United States Court of Appeals for the Federal Circuit

ELI LILLY AND COMPANY,
Plaintiff-Appellee

v.

TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA, INC., BARR LABORATORIES, INC.,
Defendants-Appellants

2015-2067

Appeal from the United States District Court for the Southern District of Indiana in No. 1:10-cv-01376-TWP-DKL, Judge Tanya Walton Pratt.

Decided: January 12, 2017

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DAVID S. FORMAN, Osha Liang LLP, Alexandria, VA, for amicus curiae Biotechnology Innovation Organization. Also represented by HANSJORG SAUER, Biotechnology Innovation Organization, Washington, DC.

Before PROST, *Chief Judge,* NEWMAN and DYK, *Circuit Judges.*

PROST, *Chief Judge*.

Eli Lilly & Co. ("Eli Lilly") is the owner of U.S. Patent No. 7,772,209 ("'209 patent"). It filed this consolidated Hatch-Waxman suit against Teva Parenteral Medicines, Inc.; APP Pharmaceuticals LLC; Pliva Hrvatska D.O.O.; Teva Pharmaceuticals USA, Inc.; and Barr Laboratories, Inc. (collectively, "Defendants") to prevent Defendants from launching a generic version of a chemotherapy drug with accompanying product literature that would allegedly infringe methods of treatment claimed by the '209 patent. The United States District Court for the Southern District of Indiana held two bench trials, one on infringement and one on invalidity. The district court found that no single actor performs all steps of the asserted claims because the actions of both physicians and patients are

required. Nonetheless, under *Akamai Technologies, Inc. v. Limelight Networks, Inc.* (*Akamai V*), 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc) (per curiam), *cert. denied*, 136 S. Ct. 1661 (2016), the court found direct infringement attributable to physicians and held Defendants liable for inducing that infringement. The court also determined that the asserted claims were not invalid for, inter alia, indefiniteness, obviousness, or obviousness-type double patenting.

For the reasons below, we affirm.

BACKGROUND

The '209 patent, which issued in 2010, relates to methods of administering the chemotherapy drug pemetrexed disodium ("pemetrexed") after pretreatment with two common vitamins—folic acid and vitamin B12. Pemetrexed is an antifolate that kills cancer cells by inhibiting the function of folates, a class of nutrients necessary for cell reproduction. The purpose of the dual vitamin pretreatments is to reduce the toxicity of pemetrexed in patients. Eli Lilly markets pemetrexed under the brand name ALIMTA®, and the drug is used to treat certain types of lung cancer and mesothelioma.

Around 2008–2009, Defendants notified Eli Lilly that they had submitted Abbreviated New Drug Applications ("ANDAs") seeking approval by the Food and Drug Administration ("FDA") to market generic versions of ALIMTA®. After the '209 patent issued, Defendants sent Eli Lilly additional notices regarding their ANDAs, including notices that they had filed Paragraph IV certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), declaring that the '209 patent was invalid, unenforceable, or would not be infringed. Eli Lilly subsequently brought this consolidated action against Defendants for infringement under 35 U.S.C. § 271(e)(2). Specifically, Eli Lilly alleged that Defendants' generic drugs would be administered with folic acid and vitamin B12 pretreatments and, thus, result

in infringement of the '209 patent. Defendants raised noninfringement and invalidity defenses.

Eli Lilly asserted claims 9, 10, 12, 14, 15, 18, 19, and 21 of the '209 patent at trial. Importantly, all of the asserted claims require patient pretreatment by "administering" or "administration of" folic acid. Claims 9 and 10 depend from claim 1, which recites:

> 1. A method of administering pemetrexed disodium to a patient in need thereof comprising *administering an effective amount of folic acid* and an effective amount of a methylmalonic acid lowering agent followed by administering an effective amount of pemetrexed disodium, wherein
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> the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano-10-chlorocobalamin, aquocobalamin perchlorate, aquo-10-cobalamin perchlorate, azidocobalamin, cobalamin, cyanocobalamin, or chlorocobalamin.

'209 patent col. 10 ll. 55–65 (emphasis added). The additional limitations of claims 9 and 10 restrict the dose of folic acid to particular ranges. *Id.* at col. 11 ll. 19–22.

Asserted claim 12 is independent and recites:

> 12. An improved method for administering pemetrexed disodium to a patient in need of chemotherapeutic treatment, wherein the improvement comprises:
>
> a) *administration of between about 350 μg and about 1000 μg of folic acid* prior to the first administration of pemetrexed disodium;
>
> b) administration of about 500 μg to about 1500 μg of vitamin B12, prior to the first

administration of pemetrexed disodium; and

c) administration of pemetrexed disodium.

Id. at col. 11 l. 25–col. 12 l. 4 (emphasis added). Asserted claims 14, 15, 18, 19, and 21 depend from claim 12 and further limit the dose, schedule, or route of folic acid or vitamin B12 administration. *Id.* at col. 12 ll. 7–11, col. 12 ll. 16–20, col. 12 ll. 24–27.

The parties agree for purposes of this appeal that no single actor performs all steps of the asserted claims; rather, the steps are divided between physicians and patients. Though physicians administer vitamin B12 and pemetrexed, patients self-administer folic acid with guidance from physicians. Eli Lilly's theory of infringement therefore requires establishing liability for divided infringement—an area of law that this court was actively reconsidering during the pendency of this case.

In June 2013, Defendants conditionally conceded induced infringement under then-current law set forth in *Akamai Technologies, Inc. v. Limelight Networks, Inc.* (*Akamai II*), 692 F.3d 1301 (Fed. Cir. 2012) (en banc) (per curiam), *rev'd*, 134 S. Ct. 2111 (2014).[1] At the time, the *Akamai II* decision was the subject of a petition to the Supreme Court for a writ of certiorari. The parties' stipulation included a provision reserving Defendants' right to litigate infringement if the Supreme Court reversed or vacated *Akamai II*.

