United States Court of Appeals for the Federal Circuit

SANOFI, SANOFI-AVENTIS U.S., LLC,
Plaintiffs-Appellees

v.

WATSON LABORATORIES INC., SANDOZ INC.,
Defendants-Appellants

2016-2722, 2016-2726

Appeals from the United States District Court for the District of Delaware in Nos. 1:14-cv-00264-RGA, 1:14-cv-00265-RGA, 1:14-cv-00292-RGA, 1:14-cv-00293-RGA, 1:14-cv-00294-RGA, 1:14-cv-00424-RGA, 1:14-cv-00875-RGA, 1:14-cv-01434-RGA, Judge Richard G. Andrews.

Decided: November 9, 2017

WILLIAM E. SOLANDER, Fitzpatrick, Cella, Harper & Scinto, New York, NY, argued for plaintiffs-appellees. Also represented by ANNA ELIZABETH DWYER, ZACHARY GARRETT, DANIEL JOHN MINION, JAMES R. TYMINSKI, JR.

MAUREEN L. RURKA, Winston & Strawn LLP, Chicago, IL, argued for defendant-appellants. Defendant-appellant Sandoz Inc. also represented by TYLER JOHANNES, JULIA MANO JOHNSON.

NATALIE CHRISTINE CLAYTON, Alston & Bird LLP, New York, NY, for defendant-appellant Watson Laboratories, Inc. Also represented by CHRISTOPHER L. MCARDLE, YI WEN WU.

Before PROST, *Chief Judge,* WALLACH, and TARANTO, *Circuit Judges.*

TARANTO, *Circuit Judge*.

Sanofi owns U.S. Patent Nos. 8,318,800 and 8,410,167, which describe and claim compositions and uses of the cardiovascular (specifically, antiarrhythmic) drug dronedarone. The '800 patent, which expires in 2019, claims pharmaceutical compositions containing dronedarone. The '167 patent, which expires in 2029, claims methods of reducing hospitalization by administering dronedarone to patients having specified characteristics. Sanofi's subsidiary, Sanofi-Aventis U.S., LLC, received approval in mid-2009 for New Drug Application No. 022425 for 400 mg tablets of dronedarone, sold as Multaq®. Both the '800 and the '167 patents are listed in the Food and Drug Administration's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") as patents claiming either Multaq® or a method of using Multaq®.

Watson Laboratories Inc. and Sandoz Inc., hoping to market generic versions of Multaq®, filed abbreviated new drug applications with the Food and Drug Administration. Both firms certified, under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), their beliefs that the '167 and '800 patents were invalid and/or that the manufacture, use, and sale of the proposed generic drugs would not infringe either patent. Upon receiving notice of the paragraph IV certifications, the two Sanofi firms, which we will simply call "Sanofi," sued Watson and Sandoz for infringement of the two patents under 35 U.S.C. § 271(e)(2)(A).

After a three-day bench trial, the district court ruled in crucial respects for Sanofi. *Sanofi v. Glenmark Pharm. Inc., USA*, 204 F. Supp. 3d 665, 704–705 (D. Del. 2016). As to the '167 patent, the court made the following rulings of relevance here: Sanofi proved that Watson's and Sandoz's sale of their proposed generic drugs, with their proposed labels, would induce physicians to infringe all but one of the asserted claims, *id.* at 673–84; and Watson and Sandoz did not prove that any of the asserted claims were invalid for obviousness, *id.* at 685–96. As to the '800 patent, the district court, rejecting the non-infringement argument made by Watson and Sandoz, concluded that the asserted claims do not exclude compositions containing polysorbate surfactants. *Id.* at 699–704. The district court then entered a final judgment rejecting the obviousness challenge to claims 1–6, 8–13, and 16 of the '167 patent; finding inducement of infringement, by both defendants, of all of those claims except claim 5; and finding infringement by both defendants of claims 1–3, 5-9, and 12–15 of the '800 patent and by Watson of claims 10 and 11 as well.

Watson and Sandoz appeal. We have jurisdiction under 28 U.S.C. § 1295(a)(1). We affirm.

I

A

In June 1998, Sanofi filed the application that established the priority date for the '800 patent on its dronedarone composition. But Sanofi did not receive FDA approval for Multaq® until mid-2009, after considerable work investigating the effects of dronedarone on heart patients. That work led to the '167 patent, which, it is undisputed here, has a priority date of February 11, 2009. J.A. 34. The prior art asserted here as a basis for invalidity of the '167 patent claims at issue all pre-dates February 11, 2008, one year before the priority date.

