United States Court of Appeals for the Federal Circuit

SPECTRUM PHARMACEUTICALS, INC., UNIVERSITY OF STRATHCLYDE,
Plaintiffs-Appellants

v.

SANDOZ INC.,
Defendant-Appellee

2015-1407

Appeal from the United States District Court for the District of Nevada in No. 2:12-cv-00111-GMN-NJK, Judge Gloria M. Navarro.

Decided: October 2, 2015

MARK HARRY IZRAELEWICZ, Marshall, Gerstein & Borun LLP, Chicago, IL, argued for plaintiffs-appellants. Also represented by AMANDA ANTONS, KEVIN M. FLOWERS, THOMAS IRVING ROSS.

DEANNE MAYNARD, Morrison & Foerster LLP, Washington, DC, argued for defendant-appellee. Also represented by BRIAN ROBERT MATSUI.

Before LOURIE, WALLACH, and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Spectrum Pharmaceuticals, Inc. ("Spectrum") appeals from the decisions of the United States District Court for the District of Nevada holding claims 1–2 of U.S. Patent 6,500,829 ("the '829 patent") invalid as obvious, and finding claims 5–9 of the '829 patent not infringed by the submission of an Abbreviated New Drug Application ("ANDA") by Sandoz Inc. ("Sandoz"). *Spectrum Pharm., Inc. v. Sandoz Inc.*, No. 2:12-cv-00111, 2015 WL 794674 (D. Nev. Feb. 25, 2015) ("*Trial Order*"); *Spectrum Pharm., Inc. v. Sandoz Inc.*, No. 2:12-cv-00111, 2014 WL 7368845 (D. Nev. Dec. 29, 2014) ("*Summary Judgment Order*"). Because the district court did not err in concluding that claims 1–2 are invalid, and additionally did not clearly err in finding claims 5–9 not infringed by Sandoz's ANDA product, we affirm.

BACKGROUND

Leucovorin is a compound used to ameliorate the toxic effects of methotrexate, a chemotherapy treatment ("methotrexate rescue"); to treat folate deficiency; and to enhance the efficacy of a 5-fluorouracil cancer treatment ("5-FU combination therapy"). Due to an asymmetric C6 carbon, leucovorin may exist as a 50/50 mixture of two diastereoisomers, the (6S) and (6R) isomers. The (6S) diastereoisomer is also known as levoleucovorin or *l*-leucovorin, and is the isomer with the desired biological activity.

The '829 patent is directed to pharmaceutical compositions of substantially pure levoleucovorin. Claim 1 of the '829 patent reads as follows:

> 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 com-

> pound 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.

'829 patent col. 9 ll. 55–67 (emphases added). The written description states that "a typical daily dose" of the (6S) isomer for methotrexate rescue would be "up to 150 mg[,] e.g.[,] in the range from 25 to 150 mg," and that "a typical daily dose [for treating folate deficiency] for an adult human is generally in the range from 2 to 25 mg." *Id.* col. 5 ll. 15–19, 21–24. Claim 2 depends from claim 1, with the additional limitation that the composition "consists of *greater than 95%* by weight of the (6S) diastereoisomer." *Id.* col. 10 ll. 1–3 (emphasis added).

Claim 5 of the '829 patent reads as follows:

> 5. A pharmaceutical composition for therapeutic use for the treatment of human beings comprising:
>
> > a pharmaceutically acceptable composition 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 composition consists of a mixture of (6S) and (6R) diastereoisomers and consists of at least about 92% by weight of the (6S) diastereoisomer, the balance of said composition consisting of the (6R) diastereoisomer; and

> a pharmaceutically acceptable carrier; and
>
> said composition being of *a quantity at least sufficient to provide multiple doses* of said mixture of (6S) and (6R) diastereoisomers *in an amount of 2000 mg per dose*.

Id. col. 10 ll. 10–24 (emphases added). Claims 6–9 depend from claim 5 and contain additional limitations not at issue in this appeal.