Eli Lilly and Defendants proceeded with a bench trial on invalidity, after which the district court held that the asserted claims were not invalid for, inter alia, obvious-

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[1] *Akamai II* held that "induced infringement can be found even if there is no single party who would be liable for direct infringement." 692 F.3d at 1317–18.

ness or obviousness-type double patenting. The court had also previously rejected Defendants' contention that the asserted claims were invalid for indefiniteness of the term "vitamin B12." Defendants filed an appeal on invalidity, which was docketed in this court as Case No. 14-1455. While that appeal was pending, the Supreme Court reversed *Akamai II*, holding that liability for inducement cannot be found without direct infringement, and remanding for this court to possibly reconsider the standards for direct infringement. *Limelight Networks, Inc. v. Akamai Techs., Inc.* (*Akamai III*), 134 S. Ct. 2111 (2014). In view of that development, the parties in this case filed a joint motion to remand the matter to the district court for the limited purpose of litigating infringement. We granted the motion.

The district court held a second bench trial in May 2015 and concluded in a decision issued on August 25, 2015 that Defendants would induce infringement of the '209 patent. As explained in further detail below, the court applied our intervening *Akamai V* decision, which had broadened the circumstances in which others' acts may be attributed to a single actor to support direct-infringement liability in cases of divided infringement.[2] *See Akamai V*, 797 F.3d at 1022. The court accordingly entered final judgment against Defendants, barring them

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[2] Following remand from the Supreme Court, a panel of this court initially found that the accused infringer in *Akamai* was not liable for direct infringement, *Akamai Techs., Inc. v. Limelight Networks, Inc.* (*Akamai IV*), 786 F.3d 899 (Fed. Cir. 2015), as had the first panel in the case, *Akamai Techs., Inc. v. Limelight Networks, Inc.* (*Akamai I*), 629 F.3d 1311 (Fed. Cir. 2010). We later vacated *Akamai IV* and took the case en banc, which resulted in the *Akamai V* decision.

from launching their generic products before the expiration of the '209 patent.

Defendants timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Defendants appeal the district court's finding of induced infringement, as well as the court's decision that the asserted claims are not invalid for indefiniteness, obviousness, or obviousness-type double patenting. We will address each of these issues in turn.

I

Pursuant to 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer."[3] Importantly, liability for induced infringement under § 271(b) "must be predicated on direct infringement." *Akamai III*, 134 S. Ct. at 2117. The patentee must also show that the alleged infringer possessed the requisite intent to induce infringement, which we have held requires that the alleged infringer "knew or should have known his actions would induce actual infringements." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006) (en banc in relevant part) (internal quotation marks omitted). A patentee seeking relief under § 271(e)(2) bears the burden of proving infringement by a preponderance of the evidence. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed. Cir. 2003).

"Infringement is a question of fact that, after a bench trial, we review for clear error." *Alza Corp. v. Mylan Labs, Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). Reversal

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[3] Section 271 was not amended by the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (2011).

for clear error is appropriate "only when this court is left with a definite and firm conviction that the district court was in error." *Id.*

The district court relied in part on Defendants' proposed product labeling as evidence of infringement. For purposes of this case, the parties have agreed that Defendants' product labeling would be materially the same as the ALIMTA® product labeling, which consists of two documents: the Physician Prescribing Information and the Patient Information. Both documents include instructions regarding the administration of folic acid—the step that the district court found would be performed by patients but attributable to physicians. For example, the Physician Prescribing Information provides, among other things:

> "Instruct patients to initiate folic acid 400 [µg] to 1000 [µg] orally once daily beginning 7 days before the first dose of [pemetrexed] . . . ." J.A. 11256.
>
> "Instruct patients on the need for folic acid and vitamin B_{12} supplementation to reduce treatment-related hematologic and gastrointestinal toxicity . . . ." J.A. 11278.

The Patient Information includes similar information:

> "To lower your chances of side effects of [pemetrexed], you must also take folic acid . . . prior to and during your treatment with [pemetrexed]." J.A. 11253 (emphasis omitted).
>
> "It is very important to take folic acid and vitamin B_{12} during your treatment with [pemetrexed] to lower your chances of harmful side effects. You must start taking 400–1000 micrograms of folic acid every day for at least 5 days out of the 7 days before your first dose of [pemetrexed]. . . ." *Id.* (emphasis omitted).

A

Where, as here, no single actor performs all steps of a method claim, direct infringement only occurs if "the acts of one are attributable to the other such that a single entity is responsible for the infringement." *Akamai V*, 797 F.3d at 1022. The performance of method steps is attributable to a single entity in two types of circumstances: when that entity "directs or controls" others' performance, or when the actors "form a joint enterprise." *Id.* Eli Lilly did not pursue a joint enterprise theory, so the question of direct infringement before us is whether physicians direct or control their patients' administration of folic acid.[4]

In *Akamai V*, we held that directing or controlling others' performance includes circumstances in which an actor: (1) "*conditions* participation in an activity or receipt of a benefit" upon others' performance of one or more steps of a patented method, and (2) "*establishes the manner or timing* of that performance." *Id.* at 1023 (emphases added). In addition to this two-prong test, we observed that, "[i]n the future, other factual scenarios may arise which warrant attributing others' performance of method steps to a single actor. Going forward, principles of attribution are to be considered in the context of the particular facts presented." *Id.*

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[4] Before the district court, Eli Lilly also asserted theories of direct infringement that did not rely on showing physicians' direction or control of patient action, arguing that: (1) as a matter of claim construction, physicians "administer" folic acid; and (2) under the doctrine of equivalents, physicians' actions are equivalent to putting folic acid into patients' bodies. The district court did not reach those issues. Although Eli Lilly asks us to reach them in the alternative, we need not do so in light of our decision to affirm the district court under *Akamai V*.