Between November 2001 and September 2003, Sanofi conducted two materially identical large-scale clinical trials, and the methods and results were described in a 2007 publication. *See* Bramah N. Singh *et al.*, *Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter*, 357 New Eng. J. Med. 987 (2007). The EURIDIS trial drew its patients from Europe; the ADONIS trial drew its patients from North and South America, Australia, and Africa. *Id.* at 987. In both, dronedarone was administered to patients who were at the time in normal sinus rhythm but had earlier experienced an episode of atrial fibrillation or flutter. *Id.* at 988.

What was primarily being measured (the "primary end point" for which the study was designed) was simply "the time to the first recurrence of atrial fibrillation or flutter." *Id.* at 987; *see id.* at 989. The studies also were set up to record "ventricular rates during the recurrence of atrial fibrillation," *id.* at 990, and certain symptoms (palpitations, dizziness, fatigue, chest pain, and dyspnea) when accompanied by atrial fibrillation during monitoring, *id.* at 989. The 2007 Singh publication described the results regarding the issues the trials were designed to address: "dronedarone reduced the incidence of a first recurrence, as well as a symptomatic first recurrence, within 12 months after randomization" and "significantly reduced the ventricular rate during the recurrence of arrhythmia." *Id.* at 995.

The 2007 Singh publication also noted that, once the data from the trials was collected, the researchers conducted a "post hoc analysis" of a particular clinical-benefit issue that the trials were not designed to address: the effect of dronedarone on rates of hospitalization or death. *Id.* at 993. As to that issue, the 2007 publication reported: "in a post hoc analysis, dronedarone significantly reduced the rate of hospitalization or death." *Id.* at 995. The figures showed some differences between the two

studies regarding hospitalization/death reduction, with the European trial (EURIDIS) showing greater reduction than the non-European trial (ADONIS), whereas the opposite difference existed regarding the primary measure of time to first recurrence. *Id.* at 993–94.

Dr. Singh and his co-author Dr. Hohnloser—the latter of whom was central to Sanofi's dronedarone studies—had already briefly reported the post-hoc analysis in public. They stated, in an abstract, that they had conducted the post-hoc analysis in order to evaluate "the potential clinical benefit of [dronedarone] at reducing hospitalization or death" and were planning a new study to assess that potential. Stefan H. Hohnloser & Bramah N. Singh, *Dronedarone Significantly Decreases the Combined Endpoint of Hospitalization and Death in Patients with Atrial Fibrillation*, 112 Circulation II-327, II-327–28, Abstract 1637 (2005) (Abstracts from Scientific Sessions 2005 in the Journal of the American Heart Association). In early 2006, *Internal Medicine News*, describing the Scientific Session presentation by Dr. Hohnloser that is apparently reflected in the 2005 abstract, noted the "potential major clinical benefit" of reduced hospitalization or death and that "Dr. Hohnloser stressed that 'potential' needs to be emphasized because this was a posthoc analysis." Bruce Jancin, *Dronedarone Cut Morbidity, Deaths in Atrial Fib*, Internal Med. News, Mar. 15, 2006.

Meanwhile, in June 2002, even as the EURIDIS and ADONIS trials were underway, Sanofi conducted a trial to investigate safety: the ANDROMEDA trial—"Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease." *See* Krista M. Dale & C. Michael White, *Dronedarone: An Amiodarone Analog for the Treatment of Atrial Fibrillation and Atrial Flutter*, 41 Annals of Pharmacotherapy 599, 602 (2007). ANDROMEDA was designed to test the effects of dronedarone on patients with symptomatic heart failure and severe left ventricular

systolic dysfunction; although atrial fibrillation was not a criterion for patient entry into the study, atrial fibrillation "patients commonly have underlying heart disease and 40% of the ANDROMEDA patients actually had" atrial fibrillation. *Sanofi*, 204 F. Supp. 3d at 686–87. As was explained in publications before February 2008, the results of the ANDROMEDA trial, as they came in, led Sanofi to terminate the study early: it appeared that dronedarone was actually increasing mortality from heart failure. *Id.*; *see* Dale & White, at 602; Mohammad J. Tafreshi & Joie Rowles, *A Review of the Investigational Antiarrhythmic Agent Dronedarone*, 12 J. Cardiovascular Pharmacology & Therapeutics 15, 24 (2007); European Medicines Agency, *Withdrawal Public Assessment Report Of the Marketing Authorisation Application for Multaq (Dronedarone), EMEA/H/C/676* at 22–23 (October 2006) (EMEA 2006 Report).