During prosecution of the application that became the '829 patent, the examiner rejected the application's claims as anticipated by or obvious over an article disclosing an enzymatic synthesis technique by which 0.91 grams of *l*-leucovorin had been synthesized. J.A. 4872–77 (office action detailing rejection over Lilias Rees et al., *Asymmetric Reduction of Dihydrofolate Using Dihydrofolate Reductase and Chiral Boron-Containing Compounds*, 42 Tetrahedron 117–136 (1986) ("Rees")). The applicants responded by adding new claims, including what later issued as claims 5–9, and by emphasizing the specific claim limitations relating to quantities of the specified mixture, which were allegedly not disclosed by the prior art. J.A. 4901–05. After a final office action rejecting the claims, the applicants appealed to the U.S. Patent and Trademark Office's Board of Patent Appeals and Interferences ("the Board"), again emphasizing that the quantity limitations could not be met by Rees. J.A. 4971, 4993–98. The patent eventually issued with the University of Strathclyde listed as the assignee.

Spectrum, as the exclusive licensee of the '829 patent, holds the approved New Drug Application for a levoleucovorin formulation, and accordingly listed the patent as claiming the drug product in the U.S. Food and Drug Administration ("FDA") publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book"). Spectrum's

product, Fusilev®, is indicated for the three uses described earlier.

Sandoz submitted an ANDA in October 2011, seeking approval from the FDA for a drug product that will be imported in the form of single-use vials with 175 mg or 250 mg of levoleucovorin, indicated for methotrexate rescue at doses of 7.5–75 mg per dose ("the ANDA product"). Its ANDA contained a certification that the '829 patent was invalid or would not be infringed by the ANDA product. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

After receiving notice of that certification, Spectrum filed a timely patent infringement suit in January 2012, alleging that Sandoz's ANDA submission infringed the '829 patent under 35 U.S.C. § 271(e)(2). The asserted claims were directed to pharmaceutical compositions comprising a mixture of (6S) and (6R) isomers, with at least 92% or 95% of the (6S) isomer. The patent discloses, but does not claim, a process for purifying the (6S) isomer from a 50/50 mixture using a chiral auxiliary group.

The district court construed the term "said composition being of a quantity at least sufficient to provide *multiple doses* of said mixture of (6S) and (6R) diastereoisomers *in an amount of 2000 mg per dose*" as having its plain and ordinary meaning. *Spectrum Pharm., Inc. v. Sandoz Inc.*, No. 2:12-cv-00111, 2013 WL 6865692, at *18–20 (D. Nev. Dec. 31, 2013) (emphases added). The court elaborated that the plain meaning required the composition to contain "enough of the (6S)/(6R) mixture to provide two or more doses of, at minimum, 2000 mg per dose." *Id.*

After construing the claims, the district court granted Sandoz's motion for summary judgment of noninfringement of claims 5–9. *Summary Judgment Order* at *1. Comparing the product described in Sandoz's ANDA to the claims of the '829 patent, the court found that because the individual vials will contain only up to 250 mg of

levoleucovorin, the approved product would not satisfy the claim limitation of at least two doses of 2000 mg. *Id.* at *5. The court also rejected Spectrum's argument that an aggregation of Sandoz's approved product—that is, the total amount of levoleucovorin drug product to be imported—would infringe the claims. *Id.*

The district court further found that Spectrum was precluded from asserting infringement under the doctrine of equivalents because of the inventors' statements during prosecution. *Summary Judgment Order* at *7–8. The court cited various instances in the prosecution history in which the applicants had distinguished Rees by emphasizing that the application claims (that issued as claims 5–9) had "more stringent quantity limitations" than claim 1. *Id.* at *7. As a result, the court found "a clear and unmistakable surrender of subject matter covering pharmaceutical composition quantities less than what is required to provide two or more doses of, at minimum, 2000 mg per dose of the mixture." *Id.* at *8. Because Spectrum did not raise a genuine issue of material fact as to literal infringement or infringement under the doctrine of equivalents of claims 5–9, the court granted summary judgment of noninfringement of those claims.

Sandoz stipulated to infringement of claims 1 and 2, and the district court subsequently conducted a bench trial only on the validity of those claims. The court found that the prior art disclosed: (i) leucovorin as a mixture of (6R) and (6S) diastereoisomers; (ii) that the therapeutic usefulness of leucovorin derives wholly from the (6S) isomer; and (iii) a rationale for investigating a purified (6S) isomer product for use in 5-FU combination therapy. *Trial Order* at *6–8, *13–14. The court also found that preparations of purified (6S) isomer by an enzymatic synthesis method and by separation methods had been publicly reported before the '829 patent's priority date. *Id.* at *6–7. In particular, the court analyzed two related prior art references that disclosed a process for separating

the diastereoisomers using the solubility differential of the (6S) and (6R) isomer salts, *i.e.*, fractional crystallization. *See id.* at *11–13 (findings relating to Donna B. Cosulich, *Diastereoisomers of Leucovorin*, 74 J. Am. Chemical Soc'y 4215–16 (1952) and U.S. Patent 2,688,018 (collectively, "Cosulich" or "the Cosulich references")).