Here, the district court decided that "the factual circumstances [we]re sufficiently analogous to those in *Akamai* [*V*] to support a finding of direct infringement by physicians." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.* (*Eli Lilly III*), 126 F. Supp. 3d 1037, 1041 (S.D. Ind. 2015). The court observed initially that taking folic acid in the manner recited by the asserted claims is a "critical" and "necessary" step to "reduc[e] . . . potentially life-threatening toxicities caused by pemetrexed," i.e., to "receive the benefit of the patented method." *Id.* at 1042. Regarding the first *Akamai V* prong, the court found, based on the product labeling, that "taking folic acid in the manner specified is a condition of the patient's participation in pemetrexed treatment." *Id.* Regarding the second prong, the court found that physicians would "prescrib[e] an exact dose of folic acid and direct[] that it be ingested daily." *Id.* at 1043. The court therefore held that, under *Akamai V*, the performance of all steps of the asserted claims would be attributable to physicians.

1

With respect to the first prong—conditioning participation in an activity or receipt of a benefit upon performance of one or more method steps—Defendants argue at the outset that the district court did not make a relevant finding because it misidentified the benefit that would be conditioned as the "benefit of the patented method, i.e., a reduction of potentially life-threatening toxicities caused by pemetrexed." Appellants' Opening Br. 21–22. We agree that a reduction in toxicities is not a benefit that physicians can condition (as it follows from folic acid pretreatment) and that the relevant benefit that may be conditioned on folic acid administration is pemetrexed treatment. But the court's discussion of reducing pemetrexed toxicities in relation to its direction-or-control analysis was not erroneous. A reduction in pemetrexed toxicities is relevant only if pemetrexed treatment is administered, and it provides a reason why physicians

would condition the receipt of pemetrexed treatment on folic acid administration. The court recognized this relationship and correctly identified pemetrexed treatment as the benefit to be conditioned: "What is relevant is whether the physician sufficiently directs or controls the acts of the patients in such a manner as to condition participation in an activity or receipt of a benefit—*in this case, treatment with pemetrexed* in the manner that reduces toxicities—upon the performance of a step of the patented method and establishes the manner and timing of the performance." *Eli Lilly III*, 126 F. Supp. 3d at 1042 (emphasis added); *see also id.* ("[T]aking folic acid in the manner specified is a condition of the patient's participation in *pemetrexed treatment*." (emphasis added)).

The district court's finding that physicians "condition" pemetrexed treatment on the administration of folic acid is supported by the record evidence. The Physician Prescribing Information, which is "directed to the physician," J.A. 2181, explains that folic acid is a "[r]equirement for [p]remedication" in order "to reduce the severity of hematologic and gastrointestinal toxicity of [pemetrexed]." J.A. 11258. Consistent with the importance of folic acid pretreatment, the product labeling repeatedly states that physicians should "[i]nstruct patients" to take folic acid and includes information about folic acid dosage ranges and schedules. J.A. 11256; *see also* J.A. 11255, 11278. The Patient Information also informs patients that physicians may withhold pemetrexed treatment: "You will have regular blood tests before and during your treatment with [pemetrexed]. *Your doctor may adjust your dose of [pemetrexed] or delay treatment* based on the results of your blood test and on your general condition." J.A. 11253 (emphasis added).

Furthermore, Eli Lilly's expert, Dr. Chabner, testified that it is "the physician's responsibility to initiate the supplementation" of folic acid. J.A. 2181. He explained that the product labeling shows that taking folic acid is

"an absolute requirement" before pemetrexed treatment because "it wouldn't be safe to take the drug without the vitamin supplementation. . . . [I]t must be done this way." J.A. 2192; *see also* J.A. 2195 ("[I]t's an absolute requirement."), 2246 ("I think it's that important."). He further testified that if a physician realizes that a patient did not follow his or her instructions to take folic acid, then the "doctor will not give the pemetrexed." J.A. 2218. Even Defendants' expert, Dr. Schulz, acknowledged that it is "standard practice"—both his personally and physicians' generally—that a patient "must have taken their required folic acid in order to have the pemetrexed administered." J.A. 2329–40; *see also* J.A. 2304 ("I would withhold the pemetrexed therapy until [the patient] had initiated or resumed their folic acid treatment . . . [s]o as to avoid the toxicities associated with pemetrexed without vitamin replacement."). Dr. Schulz agreed that he was "not aware of any reputable institution or doctor . . . who, when they think the patient hasn't taken the required folic acid" would go ahead and administer pemetrexed. J.A. 2330–31.

The record is thus replete with evidence that physicians delineate the step of folic acid administration that patients must perform if they wish to receive pemetrexed treatment.

Defendants argue that mere guidance or instruction is insufficient to show "conditioning" under *Akamai V*. But the evidence regarding the critical nature of folic acid pretreatment and physicians' practices support a finding that physicians cross the line from merely guiding or instructing patients to take folic acid to conditioning pemetrexed treatment on their administration of folic acid. If a patient does not take folic acid as instructed, a physician, in his or her discretion, need not provide pemetrexed treatment based on the patient's failure to perform the step of folic acid administration. Defendants also complain that there is no evidence that physicians go

further to "verify compliance" with their instructions or to "threaten" denial of pemetrexed treatment. Appellants' Opening Br. 22. Conditioning, however, does not necessarily require double-checking another's performance or making threats.