In 2006, the European Medicines Agency, discussing EURIDIS and ADONIS, stated that "the clinical relevance needs further consideration." EMEA 2006 Report, at 20. It further noted that "[a] reduction in time to death and hospitalisation was noted but this reflects an ancillary analysis and needs further confirmation, in particular in the context of the negative effects seen in the ANDROMEDA." *Id.* at 19. The Report concluded: "At the moment, the ratio between efficacy and safety is considered negative." *Id.* at 24. The 2007 Tafreshi & Rowles article, for its part, stated: "The efficacy and safety of dronedarone have not yet been determined. . . . The existing clinical data of dronedarone, both in terms of safety and efficacy, have been confusing and severely challenged so far." Tafreshi & Rowles, at 24.

Those assessments were made while Sanofi was conducting—between June 2005 and March 2008—the large-scale clinical trial, called ATHENA, that was designed to address the potential for clinical benefits of dronedarone that the EURIDIS/ADONIS researchers had identified in

their post-hoc analysis. The results of the ATHENA study post-date the critical date of February 2008. ATHENA involved administration of dronedarone to patients who had a recent history of atrial fibrillation and/or flutter and at least one of several specified characteristics believed to be associated with cardiovascular risk. The study assessed differences in cardiovascular hospitalization or death (secondarily, in hospitalization or death regardless of cause) between patients given dronedarone and patients given a placebo. J.A. 7846–48. The study produced positive results for dronedarone. *See* Stefan H. Hohnloser, *Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation*, 360 New Eng. J. Med. 668 (2009). Those results led to the filings that resulted in the '167 patent and to the FDA's approval of Multaq®. J.A. 177 (Tr. 101), 194 (Tr. 169).

Although the pre-February 2008 prior art does not include the results of the ATHENA study, it does include an article published by Dr. Hohnloser and his colleagues in January 2008, which describes the rationale and design of the ATHENA study. Stefan H. Hohnloser, *Rationale and Design of ATHENA: A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg Bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter*, 19 J. Cardiovascular Electrophysiology 69 (2008) (internal acronym-supporting capitalization and highlighting omitted) (Hohnloser 2008). The article notes that "dronedarone appears to be a promising new antiarrhythmic compound for treatment of [atrial fibrillation]" but "was associated with increased mortality in patients with a recent history of decompensated heart failure (ANDROMEDA)," a "finding [that] reemphasizes the need for a large dronedarone outcomes study in a typical population of elderly [atrial fibrillation] patients." *Id.* at 72. It declares that "ATHENA is the pivotal outcome study for the development of droneda-

rone," explaining that ATHENA is the first randomized clinical study that uses "exclusively the combined endpoint of all-cause mortality and rehospitalization for cardiovascular causes," as opposed to an "endpoint directly related to" atrial fibrillation such as time to first recurrence. *Id.* The article then includes the following sentence:

> Since it was shown that dronedarone is not only capable of maintaining [sinus rhythm] in many patients, but also of controlling heart rate in case of [atrial fibrillation] relapses, it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalization for cardiovascular reasons.

Id. The second part of that sentence became a centerpiece of the obviousness challenge in this case.

B

The '167 patent claims methods of reducing cardiovascular hospitalization by administering dronedarone to patients meeting conditions mirroring those stated in the in the ATHENA trial. Claim 1 is representative:

> A method of decreasing a risk of cardiovascular hospitalization in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, twice a day with a morning and an evening meal, wherein said patient does not have severe heart failure, (i) wherein severe heart failure is indicated by: a) NYHA Class IV heart failure or b) hospitalization for heart failure within the last month; and (ii) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent atrial fibrillation or flutter; and (iii) wherein the patient has at least

> one cardiovascular risk factor selected from the group consisting of:
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> i. an age greater than or equal to 75;
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> ii. hypertension;
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> iii. diabetes;
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> iv. a history of cerebral stroke or of systemic embolism;
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> v. a left atrial diameter greater than or equal to 50 mm; and
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> vi. a left ventricular ejection fraction less than 40%.

'167 patent, col. 28, line 64 through col. 29, line 15.

C

The extensive information (the "label") that Sanofi includes along with its Multaq® product—which Watson and Sandoz propose to use for their generic versions without any change material to this case, J.A. 7784, 7797–801—relies on the key studies described above. *See* J.A. 7609, 7623–27. Section 1 of the label, as revised in March 2014, is titled "Indications and Usage." It provides:

> Multaq® is indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF) *[see Clinical Studies (14)]*.

J.A. 7609 (emphasis and brackets in original). That sentence says that Multaq® is indicated for use in certain patients and refers to section 14 on "Clinical Studies" for identification of those patients. Section 14 primarily describes the ATHENA study (section 14.1), but also contains a short description of the EURIDIS and ADONIS studies (section 14.2). And it refers to two studies that

had to be terminated early because of negative results in their patient pools: the ANDROMEDA study (section 14.3) and the PALLAS study (section 14.4).[1] J.A. 7623–27.