The district court further found that the process taught by Cosulich would have "invariably" produced a mixture containing the (6R) isomer as an impurity, and that the data in the Cosulich references demonstrated that Dr. Cosulich also obtained a highly pure (6S) isomer compound. *Trial Order* at *10–12. The court concluded that those facts alone made the subject matter of the claims prima facie obvious in light of the prior art. The court also rejected Spectrum's argument that using the Rees method would not have produced sufficient quantities of the (6S) isomer, because the applicants had submitted a declaration during prosecution stating that the reaction could have been scaled up to produce about 500 grams of the (6S) isomer per year. *Id.* at *15–16.

The district court then found that Spectrum did not rebut the prima facie case of obviousness because it failed to prove any nexus between what was claimed and the so-called secondary factors, much less prove a long-felt need or successful licensing. *Id.* at *25–27. In particular, the court found that the only "distinguishing feature" of the claims compared to the prior art was "the small presence of the unwanted (6R) isomer," and that Spectrum did not prove a nexus between that amount and any secondary consideration. *Id.* at *25. Moreover, as leucovorin was not used in 5-FU combination therapy until much later than the claimed uses (and thus the effect of the (6R) isomer was not previously a concern), the court found that no nexus was shown between the claims and the asserted long-felt need. *Id.* The court found that even if there were a nexus and a long-felt need, the invention would not have satisfied the need because substantially

pure levoleucovorin is clinically interchangeable with the prior art leucovorin. *Id.* at *26. The district court also rejected Spectrum's proof of commercial success. *Trial Order* at *26–27. The court thus concluded that the evidence as a whole showed that claims 1 and 2 were invalid as obvious. *Id.* The district court accordingly entered final judgment in favor of Sandoz.

Spectrum timely appealed to this court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal from a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is only clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948); *see also Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1559 (Fed. Cir. 1986) ("The burden of overcoming the district court's factual findings is, as it should be, a heavy one.").

At the summary judgment stage, we review the grant of summary judgment under the law of the regional circuit in which the district court sits, here the Ninth Circuit. *Classen Immunotherapies, Inc. v. Elan Pharm., Inc.*, 786 F.3d 892, 896 (Fed. Cir. 2015). Applying the law of the Ninth Circuit, we review a district court's grant of summary judgment *de novo*. *Burke v. Cty. of Alameda*, 586 F.3d 725, 730 (9th Cir. 2009). Summary judgment is appropriate when, drawing all reasonable inferences in favor of the nonmovant, there is "no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *see Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

This appeal raises questions of validity and infringement, but, unlike most such appeals, does not challenge the district court's claim construction. As we find no reason to disturb the district court's claim construction in these cases, we will only address the issues raised.

I. Invalidity

We first address Spectrum's argument that the district court erred in holding claims 1 and 2 of the '829 patent invalid as obvious.

Patents are presumed to be valid, and overcoming that presumption requires clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. __, 131 S. Ct. 2238, 2242 (2011). A patent claim is invalid as obvious if an alleged infringer proves that the differences between the claims 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) (2006).[1]

Obviousness is ultimately a conclusion of law premised on underlying findings of fact, including the scope and content of the prior art, the differences between the claimed invention and the prior art, and the level of ordinary skill in the pertinent art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *Alza Corp. v. Mylan Labs.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). In addition to common knowledge or teachings in the prior

---

[1] Because the '829 patent was filed before the effective date of the America Invents Act, the earlier, pre-Act version of § 103(a) applies. *See* Leahy–Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 293 (2011).

art itself, a "design need or market pressure or other motivation" may provide a suggestion or motivation to combine prior art elements in the manner claimed. *Rolls Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1339 (Fed. Cir. 2010); *accord KSR*, 550 U.S. at 420. These principles are relevant here.