We also reject Defendants' argument that an actor can only condition the performance of a step "by imposing a legal obligation to do so, by interposing that step as an unavoidable technological prerequisite to participation, or, as in [*Akamai V*], both." *Id.* In *Akamai V*, we found "conditioning" based on evidence that the defendant required all of its customers to sign a standard contract delineating the steps that customers had to perform to use the defendant's service. 797 F.3d at 1024. But we did not limit "conditioning" to legal obligations or technological prerequisites.[5] We cautioned that "principles of attribution are to be considered in the context of the particular facts presented" and even expressly held that § 271(a) infringement "is not limited solely to principal-agent relationships, contractual arrangements, and joint enterprise." *Id.* at 1023.

The product labeling, combined with the testimony discussed above, provide sufficient evidence that physicians condition pemetrexed treatment on folic acid pretreatment.

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[5] As Eli Lilly points out, nor did we rely on legal obligations or technological prerequisites to reach our decision in *Akamai V*. The standard contract in that case was not significant for imposing potential civil liability but for "delineat[ing] the steps" that customers would have to perform "if [they] wish[ed] to use [defendant's] product." *Akamai V*, 797 F.3d at 1024. And we did not focus on whether a customer's failure to perform certain steps might have made it technologically impossible for other steps to occur. *Id.*

2

With respect to the second prong—establishing the manner or timing of performance—Defendants argue that the product labeling "gives patients wide berth to select the dose . . . , the dosage form . . . , and the timing . . . of folic acid self-administration." Appellants' Opening Br. 23. Eli Lilly submits that expert testimony and product labeling demonstrate that "physicians prescribe or specify a dose of folic acid, specify that patients must ingest the folic acid daily during a particular span of days, and withhold pemetrexed if patients do not follow orders." Appellee's Br. 25. We agree with Eli Lilly.

The product labeling is again informative. For instance, the Physician Prescription Information instructs physicians not only to tell patients to take folic acid orally, but also to take "400 [µg] to 1000 [µg] [of folic acid] once daily beginning 7 days before the first dose of [pemetrexed]," accompanied with warnings about the consequences of non-compliance. J.A. 11256. That dosage range and schedule overlaps with all of the asserted claims' dosage ranges and schedules.[6] In addition, Dr. Chabner testified that "it's the doctor" who "decides how much [folic acid] the patient will take and when the patient takes it." J.A. 2197. In view of the record evi-

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[6] Asserted claims 9, 12, 14, and 15 recite administering "about 350 µg to about 1000 µg" of folic acid. '209 patent col. 11 ll. 19–20, col. 11 l. 25–col. 12 l. 4, col. 12 ll. 7–11. Asserted claims 10, 18, and 19 recite administering "350 µg to 600 µg" of folic acid. *Id.* at col. 11 ll. 21–23, col. 12 ll. 16–20. Asserted claim 21 recites either of those folic acid dosage ranges. *Id.* at col. 12 ll. 24–27. Asserted claim 19 further recites a schedule for folic acid administration "wherein folic acid is administered 1 to 3 weeks prior to the first administration of the pemetrexed." *Id.* at col. 12 ll. 18–20.

dence, the court's finding that physicians establish the manner and timing of patients' folic acid intake is not clearly erroneous. Even if, as Defendants argue, patients are able to seek additional outside assistance regarding folic acid administration, such guidance is beyond what is required here to establish the manner or timing of performance and is therefore immaterial.

We therefore see no reversible error in the district court's finding that physicians condition patient participation in an activity or receipt of a benefit (pemetrexed treatment) on folic acid administration and also establish the manner or timing of performance. Our holding today does not assume that patient action is attributable to a prescribing physician solely because they have a physician-patient relationship. We leave to another day what other scenarios also satisfy the "direction or control" requirement. The two-prong test that we set forth in *Akamai V* is applicable to the facts of this case and resolves the existence of underlying direct infringement.

B

Although we conclude that the two-prong *Akamai V* test is met here, this does not end our inquiry. "The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). To show inducement, Eli Lilly carries the burden of further proving "specific intent and action to induce infringement." *Takeda*, 785 F.3d at 631. Mere "knowledge of the acts alleged to constitute infringement" is not sufficient. *DSU Med.*, 471 F.3d at 1305.

As noted before, the district court found that the administration of folic acid before pemetrexed administration was "not merely a suggestion or recommendation, but a critical step." *Eli Lilly III*, 126 F. Supp. 3d at 1042. It further held that Defendants induce physicians' infringe-

ment because physicians act "in accordance with Defendants' proposed labeling." *Id.* Accordingly, the district court concluded that Defendants would induce infringement of the '209 patent.

Defendants submit that, even if there is direct infringement, their product labeling does not induce such infringement. They argue that Eli Lilly has not offered any evidence of what physicians do "*in general*," offering instead only "speculation about how physicians *may* act." Appellants' Opening Br. 24 (second emphasis added). Furthermore, they submit that physicians "who merely follow the product label" are not induced to infringe because physicians must go beyond the labeling instructions—such as by prescribing specific doses of folic acid or requiring patients to keep "pill counts" or "pill diaries"—to infringe. *Id.* at 23, 26. We agree with Eli Lilly that Defendants' arguments are unavailing.

We make two observations at the outset. First, to be clear, the intent for inducement must be with respect to the actions of the underlying direct infringer, here physicians. Second, we have not required evidence regarding the general prevalence of the induced activity. When the alleged inducement relies on a drug label's instructions, "[t]he question is not just whether [those] instructions describ[e] the infringing mode, . . . but whether the instructions teach an infringing use *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent." *Takeda*, 785 F.3d at 631 (internal quotation marks omitted). "The label must encourage, recommend, or promote infringement." *Id.* For purposes of inducement, "it is irrelevant that some users may ignore the warnings in the proposed label." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010).