Both Watson and Sandoz plan to market their generic versions of Multaq® with the same labeling, including sections 1 and 14. J.A. 7643, 7784; *see AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045–46 (Fed. Cir. 2010) (explaining that, in general, an applicant for an abbreviated new drug application must "show that 'the labeling proposed for the new drug is the same as the labeling approved for the listed drug.'" (quoting 21 U.S.C. § 355(j)(2)(A)(v))).

II

Watson and Sandoz challenge the district court's inducement finding as to the '167 patent, the district court's rejection of their obviousness challenge to that patent, and the district court's rejection of their prosecution-disclaimer argument for limiting the scope of the '800 patent claims.

A

Under 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." Here, the district court found, the inducing act will be the marketing by Watson and Sandoz of their generic dronedarone drugs with the label described above. And the induced act will be the administration of dronedarone by medical providers to patients meeting the criteria set forth in the '167 patent claims.

"In contrast to direct infringement, liability for inducing infringement attaches only if the defendant knew of

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[1] The details of the PALLAS study are not important for purposes of this appeal.

the patent and that 'the induced acts constitute patent infringement.'" *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015) (quoting *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011) (stating that "we now hold that induced infringement under § 271(b) requires knowledge that the induced acts constitute infringement")). Neither of those two knowledge requirements is disputed here. If and when Watson and Sandoz receive FDA approval and market dronedarone with the label at issue, they will know of the '167 patent (they already do) and that a medical provider's administration of the drug to the claimed class of patients is an act of infringement (which Watson and Sandoz do not dispute).

The dispute in this case involves an aspect of the connection between the marketing and the medical providers' infringement that is different from the two knowledge requirements and is inherent in the word "induce" as it has been understood in this area. The Supreme Court stated the following in *Global-Tech*:

> The term "induce" means "[t]o lead on; to influence; to prevail on; to move by persuasion or influence." Webster's New International Dictionary 1269 (2d ed. 1945). The addition of the adverb 'actively' suggests that the inducement must involve the taking of affirmative steps to bring about the desired result, see *id.,* at 27.

563 U.S. at 760 (brackets in original). The purposeful-causation connotation of that language is reinforced by the Court's statement: "When a person actively induces another to take some action, the inducer obviously knows the action that he or she wishes to bring about." *Id.*

Further reinforcement is found in the Supreme Court's discussion of inducement of copyright infringement in *Metro-Goldwyn-Mayer Studios Inc. v. Grokster Ltd.*, 545 U.S. 913, 936–37 (2005), which the Court in

Global-Tech cited in discussing patent infringement, *see* 563 U.S. at 763. In *Grokster*, the Court explained that inducement is present where "'active steps . . . taken to encourage direct infringement,' such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe." 545 U.S. at 936 (citation omitted). The Court cited, for support, this court's decision in *Water Techs. Corp. v. Calco, Ltd.*, which focused on intent and noted that intent is a factual determination that may rest on circumstantial evidence. 850 F.2d 660, 668 (Fed. Cir. 1988). The Supreme Court in *Grokster* held: "one who distributes a device with the object of promoting its use to infringe copyright, as shown by clear expression or other affirmative steps taken to foster infringement, is liable for the resulting acts of infringement by third parties." 545 U.S. at 936–37.

This court has accordingly explained that, for a court to find induced infringement, "[i]t must be established that the defendant possessed specific intent to encourage another's infringement." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part) (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed.Cir.1990)); *see ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007). The court has articulated certain necessary conditions: the plaintiff must show "that the alleged infringer's actions induced infringing acts and that he knew or should have known his actions would induce actual infringements." *DSU Med.*, 471 F.3d at 1306 (emphasis omitted) (quoting *Manville*, 917 F.2d at 553). And the court has repeatedly explained that, for the finder of fact to find the required intent to encourage, "[w]hile proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice." *Id.* (quoting *Water Techs.*, 850 F.2d at 668); *see Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1342 (Fed. Cir.

2008) (similar). When proof of intent to encourage depends on the label accompanying the marketing of a drug, "[t]he label must encourage, recommend, or promote infringement." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (citations omitted).