Spectrum asserts that the district court improperly used hindsight to provide a reason or motivation to modify the prior art pure (6S) isomer compound to obtain a slightly impure compound. Even though one of skill in the art admittedly could have added some (6R) isomer to contaminate the 100% pure (6S) isomer disclosed by Rees to produce the claimed substantially pure compound, Spectrum argues that none of the record evidence supplied a logical *motivation* to do so.

Sandoz responds that the district court correctly found that one of skill would have been motivated to make substantially pure (6S) leucovorin starting with the 50/50 mixture to have a more effective pharmaceutical treatment, and would have reasonably expected to succeed in doing so. Sandoz contends that it had no burden to show a motivation to *contaminate* the prior art pure (6S) isomer compound, because the court's analysis began with the 50/50 mixture and rejected Spectrum's arguments on the inoperability of the prior art. Moreover, Sandoz argues, the court found no patentable difference between the claimed substantially pure compound and the prior art pure compound, which presented a prima facie case of obviousness that Spectrum failed to rebut.

Most issues relating to purified diastereoisomers or enantiomers involve the question whether a pure, resolved compound would have been obvious over the corresponding mixture. *See, e.g.*, *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301–03 (Fed. Cir. 2007); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086–90 (Fed. Cir. 2008); *Forest Labs., Inc. v. Ivax*

Pharm., Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007); *In re Adamson*, 275 F.2d 952, 953–54 (CCPA 1960); *In re Anthony*, 414 F.2d 1383, 1386 (CCPA 1969). This case is unusual in involving a slightly different question, namely, whether a *substantially pure* compound would have been obvious when both the 50/50 mixture and the pure compound were known in the art. We agree with the district court that the claimed substantially pure compound would have been obvious over both the 50/50 mixture and the pure (6S) isomer compound in the prior art.

First, the district court did not clearly err in finding that one of skill would have been motivated to modify the prior art 50/50 mixture to make the claimed mixture. If it is known that the desired activity all lies in one isomer, surely, it is better, and there is generally motivation, to try to obtain the purest compound possible. *See Aventis*, 499 F.3d at 1301 ("[A] purified compound is not always prima facie obvious over the mixture; . . . [h]owever, if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, . . . the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified."). A physician would not likely want to administer a contaminant or a less pure material to a patient if one could use a pure material. Thus, there is always in such cases a motivation to aim for obtaining a pure, resolved material.

Conversely, if the pure material is known, no reason has been shown why one would want to have an impure material. Although one may not be motivated to obtain an impure material and, in effect, it therefore can be argued to have been nonobvious—which is Spectrum's position here, that the 92–95% pure material was nonobvious over the known pure material—that position, despite its superficial appeal, is not persuasive. As the district court correctly decided, because the desirable properties of the prior art 50/50 mixture are attributable

to only one component, and the slightly impure mixture—one that contains the substantially pure (6S) isomer in an amount of at least 92–95%—has not been shown to possess unexpected advantages over the prior art pure material, the less-than-pure material, and any others of similar concentration, cannot be found to have been nonobvious.

We also agree with the district court that, given the 50/50 mixture, there would have been a motivation to pursue the goal of obtaining either pure or the clinically interchangeable substantially pure (6S) isomer. A person of skill knew that the desired activity of leucovorin came from the (6S) isomer, which therefore provided a motivation to purify the (6S) isomer, even without an explicit teaching. Although the claimed compounds are not 100% pure, they are described as "substantially pure" and as not patentably different from pure material.

The evidence showed that "numerous other research groups had responded to the motivation to obtain a pure isomer and were pursuing purified (6S) leucovorin prior to the priority date for the '829 patent," and, as the district court noted, "[i]n short time, many succeeded." *Trial Order* at *14–15 (citation omitted). As in *Aventis*, here there was no need to find an express teaching to prove sufficient motivation to modify the prior art to arrive at the claimed invention, where various techniques to purify the isomers were reported in the art and, importantly, it was known that the (6S) isomer alone provided the therapeutic effect.

In the face of that evidence of obviousness, Spectrum did not provide any evidence of unexpected results for the substantially pure compound as compared to the 50/50 mixture or the 100% pure compound. The district court found that "clinical trials have established that purified (6S) leucovorin and leucovorin are clinically interchangeable" and that one of 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 . . . because small amounts of the inactive isomer would not be noticeable in terms of therapeutic effects." *Trial Order* at *16.