Depending on the clarity of the instructions, the decision to continue seeking FDA approval of those instructions may be sufficient evidence of specific intent to

induce infringement. *Id.* at 1059. With respect to those instructions, we held in *AstraZeneca* that a label that instructed users to follow the instructions in an infringing manner was sufficient even though some users would not follow the instructions. *Id.* at 1059–60. This was true even though the product in question had substantial noninfringing uses. *Id.*

Conversely, "vague" instructions that require one to "look outside the label to understand the alleged implicit encouragement" do not, without more, induce infringement. *Takeda*, 785 F.3d at 632, 634. Defendants try to analogize the product labeling here to the labeling in *Takeda* that we held did not provide clear enough instructions for the infringing use to show inducement. *Takeda*, however, is distinguishable. The generic manufacturer in that case sought FDA approval for a generic drug to be used as a prophylaxis for gout flares—a use not covered by the patents that had been asserted. *Id.* at 628. The only link between the proposed use described on the labeling and the patented use was an instruction stating, "[i]f you have a gout flare while taking [the drug], tell your healthcare provider." *Id.* at 632 (first alteration in original) (internal quotation marks omitted). The patent owner argued that physicians who are accordingly consulted might prescribe the drug for the infringing, off-label use and that the accused infringer was willfully blind to this possibility. *Id.* We rejected the patent owner's reliance on such "vague label language" and "speculation about how physicians may act." *Id.* The product labeling here is not so tenuously related to the use covered by the asserted claims, and Eli Lilly does not need to rely on speculation about physician behavior.

Again, the product labeling includes repeated instructions and warnings regarding the importance of and reasons for folic acid treatment, and there is testimony that the Physician Prescribing Information, as the name indicates, is directed at physicians. *See* J.A. 2181, 11253,

11255, 11256, 11258, 11278. The instructions are unambiguous on their face and encourage or recommend infringement.

Defendants rely heavily on evidence that physicians as a matter of practice take steps beyond the instructions in the product labeling, such as asking patients to keep pill diaries or pill counts, or confirming compliance with folic acid administration. For example, they point to Dr. Chabner's testimony that he gives patients instructions "beyond what the instruction is in th[e] patient information." J.A. 2235–36. But the asserted claims do not recite additional steps such as pill diaries, pill counts, and compliance measures. Where the product labeling already encourages infringement of the asserted claims, as it does here, a physician's decision to give patients even more specific guidance is irrelevant to the question of inducement.[7]

In sum, evidence that the product labeling that Defendants seek would inevitably lead some physicians to infringe establishes the requisite intent for inducement. The district court did not clearly err in concluding that Defendants would induce infringement of the asserted claims of the '209 patent.

II

We turn next to the district court's holding that the limitation "vitamin B12" was not indefinite. Pursuant to 35 U.S.C. § 112, ¶ 2, a patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant

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[7] As Dr. Chabner testified, such additional instructions are rightfully "left to the medical judgment of [the] doctor," depending on the circumstances. J.A. 2231.

regards as his invention."[8] The district court considered the indefiniteness of the asserted claims before the Supreme Court changed the relevant standard in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120 (2014), and held that "vitamin B12" was not indefinite.[9] *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.* (*Eli Lilly I*), No. 1:10-cv-1376-TWP-DKL, 2012 WL 2358102, at *11–12 (S.D. Ind. June 20, 2012). The district court further construed "vitamin B12" to mean "cyanocobalamin," a particular vitamin supplement. *Id.* at *12.

In *Nautilus*, the Supreme Court rejected our "not amenable to construction or insolubly ambiguous" standard for indefiniteness and articulated, instead, that "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." 134 S. Ct. at 2124. Indefiniteness is a question of law that we review de novo. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). We have reiterated post-*Nautilus* that "general principles of claim construction apply" to the question of indefinite-

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[8] Paragraph 2 of 35 U.S.C. § 112 was replaced with § 112(b) by § 4(c) of the AIA, and § 4(e) makes that change applicable "to any patent application that is filed on or after" September 16, 2012. Pub. L. No. 112–29, § 4, 125 Stat. at 296–97. Because the application resulting in the '209 patent was filed before that date, we refer to the pre-AIA version of § 112.

[9] Under the prevailing standard at the time, a term was indefinite only if it was "not amenable to construction" or was "insolubly ambiguous." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005) (internal quotation marks omitted), *overruled by Nautilus*, 134 S. Ct. at 2124.

ness. *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377 (Fed. Cir. 2015) (internal quotation marks omitted). Accordingly, we review subsidiary factual determinations made by the district court based on extrinsic evidence for clear error. *Id.*; *see also Teva*, 789 F.3d at 1341–42 (reviewing subsidiary factual findings in the indefiniteness context for clear error).

The parties do not dispute that, depending on the context, "vitamin B12" can be used in the art to refer either to cyanocobalamin specifically or, more broadly, to a class of compounds including pharmaceutical derivatives of cyanocobalamin. The parties do not dispute that the written description of the '209 patent uses the term both ways.[10] Defendants argue that, because "vitamin B12" is used in two different ways in the intrinsic record, "it is impossible to determine" which meaning applies to the claims "with any reasonable certainty," as required by *Nautilus*. Appellants' Opening Br. 31. Eli Lilly counters that the claims of the '209 patent "involve administering a vitamin B_{12} supplement to a patient," and in that context, "the one and only meaning" of vitamin B12 to a person of ordinary skill is cyanocobalamin. Appellee's Br. 35.