In this case, the district court relied on those standards. *Sanofi*, 204 F. Supp. 3d at 673. And, applying those standards, the court found that Sanofi had proven intentional encouragement of infringement of the independent claims. *Id.* at 677 ("Sanofi has proven that Defendants' proposed labels demonstrate specific intent to encourage physicians to infringe independent claims 1 and 8 of the '167 patent and will lead to such infringement . . . ."); *see id.* (finding the "proposed labels encourage physicians to prescribe dronedarone to patients with at least one of the cardiovascular risk factors claimed in the '167 patent"; Watson and Sandoz "kn[o]w that their proposed labels would actually cause physicians to prescribe dronedarone to patients with the cardiovascular risk factors claimed" and that "such a use would infringe the '167 patent"). Watson and Sandoz, in this court, make no separate argument about any dependent claim except claim 4, which they discuss in one paragraph. Appellants' Br. 37. But they do not suggest, and we see no sound basis for a conclusion, that the district court made any lesser findings for claim 4. *See id.* at 682–84 (finding inducement for claims 4 and 10, but not claim 5).

We review the district court's finding of inducement based on encouragement and inferred intent for clear error. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010). We find no such error. The label itself has a short "Indications and Usage" section, one sentence long. It states what dronedarone is indicated for: it "is indicated to reduce the risk of hospitalization for atrial fibrillation." J.A. 7609; *see* J.A. 7784. And it states which patients are covered by this indication: "patients in

sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF) *[see Clinical Studies (14)]*." J.A. 7609; *see* J.A. 7784. The reference to the Clinical Studies section (14) of the label expressly directs the reader to that section for elaboration of the class of patients for whom the drug is indicated to achieve the stated objective, *i.e.*, reduced hospitalization. Section 14 leads with and features a subsection on the ATHENA study, which sets forth the positive results, relating to reduced hospitalization, for patients having the risk factors written into the '167 patent. And it is only the ATHENA subsection—not any of the three other brief subsections—that identifies a class of patients as having been shown to achieve reduced hospitalization from use of dronedarone. The EURIDIS/ADONIS subsection says nothing about reduced hospitalization; and the ANDROMEDA and PALLAS subsections are negative warnings, describing studies that had to be terminated early because of adverse results. *See* J.A. 7626–27, J.A. 7800–801. The label thus directs medical providers to information identifying the desired benefit for only patients with the patent-claimed risk factors.[2]

There was considerable testimony that this label encourages—and would be known by Watson and Sandoz to encourage—administration of the drug to those patients, thereby causing infringement. Approximately 77% of Multaq® prescriptions have actually been written for

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[2] As to claim 4, the district court made findings, which are not clearly erroneous, that the label's description of the ATHENA study as covering patients already receiving "conventional therapy" embraced the taking of diuretics as claimed in claim 4. Administration of diuretics is just such a conventional therapy—one received, in fact, by more than half of the patients in the ATHENA study. *Sanofi*, 204 F. Supp. 3d at 682–83.

patients with the claimed risk factors. *Sanofi*, 204 F. Supp. 3d at 677, 684; *see* J.A. 8069. Moreover, Dr. Kim, an expert for Sanofi, testified that a person of ordinary skill in the art would read the drug label and understand that the only FDA-approved use of dronedarone came out of the ATHENA trial, J.A. 177–79, and that a physician would find "clear encouragement" from the label to use dronedarone in a manner that infringes the '167 patent, J.A. 174, especially in light of label's description of the ANDROMEDA study, which warns of the safety concerns of using dronedarone on patients other than those for whom the ATHENA trial showed reduced hospitalization, J.A. 175–76. *See also* J.A. 302–304 (Dr. Reiffel, expert for Sanofi, discussing physicians' reluctance to use dronedarone in a manner that has not yet been proven successful, given the drug's poor performance in the ANDROMEDA trial and the inconsistent clinical history of antiarrhythmic drugs in general). Dr. Zusman, who testified for Watson and Sandoz, agreed that persons of skill in the art "look[] to drug labels, in part, 'for information about the use of the drug in special or specific populations,' and that it is important for the [person of skill] to look at the label's indications section to see if a drug 'is indicated for administration to patients of certain characteristics with a certain intent.'" *Sanofi*, 204 F. Supp. 3d at 678 (quoting J.A. 196–97). On the record in this case, the district court could draw the required inducement inferences.

Watson and Sandoz contend that, because Multaq® has substantial noninfringing uses not forbidden by the proposed labels, *Sanofi*, 204 F. Supp. 3d at 684, the district court could not permissibly find intent to encourage an infringing use. But there is no legal or logical basis for the suggested limitation on inducement. Section 271(b), on inducement, does not contain the "substantial noninfringing use" restriction of section 271(c), on contributory infringement. And the core holding of *Grokster*, a copyright decision that drew expressly on patent and other

inducement law, is precisely that a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses (like the peer-to-peer software product at issue there, which was capable of infringing and non-infringing uses). 545 U.S. at 934–37. There is no basis for a different inducement rule for drug labels.