The district court also found that the prior art as a whole enabled one of skill in the art to make and use the claimed invention. Spectrum asserts that the court made no explicit finding that Cosulich was enabling, and therefore nothing in the record showed that one of skill in the art had the *means* to separate the (6S) and (6R) isomers from a 50/50 mixture. Accordingly, Spectrum argues, because the '829 patent enabled one of skill in the art to produce viable quantities of the substantially pure (6S) isomer, the claims are directed to both the compound *and* the method of making that compound.

Sandoz responds that the district court made factual findings that the prior art was enabling because multiple teams independently developed different methods for purifying a (6S) isomer compound around the time of the claimed invention, and that the specification admits that the prior art methods worked. Sandoz also notes that the court acknowledged the evidence of failures to repeat the results of the method disclosed in Cosulich, but did not find that the purification could not be accomplished.

Regardless whether the Cosulich references were enabling or not, the whole spectrum of prior art available before the invention was made would have enabled one of skill in the art to make and use the claimed substantially pure leucovorin compound. We agree with the district court's conclusion on that point.

Finally, the district court found that the objective indicia did not rebut the prima facie case of obviousness. Spectrum argues that the district court erred by finding that, despite the motivation to purify the prior art 50/50 mixture and the knowledge in the art that the (6R) isomer

was undesirable, there was not a long-felt but unmet need. Spectrum also asserts that the district court improperly used evidence of later clinical studies. Sandoz responds that such a need does not always exist whenever there is a motivation to modify the prior art, and that post-filing evidence is usually required to determine if the claimed invention satisfied the alleged long-felt need.

We agree that the district court did not clearly err in finding that there was no long-felt but unmet need. Moreover, even if there were a long-felt need, the district court found that a purified (6S) isomer compound would not have satisfied that need because it was shown to be clinically interchangeable with the 50/50 mixture. *Id.* at *18. The court also credited expert testimony, including that of Spectrum's expert, that the claimed substantially pure (6S) isomer compound "offers no meaningful difference" from the pure (6S) isomer compound. *Id.* at *16. As a long-felt but unmet need was the only indicium argued on appeal, we agree with the district court that Spectrum did not provide evidence of objective indicia of nonobviousness.

We owe the district court's factual findings considerable deference on appeal, and we see no clear error based on the record before us. Based on those findings, we affirm the district court's conclusion that Sandoz proved by clear and convincing evidence that claims 1 and 2 of the '829 patent are invalid as obvious.

II. Noninfringement

We also address the district court's finding that claims 5–9 of the '829 patent would not be infringed by Sandoz's ANDA product. The key language at issue in claim 5, and by extension in dependent claims 6–9, is "said composition being of a quantity at least sufficient to provide *multiple doses* of said mixture of (6S) and (6R) diastereoisomers *in an amount of 2000 mg per dose*." '829 patent col. 10 ll. 10–24 (emphasis added). Based on its

claim construction, the district court found that Sandoz's ANDA product, in vials of 175 mg or 250 mg of levoleucovorin, would not meet the limitation of at least two doses of 2000 mg each. The court also found that the patent applicant had explicitly disclaimed smaller dosage amounts during prosecution. The district court therefore decided that no genuine issue of material fact on the infringement question had been raised, finding that Spectrum had not shown literal infringement and was estopped from applying the doctrine of equivalents.

Under the framework of the Hatch–Waxman Act, the infringement inquiry focuses on a comparison of the asserted patent claims against the ANDA product that is likely to be sold following FDA approval. *Warner–Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365–66 (Fed. Cir. 2003) (citing *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1567–68 (Fed. Cir. 1997)). The burden of proving infringement by a preponderance of the evidence remains on the patentee. *Id.* Evaluating the grant of summary judgment of noninfringement requires two steps: (1) claim construction, where contested, and (2) comparison of the properly construed claims to the accused product. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1288 (Fed. Cir. 2009). The second step of the analysis is a question of fact. *Bai v. L&L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). As such, it is amenable to summary judgment where no reasonable factfinder could find that the accused product contains every claim limitation or its equivalent. *Id.*; *see Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29, 39 n.8 (1997).

Even without literal infringement, a patentee may establish infringement under the doctrine of equivalents if an element of the accused product "performs substantially the same function in substantially the same way to obtain the same result as the claim limitation." *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1167 (Fed. Cir. 2012) (citation omitted).

