. 1983) (holding claims obvious despite purported showing of commercial success because patentee failed to show that commercial success "was due to anything disclosed in the patent in suit which was not readily available in the prior art").

199. The Federal Circuit specifically requires affirmative evidence of nexus where the evidence of commercial success presented is a license, because it is often cheaper to take licenses than to defend infringement suits. Iron Grip, 392 F.3d at 1324; see also In re GPAC Inc., 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("Licenses taken under the patent in suit may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate a nexus between the merits of the invention and the licenses of record.") (internal quotation marks and citation omitted).

200. The only distinguishing feature about claims 1 and 2 of the '829 patent compared to the enzymatically prepared (6S) leucovorin in the prior art is the small presence of the

unwanted (6R) isomer in the claimed composition.

201. Spectrum has not established any nexus between the distinguishing amount of unwanted (6R) isomer and any alleged secondary consideration.

202. There is important, additional lack of nexus evidence that refutes Spectrum's assertion of the claims satisfying a long-felt, unmet need for a sufficient quantities of the (6S) and (6R) isomer to conduct research on the potential effect of the (6R) isomer in 5-FU modulation. Claims 1 and 2 of the '829 patent cover only two indications: methotrexate rescue and folate deficiency. The 5-FU combination therapy use did not arise until the 1980s, which was decades after the methotrexate rescue and folate deficiency uses arose. Thus, Spectrum cannot establish a nexus between its alleged long-felt need and the asserted claims.

ii. Spectrum's Secondary Consideration Evidence Is Weak

203. Furthermore, "weak secondary considerations generally do not overcome a strong prima facie case of obviousness." W. Union Co., 626 F.3d at 1373.

204. Secondary considerations will not be a significant factor where the record establishes a strong prima facie case of obviousness. See, e.g., Pfizer, 480 F.3d at 1372; Leapfrog Enters., Inc. v. Fisher-Price, Inc., 485 F.3d 1157, 1162 (Fed. Cir. 2007); DyStar Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356, 1371 (Fed. Cir. 2006); Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1483 (Fed. Cir. 1997); see also In re GPAC, Inc., 57 F.3d at 1580-81.

205. Based on the strength of the prima facie obviousness case here, even if Spectrum had been able to establish the required nexus for any secondary consideration to be probative (and to be clear, Spectrum has not established the nexus), the evidence of secondary considerations set forth by Spectrum would still be too weak to overcome the prima facie obviousness case.

206. The only secondary considerations Spectrum asserted at trial were long-felt need

and commercial licensing or interest in licensing—in other words, there was no evidence of other typical objective considerations such as unexpected results, prior failure, or skepticism of those in the art.

207. As explained above, even if there was a nexus and a long-felt need for a purified (6S) pharmaceutical product, the claimed invention could not have satisfied any need because levoleucovorin is clinically interchangeable with the prior art leucovorin.

208. Spectrum presented evidence of an exclusive option agreement in 1987 for rights to the '829 patent between the University and Burroughs Wellcome. (Tr. 130:3–5 (Suckling); PTX 7). Burroughs Wellcome, however, never exercised its option. (Tr. 131:9–10, 182:15–17 (Suckling); Tr. 568:15–22 (Sullivan)). The fact that an option was not exercised and no license agreement was entered into is not evidence of commercial success. (Tr. 569:13–24 (Sullivan)).

209. Other organizations reached out to the University regarding the '829 patent, but the University did not enter into any licensing agreements with these organizations. (Tr. 132:15–134:23 (Suckling); PTX 8; PTX 9). After the lapse of the option agreement with Burroughs Wellcome, the University had the ability to license the '829 patent to other parties but no companies besides American Cyanamid and Spectrum ever took a license to the '829 patent. (Tr. 201:20–202:8 (Suckling); Tr. 571:17–572:1 (Sullivan)). Expressing interest without actually entering into a license agreement again is not probative of commercial success. (Tr. 569:13–15 (Sullivan)).

210. The license with American Cyanamid included not only the application that became the '829 patent but also patent applications in several other countries including Canada, Japan, and countries in Europe. (Tr. 199:17–21 (Suckling); PTX 12). Dr. Suckling admitted he could not "subdivide" the amount received specifically for the license for the '829 patent from the total income received for the whole leucovorin project from American Cyanamid. (Tr. 197:17–198:13 (Suckling)). There thus is no evidence of what royalties were paid by American

Cyanamid.

211. Dr. Suckling also conceded that "not a lot of money" was made by the University from Spectrum's license to the '829 patent. (Tr. 197:23–198:1 (Suckling)). The University received a one-time, up-front payment of $50,000 and a one percent running royalty limited to the methotrexate rescue indication. (Tr. 581:10–582:16 (Sullivan); DX 611). Dr. Suckling also did not know how much money the University has been paid by Spectrum for the license to the '829 patent for the sale of Fusilev products in the United States. (Tr. 202:17–22 (Suckling)).

212. In sum, none of Spectrum's evidence on licensing supports a secondary consideration of nonobviousness. Rather, the evidence on licensing and revenues as a whole shows that the licensing program for the '829 patent was not a success.

D. CONCLUSIONS ON OBVIOUSNESS

213. Based on all the Court's factual findings, set forth above, Sandoz has proven by clear and convincing evidence that claims 1 and 2 of the '829 patent would have been obvious to a person of skill in the art in September 1986.

E. EXCEPTIONAL CASE—35 U.S.C. § 285

214. Sandoz seeks an exceptional case determination and all its attorneys' fees pursuant to 35 U.S.C. § 285. See Octane Fitness, LLC v. ICON Health & Fitness, Inc., 134 S. Ct. 1749, 1756 (2014) ("exceptional" case is one that stands out from others with respect to strength of position or unreasonable manner of litigation).

215. These issues will be determined after the Court renders a judgment.

IV. CONCLUSION

IT IS HEREBY ORDERED that Plaintiffs' request for an order pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Sandoz's ANDA shall not be earlier than the expiration date of the '829 patent, is hereby **DENIED**.

IT IS FURTHER ORDERED that claims 1 and 2 of the '829 patent are invalid

as obvious for the reasons set forth herein.

IT IS FURTHER ORDERED that judgment is entered fully in favor of Defendant Sandoz.

The Clerk of the Court shall enter judgment accordingly.

DATED this 20th day of February, 2015.

Gloria M. Navarro, Chief Judge
United States District Judge