The content of the label in this case permits the inference of specific intent to encourage the infringing use. As noted above, inducement law permits the required factual inferences about intended effects to rest on circumstantial evidence in appropriate circumstances. Moreover, in *AstraZeneca v. Apotex*, the court upheld an inducement finding without the kind of explicit limiting commands that Watson and Sandoz suggest a label must contain. 633 F.3d at 1058–60. In *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, the court stated that "[d]epending on the clarity of the [drug label's] instructions, the decision to continue seeking FDA approval of those instructions may be sufficient evidence of specific intent to induce infringement." 845 F.3d 1357, 1368−69 (Fed. Cir. 2017) (internal citations omitted). Unlike in *Takeda*, the inference in the present case is based on interpreting the label's express statement of indications of use and the internally referred-to elaboration of those indications. *See* 785 F.3d at 625. And this case is not like *Vita-Mix Corp v. Basic Holding, Inc.*, in which the defendant, in its (non-pharmaceutical) product instructions, encouraged a non-infringing use in a way that showed an intent to discourage infringement. 581 F.3d 1317, 1328–29 (Fed. Cir. 2009). The evidence in this case supports the finding of intentional encouragement of infringing use and, therefore, of inducement.

B

Obviousness under 35 U.S.C. § 103 is a question of law based on underlying questions of fact. *Allergan, Inc.*

v. Sandoz Inc., 726 F.3d 1286, 1290 (Fed. Cir. 2013).[3] Watson and Sandoz accept the legal framework under which they had to establish that, as of February 2008, a person of ordinary skill in the art would have had a reasonable expectation that the processes claimed would succeed in their (claimed) aims, a factual issue. *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1221–23 (Fed. Cir. 2017); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007). On appeal, Watson and Sandoz make no argument as to obviousness independent of their challenge to the district court's finding of no such expectation. We reject the contention that the district court adopted an incorrect legal standard on the issue, and we are unpersuaded that the district court was clearly erroneous in determining that Watson and Sandoz failed to prove the required reasonable expectation. Based on those conclusions, we affirm the nonobviousness judgment.

Watson and Sandoz initially argue that the district court committed legal error by applying too high a standard for proving a reasonable expectation of success. We disagree.

The district court held that the claims of the '167 patent were not proved to be obvious based on its factual finding that, in light of all the evidence, "a [person of ordinary skill in the art] in 2008 would not have had a reasonable expectation that dronedarone would reduce the risk of cardiovascular hospitalization and hospitalization for [atrial fibrillation] in patients with paroxysmal or persistent [atrial fibrillation] and the associated risk factors of the ATHENA patient population." *Sanofi*, 204

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[3] Given the filing date of the '167 patent, this case is governed by the version of section 103 in force preceding the changes by the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 293 (2011).

F. Supp. 3d at 691. In making that finding, the court invoked the language of "reasonable expectation" repeatedly. *Id.* at 686, 687, 688, 689, 691, 693, 696, 696 n.7; *see also id.* at 693 (crediting Sanofi's expert testimony that the EURIDIS/ADONIS post-hoc analysis did not support "any sort of scientifically reasonable likelihood that dronedarone would successfully reduce the risk of cardiovascular hospitalization in patients with persistent or paroxysmal [atrial fibrillation] and the associated risk factors").

Contrary to the contention of Watson and Sandoz, the court did not expressly or by necessary implication demand known certainty as to the objective of reduced hospitalization. No such demand is implicit in the court's finding that the Hohnloser 2008 "it is expected" statement was not a "concrete" factual assertion, *id.* at 688, 692, but instead a mere "hypothesis," *id.* at 688, 692. Nor did the court demand certainty when it simply described the proposed information for ATHENA enrollees as presenting the EURIDIS/ADONIS data "in less than certain terms," *id.* at 693, as one piece of evidence supporting the court's determination to credit Sanofi's expert testimony that there was no "scientifically reasonable likelihood" of the claimed hospitalization reduction based on the EURIDIS/ADONIS post-hoc analysis, *id.* Watson and Sandoz have not shown that the court demanded some degree of or foundation for the required expectation that is contrary to any refinement we have adopted to elaborate on the "reasonable expectation" standard. The court used and applied the terminology from our decisions that Watson and Sandoz accept.

Watson and Sandoz's appeal on obviousness thus ultimately rests on the contention that the district court's finding under the standard was clearly erroneous. We conclude that it was not. Although the evidence might well have supported the opposite finding, we cannot conclude that the district court clearly erred in its finding

that Watson and Sandoz did not carry their burden of showing that a person of ordinary skill in the art in February 2008 would have had a reasonable expectation that dronedarone would succeed in reducing cardiovascular hospitalization in the ATHENA patient population.