The district court expressly "accept[ed]" the testimony of Eli Lilly's expert, Dr. O'Dwyer, who concluded that a person of ordinary skill would understand "vitamin B12" to mean cyanocobalamin in the context of the patent claims. *Eli Lilly I*, 2012 WL 2358102, at *11. We do not

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[10] The specification provides that "[t]he term 'vitamin B12' refers to vitamin B12 and its pharmaceutical derivatives," and that "[p]referably the term refers to vitamin B12, cobalamin, and chlorocobalamin." '209 patent col. 5 ll. 5–10. The district court held, and Defendants do not dispute on appeal, that this language did not signify that the patentee was redefining the term "vitamin B12." *Eli Lilly I*, 2012 WL 2358102, at *10–11.

defer to Dr. O'Dwyer's "ultimate conclusion about claim meaning in the context of th[e] patent," as that is a legal question. *Teva*, 789 F.3d at 1342. But the district court's underlying determination, based on extrinsic evidence, of what a person of ordinary skill would understand "vitamin B12" to mean in different contexts is a question of fact. *See id.* ("Understandings that lie outside the patent documents about the meaning of terms to one of skill in the art or the science or state of the knowledge of one of skill in the art are factual issues."). Dr. O'Dwyer testified that, although "vitamin B12" can refer to a class of compounds in other contexts, it refers specifically to cyanocobalamin when "vitamin B12" is prescribed in the medical field. *See, e.g.*, J.A. 3571 ("'Vitamin B12' is used by medical oncologists to mean a particular vitamin supplement, and medical oncologists refer to 'vitamin B12,' and prescribe 'vitamin B12,' without further explanation or definition."). We see no clear error in the district court's acceptance of the understanding that "vitamin B12," when used to refer to vitamin B12 supplementation in a medical context, refers to cyanocobalamin.[11] In view of this understanding, and because the specification uses "vitamin B12" primarily in two ways, we do not face the problem that we did in *Teva*, in which the disputed term did "not have a plain meaning to one of skill in the art" that could be determined from context. 789 F.3d at 1345.

The claim language here would inform a person of ordinary skill that the term "vitamin B12," as used in the '209 patent claims, refers to "cyanocobalamin." First, the claims, on their face, are directed to administering vita-

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[11] Indeed, Defendants' expert, Dr. Green, agreed that "in the strict biochemical nomenclature, the term 'vitamin B12' is restricted to cyanocobalamin," J.A. 3767, and that it can refer specifically to cyanocobalamin in the context of vitamin B12 injections, J.A. 3748–49.

min supplements, including vitamin B12, followed by chemotherapy treatment. This context informs persons of ordinary skill that "vitamin B12" is being used to refer to the supplementation form of vitamin B12, cyanocobalamin. Second, the structure of the claims also supports such an understanding. Claim 1 requires administering a "methylmalonic acid lowering agent . . . selected from the group consisting of," inter alia, vitamin B12 and cyanocobalamin. '209 patent col. 10 ll. 61–65. Claim 2, which depends from claim 1, further requires that "the methylmalonic acid lowering agent is vitamin B12." *Id.* at col. 10 ll. 66–67. Eli Lilly asserts, and Defendants do not dispute, that if "vitamin B12" were to refer to a class of compounds, then claim 2 would be the same scope as claim 1, as claim 2 "would encompass the same methylmalonic acid lowering agents set forth in claim 1." Appellee's Br. 36. The doctrine of claim differentiation, however, presumes that dependent claims are "of narrower scope than the independent claims from which they depend." *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003). Reading the claims to require "vitamin B12" to be a specific compound in the class of "methylmalonic acid lowering agents" would avoid this problem, as it would render claim 2, and all of the claims that depend from it, narrower than claim 1.

Defendants submit that, if "vitamin B12" means "cyanocobalamin," then claim 1 recites a Markush group of "methylmalonic acid lowering agents" that lists the same compound twice. Although we have in some instances interpreted claim terms to avoid redundancy, "the rule is not inflexible." *Power Mosfet Techs., LLC v. Siemens AG*, 378 F.3d 1396, 1409–10 (Fed. Cir. 2004); *see also Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1363–64 (Fed. Cir. 2016); Manual of Patent Examining Procedure § 2173.05(h)(I) ("The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not

necessarily render the scope of the claim unclear."). Here, the redundancy is supported by the prosecution history, during which the examiner stated that vitamin B12 and cyanocobalamin "are the same" agents. J.A. 4239. Therefore, faced with an interpretation that would read redundancy into claim 1 and another that would violate the doctrine of claim differentiation, we hold that the claims here support the former result over the latter.

We are not persuaded by Defendants' contention that the prosecution history fails to "provide reasonable confidence in any particular meaning of the term 'vitamin B12.'" Appellants' Opening Br. 30. In response to the examiner's statement that "vitamin B12" and "cyanocobalamin" are synonymous, the patentee initially removed the term "cyanocobalamin" from the proposed claims. *See* J.A. 4825–27, 4832–33. Later during prosecution, the patentee added "cyanocobalamin" back into the claim that eventually issued as claim 1. J.A. 4836. Defendants do not point to any reason, though, that a person of ordinary skill would understand the patentee's decision to ultimately include "cyanocobalamin" in the claim language to be a departure from the understanding expressed by the examiner that "vitamin B12" and "cyanocobalamin" refer to the same compound. The prosecution history here does not detract from, and is consistent with, the other intrinsic evidence that would inform a skilled artisan regarding the scope of the claim term "vitamin B12."

We therefore hold that a person of ordinary skill in the art would understand the scope of the claim term "vitamin B12" with reasonable certainty. Applying *Nautilus* in this case does not lead us to a different result from the district court's conclusion on the question of indefiniteness.

III

Next, we address Defendants' arguments that the asserted claims were obvious over several references that

are not disputed to be prior art as of the critical date in June 1999. To prevail on obviousness, an alleged infringer must prove by clear and convincing evidence "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation marks omitted). Obviousness is a question of law based on underlying facts, and "[o]n appeal from a bench trial, this court reviews the district court's conclusions of law de novo and findings of fact for clear error." *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1097 (Fed. Cir. 2015) (internal quotation marks omitted).