Whether prosecution history estoppel applies, and thus whether the doctrine of equivalents is available for a particular claim limitation, is a question of law reviewed *de novo*. *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1290–91 (Fed. Cir. 2010). That situation arises when an applicant during prosecution either makes an argument evincing a "clear and unmistakable surrender" of subject matter, *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 979 (Fed. Cir. 1999), or narrows a claim "to avoid the prior art, or otherwise to address a specific concern . . . that arguably would have rendered the claimed subject matter unpatentable," *Warner–Jenkinson*, 520 U.S. at 30–31. The applicant is then estopped from later invoking the doctrine of equivalents to recapture the surrendered subject matter. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 734 (2002). The patentee bears the burden of rebutting the application of prosecution history estoppel. *Id.* at 740–41.

Spectrum asserts that the claims do not require that the end product be distributed or administered in the packaged dosage. Because Sandoz stipulated to future importation of more than 10 grams of its product, Spectrum argues that such importation will literally infringe the claims. Spectrum also asserts that the court erred in finding that prosecution history estoppel applied. Spectrum insists that the applicants did not surrender coverage of *aggregate* quantities of the mixture. Moreover, Spectrum argues, claim 5 was added by amendment in addition to, not in place of, the original claims, and was not amended to relinquish any claim scope.

Sandoz responds that the district court rejected Spectrum's argument during claim construction that the "2000 mg per dose" limitation could be satisfied by multiple doses as long as they added up to 4000 mg total, because that ignored the "per dose" language in the claim. Sandoz also contends that Spectrum is barred from asserting infringement under the doctrine of equivalents because of

the statements of disclaimer made during prosecution that were described as defining a significant aspect of the invention. Even without the disclaimer, Sandoz argues that amendment-based estoppel would apply because those claims were added with the dosage limitation to overcome an obviousness rejection based on Rees.

Viewing the record in the light most favorable to Spectrum and drawing all reasonable inferences in its favor, we do not find the evidence in the record sufficient to prove infringement. The product that is likely to be sold following FDA approval is what Sandoz's ANDA describes: single-use vials with 175 mg or 250 mg of substantially pure levoleucovorin, indicated only for methotrexate rescue at doses between 7.5 mg and 75 mg per dose, which would be far less than at least two doses of 2000 mg each. We discern no clear error in the district court's finding that Sandoz's approved product would not meet the dosage claim limitation, and thus would not literally infringe claims 5–9.

Moreover, by claim amendments and distinguishing statements on the prior art during prosecution, Spectrum is now estopped from invoking the doctrine of equivalents to prove infringement. When submitting an amendment with the application claims that eventually issued as claims 5–9, the applicants asserted that the newly added claims "include specific limitations as to quantities of materials," and distinguished the prior art by pointing to the "quantities of these specific mixtures specified in the claims." J.A. 4904–05. Those claims were also added following an office action rejecting the previous original claims as obvious in view of Rees. The applicants again explicitly highlighted the significance of the dosage limitation during an appeal to the Board, their brief stating that the claims "require a minimum of four grams," the "quantity limitations set forth in the claims" which "define an aspect of the invention that is of great practical significance." J.A. 4996–97. The applicants unequivocal-

ly argued that Rees, which allegedly only produced experimental quantities, "do[es] not teach, suggest, or otherwise render obvious the claimed compositions *in the quantity specified*" in the application claims that became claims 5–9. J.A. 4998 (emphasis in original). Those statements are clear and unmistakable expressions of the applicants' intent to surrender coverage of quantities of the compound in lower doses.

Accordingly, we agree with the district court that Spectrum did not sufficiently raise a genuine issue of material fact as to infringement to defeat the motion for summary judgment. The court did not clearly err in finding that Spectrum failed to prove that the approved product would literally infringe claims 5–9. The court also did not err in concluding that Spectrum was barred from invoking the doctrine of equivalents by prosecution history estoppel. The district court thus did not err in granting summary judgment of noninfringement.

CONCLUSION

We have considered the remaining arguments and conclude that they are without merit. For the foregoing reasons, we conclude that the district court did not err in holding that claims 1–2 of the '829 patent are invalid as obvious under 35 U.S.C. § 103, and we therefore affirm that decision. We further conclude that the district court did not err in holding that Spectrum failed to prove by a preponderance of the evidence that Sandoz's ANDA product would infringe claims 5–9 of the '829 patent, and we also affirm that decision.

AFFIRMED