We have described the key publications available to the relevant community of skilled artisans before February 2008. The EURIDIS/ADONIS pair of studies showed some positive results in the time to recurrence of atrial fibrillation and in ventricular rates, but they were not designed to investigate reduced hospitalization, let alone to do so for the patient population covered by the patent claims at issue. A post-hoc analysis of the results suggested a potential reduced-hospitalization benefit, but publications in 2005 and 2006 indicated that the suggested benefit was a "potential," no more. Meanwhile, the ANDROMEDA study showed dangers of dronedarone severe enough to have spurred early termination of the study. A 2006 European Medicines Agency report doubted the presence of clinical benefits and deemed the efficacy/safety ratio to be "negative." A 2007 article characterized the safety and efficacy data as confusing and severely challenged.

In light of that body of publications, Watson and Sandoz relied heavily on the final publication of relevance, the January 2008 article by Dr. Hohnloser and his colleagues, in which they described the benefit of reduced hospitalization as "expected." Hohnloser 2008 at 72 ("it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons"). But there was an evidentiary dispute about how that statement would be understood by a person of ordinary skill in the art.[4] Dr.

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[4] The district court found that the person of ordinary skill in the art "was a clinician with a medical degree

Zusman, for Watson and Sandoz, testified that the statement would be taken as a concrete assertion of fact about what the authors expected, and perhaps what a relevant skilled artisan should expect. J.A. 209. But Dr. Reiffel, for Sanofi, testified that, in this context, the statement would be understood as nothing more than a statement of the hypothesis being tested in ATHENA. J.A. 351. The district court credited Dr. Reiffel's testimony, explaining why. *Sanofi*, 204 F. Supp. 3d at 692–95. We have been furnished no basis on which to say, in light of the other evidence in the case, that the district court clearly erred in doing so. *See Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1351 (Fed. Cir. 2015) (stressing need for exceptional evidentiary reasons for appellate court not to defer to trial court's determination to credit expert testimony about what prior art taught). This is not a case like *PharmaStem*, in which the expert testimony about prior-art references was rejected because the testimony could not "be reconciled with statements made by the inventors in the [patent] specification and with the prior art references themselves." 491 F.3d at 1361; *id.* at 1361–63.

Watson and Sandoz also point to the post-hoc analysis based on the EURIDIS and ADONIS trials. But the district court did not clearly err in finding that a relevant skilled artisan would not have relied on that analysis to form a reasonable expectation of reduced hospitalizations in the claimed populations. *Sanofi*, 204 F. Supp. 3d at 690–91. The record contains evidence about the unreliability of post-hoc analyses generally. Rothwell, *Subgroup*

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who was board certified either in cardiology or electrophysiology and had at least two years of clinical experience after fellowship, and because of such fellowship, would have had some knowledge of the design, implementation, and analysis of clinical studies." *Sanofi*, 204 F. Supp. 3d at 686. That finding is not challenged on appeal.

Analysis in Randomised Controlled Trials: Importance, Indications, and Interpretation (2006) (explaining that "[p]ost hoc observations are not automatically invalid . . . but they should be regarded as unreliable unless they can be replicated"). And Sanofi's expert Dr. Reiffel testified that a person of ordinary skill in the art would not "draw an expectation" about dronedarone from the post-hoc analysis in this case specifically. J.A. 348–52. He cited differences in the respective patient populations as well as the "discordant results" between the EURIDIS and ADONIS trials as to hospitalization/death reduction versus time of recurrence of atrial fibrillation. *Id.* at 349. And he testified that a person of ordinary skill in the art would be especially skeptical about what to draw from the particular post-hoc analysis relating to dronedarone here due to the safety concerns that arose after the failed ANDROMEDA trial. J.A. 352.

Finally, Watson and Sandoz presented evidence that Sanofi sent to some hospitals that participated in the ATHENA trial a document called "Written Subject Information," proposed to be given to ATHENA enrollees, that contained predictions about the benefits of dronedarone. J.A. 7444 (JTX-55, proposed Written Subject Information, containing the language, "it is expected, that dronedarone improves the outcome in atrial fibrillation and atrial flutter patients by reducing the admissions to hospital and by prolonging the time in normal heart rhythm"); J.A. 7977 (DTX-24, same). But there was no evidence that the documents containing "it is expected" language were ever actually given to patients in the ATHENA trial.[5] To the