In a thorough opinion, the district court found, inter alia, that a skilled artisan would not have been motivated to: (1) use folic acid pretreatment with pemetrexed; (2) use vitamin B12 pretreatment with pemetrexed; or (3) use the claimed doses and schedules of folic acid and vitamin B12 pretreatments with pemetrexed. The court also found that Eli Lilly had established several secondary considerations in favor of nonobviousness. On appeal, Defendants contend that all of those findings were erroneous. Eli Lilly submits that Defendants' arguments "amount to nothing more than an effort to reargue the facts." Appellee's Br. 46.

We agree with Eli Lilly that Defendants' arguments fail to raise reversible error with respect to at least the findings that a skilled artisan would not have been motivated to use vitamin B12 pretreatment with pemetrexed, let alone the appropriate doses and schedules of such vitamin B12 pretreatment.

A

The district court found, based upon two abstracts published in 1998 by Dr. Niyikiza ("the Niyikiza abstracts"),[12] that a skilled artisan "would have concluded that vitamin B_{12} deficiency was not the problem in pemetrexed toxicity." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.* (*Eli Lilly II*), No. 1:10-cv-01376-TWP-DWL, 2014 WL 1350129, at *10 (S.D. Ind. Mar. 31, 2014). It further found that a skilled artisan would not have used vitamin B12 supplementation to address antifolate toxicities because of "concern[] about . . . a reduction of efficacy of the antifolate" treatment. *Id.* at *11.

Dr. Niyikiza was an Eli Lilly scientist at the time and is the named inventor on the '209 patent. In 1997, he performed statistical analyses to try to determine which clinical trial patients were likely to develop toxicities from pemetrexed treatment. J.A. 1045, 1071–72. He published the results in the Niyikiza abstracts and reported a correlation between increased pemetrexed toxicities and elevated homocysteine levels. J.A. 7948, 7950–51. Elevated homocysteine levels serve as an indicator of either a folic acid or vitamin B12 deficiency, but they do not indicate which of those two vitamins is specifically lacking. J.A. 622, 719, 7910. Levels of another marker, methylmalonic acid ("MMA"), serve more specifically as an indicator of vitamin B12 deficiency. J.A. 720. But the Niyikiza abstracts reported that "no correlation between toxicity . . . and [MMA levels] was seen." J.A. 7948.

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[12] C. Niyikiza et al., *LY231514 (MTA): Relationship of Vitamin Metabolite Profile to Toxicity*, 17 PROC. OF AM. SOCIETY OF CLINICAL ONCOLOGY 558a, Abstract 2139 (1998); C. Niyikiza et al., *MTA (LY231514): Relationship of Vitamin Metabolite Profile, Drug Exposure, and Other Patient Characteristics to Toxicity*, 9 ANNALS OF ONCOLOGY 126, Abstract 609P (4th Supp. 1998).

Given the toxicity correlations that Dr. Niyikiza observed with homocysteine levels but not with MMA levels, Eli Lilly's experts testified that the Niyikiza abstracts "present[ed] no evidence for a relationship of vitamin B12 and pemetrexed toxicity" and would not have motivated a skilled artisan to administer vitamin B12 to patients to address pemetrexed toxicity. J.A. 1466–67; *see also* J.A. 1475, 1942. Defendants' expert, Dr. Ratain, confirmed that if a patient exhibits elevated homocysteine but normal MMA levels, a skilled artisan "would conclude that that patient was folate deficient" but "not [vitamin] B12 deficient." J.A. 622–23.

To try to overcome this missing link between vitamin B12 deficiency and pemetrexed toxicity, Defendants turn to other prior art references. They argue that, based on those references and perhaps preexisting knowledge, a person of ordinary skill would have known that folate deficiency is correlated with pemetrexed toxicity and that vitamin B12 "directly affect[s] the amount of folate available to healthy cells." Appellants' Opening Br. 45 (citing J.A. 2482, 7894, 7910–11, 8086). As a result, they argue, skilled artisans would have been motivated to use vitamin B12, along with folic acid, to address pemetrexed toxicities. *Id.* Put another way, if we assume that the prior art would have motivated skilled artisans to use folic acid pretreatment to counter pemetrexed toxicity (an issue we do not reach), Defendants submit that those skilled artisans would have also used vitamin B12 as part of the pretreatment because the biochemical pathways for vitamin B12 and folic acid are related. Defendants further submit that other prior art "expressly teaches that folic acid supplementation *improves* the therapeutic index of pemetrexed," so a skilled artisan would not have been concerned about using vitamin B12 supplementation to reduce pemetrexed toxicities. *Id.* at 46.

But the parties' experts agreed that nothing in the literature as of the critical date described "cancer patients

being provided with vitamin B12 supplementation prior to receiving any antifolate," with or without folic acid. J.A. 597–98; *see also* J.A. 1957. Defendants fail to point to evidence that, even if folic acid supplementation were known to improve effects of pemetrexed treatment, a skilled artisan would have thought the same of vitamin B12. Indeed, Eli Lilly offered expert testimony that a skilled artisan would have viewed the use of vitamin B12 with antifolates as "a problem" based on "having to increase the [antifolate] dose to get the same activity" of cancer treatment. J.A. 1453–54.

We are therefore not convinced that the district court committed clear error in concluding that Defendants failed to carry their burden of proving that it would have been obvious to a person of ordinary skill to use vitamin B12 pretreatment to reduce pemetrexed toxicities.

B

Regarding the dose and schedule of vitamin B12, the district court reiterated that "there are no prior art references where *any amount* of vitamin B_{12} pretreatment had been used with an antifolate in the treatment of cancer." *Eli Lilly II*, 2014 WL 1350129, at *13 (emphasis added). The court also discounted Defendants' citations to literature outside the field of oncology. *Id.* at *13–14.

Defendants argue that, "[o]nce a [skilled artisan] is motivated to use vitamin B12 pretreatment," selecting a dose and schedule for vitamin B12 "would have been routine." Appellants' Opening Br. 47. Setting aside motivation to use vitamin B12 pretreatment in the first instance, Defendants only cite evidence of vitamin B12 doses and schedules that are "routine" in other medical contexts. *See, e.g.*, J.A. 8150, 8169, 756–57. There is no evidence that, considering the context of pemetrexed treatment and associated toxicity problems, a person of ordinary skill would have applied such doses and schedules wholesale.

We therefore also see no clear error in the court's finding that Defendants failed to carry their burden of proving that the prior art disclosed the claimed doses and schedules of vitamin B12 for purposes of pemetrexed pretreatment.

C

Defendants make two additional, overarching arguments that we also find unavailing.

First, Defendants cite *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007), to argue that the district court erred by accepting expert testimony that was inconsistent with the express disclosures of the prior art. But *PharmaStem* is distinguishable. In that case, we discounted testimony regarding prior art references that "[could not] be reconciled with statements made by the inventors in the joint specification [of the asserted patents] and with the prior art references themselves." *Id.* at 1361. Here, despite Defendants' averments, we do not perceive any irreconcilable differences between the prior art disclosures on their face and the testimony regarding whether a person of ordinary skill would have been motivated to use vitamin B12 pretreatment in the claimed doses and schedules with pemetrexed treatment.

Second, Defendants argue that the district court committed legal error by requiring an express prior art disclosure of the claimed combination because *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), rejected such a "rigid" formula in favor of a more flexible inquiry. *Id.* at 402–03. While *KSR* did make the obviousness inquiry more flexible, it does not advance Defendants' position here. Defendants cite to two prior art references that would purportedly "motivate a [skilled artisan] to

review literature regarding known doses and schedules for vitamin B12 supplementation." Appellants' Opening Br. 51. But those references merely note in passing that vitamin B12 can be related to homocysteine levels and folate biochemical pathways. *See* J.A. 7894, 7910. Defendants do not cite to any testimony to support their contention that those references would motivate a skilled artisan to arrive at the claimed use of vitamin B12 as a pretreatment for pemetrexed, especially in view of the evidence of gaps and concerns regarding the prior art discussed above.

The district court did not commit reversible error in finding that the prior art fails to render obvious use of vitamin B12 pretreatment with pemetrexed, or use of the doses and schedules of vitamin B12 that are recited in the asserted claims. We therefore affirm the determination of nonobviousness. We need not reach the other grounds put forth for obviousness.

IV

Finally, we address Defendants' argument that the district court erred in holding that the asserted claims are not invalid for obviousness-type double patenting over U.S. Patent No. 5,217,974 ("'974 patent"), an earlier patent also owned by Eli Lilly.

The judicially-created "doctrine of obviousness-type double patenting is intended to 'prevent the extension of the term of a patent . . . by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent.'" *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1376 (Fed. Cir. 2012) (alteration in original) (quoting *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985)). After determining the differences in the claims of the earlier and later patents, the court must determine if the alleged infringer has proven by clear and convincing evidence that the claims are not patentably

distinct. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 962, 968 (Fed. Cir. 2001). "A later patent claim is not patentably distinct from an earlier claim if the later claim is obvious over, or anticipated by, the earlier claim." *Id.* Even where a patent is found invalid for obviousness-type double patenting, though, a patentee may file a terminal disclaimer. *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1347 (Fed. Cir. 2010); *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005) (noting that there is no "prohibition on post-issuance terminal disclaimers" and that "[a] terminal disclaimer can indeed supplant a finding of invalidity for double patenting"). Obviousness-type double patenting is a question of law based on underlying facts, so "[o]n appeal from a bench trial, this court reviews the district court's conclusions of law de novo and findings of fact for clear error." *Prometheus*, 805 F.3d at 1097 (internal quotation marks omitted).

Defendants argued to the district court that the asserted claims of the '209 patent are obvious variants of claim 20 of the '974 patent. The court found that the asserted claims differ from claim 20 of the '974 patent "in that the Asserted Claims limit the drug to pemetrexed and the administration to a patient, use a dose range for folic acid of 350–1000 µg or 350–600 µg and add[] vitamin B_{12}, whereas claim 20 of the '974 Patent discloses the use of a much greater amount of folic acid—500–30,000 µg—with an antifolate . . . administered to a mammal." *Eli Lilly II*, 2014 WL 1350129, at *17. In particular, the '974 patent lacks any recitation of vitamin B12 pretreatment, let alone dosage ranges or schedules of such pretreatment.

For many of the same reasons it articulated in its obviousness analysis and with additional explanation, the district court found that the use of pemetrexed, use of vitamin B12, and doses and schedules of the asserted claims were patentably distinct from claim 20 of the '974 patent. *Id.* at *17–18. In relevant part, the district court

held that, "as previously discussed, there would have been no reason for a [skilled artisan] to add vitamin B_{12} to the folic acid pretreatment." *Id.* at *17. For the same reasons that we discussed with respect to nonobviousness, the court did not err in finding that those limitations regarding vitamin B12 would not have been obvious to a person of ordinary skill.

Therefore, we affirm the district court's conclusion that the asserted claims are not invalid for obviousness-type double patenting.

CONCLUSION

For the foregoing reasons, we affirm the district court's judgment.

AFFIRMED