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[5] The district court referred to the Written Subject Information (DTX-24) as "provided to ATHENA trial patients." *Sanofi*, 204 F. Supp. 3d at 689 (citing DTX-24 and Tr. 236–37 (J.A. 210–11)). The cited evidence says only that the document was what was "proposed" to be

contrary, experts for both Sanofi and Watson/Sandoz stated that the Institutional Review Boards at their hospitals altered the benefits language from the Written Subject Information. J.A. 236 (Dr. Zusman, expert for Watson and Sandoz, testifying that the Written Subject Information actually given to patients at Massachusetts General Hospital, JTX-218, was changed by the Institutional Review Board to tell enrollees that, as to the effect of placebo versus dronedarone on "the long-term outcome of your disease," "there is no clear evidence that this will be a positive or negative difference" "based on the currently available information"); J.A. 373 (Dr. Reiffel, expert for Sanofi, testifying that the Institutional Review Board at his hospital changed the wording proposed by Sanofi before distributing the Written Subject Information to patients); JTX-218 (Massachusetts General Hospital form, not containing "it is expected" language, but saying, in addition to the above-quoted statements: "It is possible that you may receive no benefit from this research study. . . . Your participation in this study might be a direct benefit to you and could help in the development of new treatments for the benefit of future patients."). The initially proposed enrollee-information "it is expected" language cannot show that the district court's finding regarding reasonable expectation is clearly erroneous when, as far as the record shows, that language was not actually given to enrollees and, indeed, was deleted by Institutional Review Boards (which, we must presume, were concerned about overstatements to lay patients in securing informed consent).[6]

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given to ATHENA enrollees. We do not read the court's language as finding more than what the cited evidence supports.

[6] We note that a longstanding "Federal Policy for the Protection of Human Subjects," where applicable,

We conclude that the district court did not commit clear error in finding that a person of ordinary skill in the art "would have been at best cautiously optimistic that dronedarone could reduce the risk of cardiovascular hospitalization and hospitalization for AF in the ATHENA patient population" and that Watson and Sandoz had failed to prove obviousness by clear and convincing evidence. *Sanofi*, 204 F. Supp. 3d at 696.

C

In seeking to reverse the finding of infringement of the '800 patent, Watson and Sandoz raise just one issue. They argue that the district court erred by failing to limit the claims of the '800 patent to exclude polysorbate surfactants. They point to the fact that, while prosecuting the parent application, which issued as U.S. Patent No. 7,323,493, Sanofi amended the sole independent claims (hence all claims) so as expressly to exclude pharmaceutical compositions with a "polysorbate surfactant" from the claims of the '493 patent. Based on that amendment, Watson and Sandoz contend that Sanofi made a "prosecution disclaimer" that also limits the scope of the claims of the '800 patent, despite the absence of any limiting language in the '800 patent's claims. We review the district court's rejection of this prosecution-disclaimer argument de novo. *Shire Dev., LLC v. Watson Pharms., Inc.*, 787 F.3d 1359, 1365 (Fed. Cir. 2015). We agree with the district court.

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requires investigators to obtain informed consent from human subjects of research and generally requires, as a basic element of informed consent, that the information given to prospective subjects include "[a] description of any benefits to the subject or to others which may reasonably be expected from the research." 45 C.F.R. § 46.116(a)(3).

A prosecution disclaimer occurs "when a patentee, either through argument or amendment, surrenders claim scope during the course of prosecution." *Heuft Systemtechnik GmbH v. Indus. Dynamics Co., Ltd.*, 282 F. App'x 836, 839 (Fed. Cir. 2008). But "[w]hen the purported disclaimers are directed to specific claim terms that have been omitted or materially altered in subsequent applications (rather than to the invention itself), those disclaimers do not apply." *Saunders Grp., Inc. v. Comfortrac, Inc.*, 492 F.3d 1326, 1333 (Fed. Cir. 2007). "In general, a prosecution disclaimer will only apply to a subsequent patent if that patent contains the same claim limitation as its predecessor." *Regents of Univ. of Minn. v. AGA Med. Corp.*, 717 F.3d 929, 943 (Fed Cir. 2013).

In this case, all that Sanofi did, in prosecuting the application that issued as the '493 patent, was to write an express limitation into the claims: "provided that the pharmaceutical composition does not contain a polysorbate surfactant." *See Sanofi*, 204 F. Supp. 3d at 701. That language does not appear in the '800 patent claims at issue. As the district court noted, Sanofi did not argue during prosecution that the unamended claim language of the '493 patent, or the disclosed invention generally, excluded polysorbate surfactants. *Id.* at 702–03. In these circumstances, the process in this case fit a familiar pattern: an applicant adopts an explicit claim-narrowing limitation to achieve immediate issuance of a patent containing the narrowed claims and postpones to the prosecution of a continuation application further arguments about claims that lack the narrowing limitation. Without more than exists here, that process does not imply a disclaimer as to claims, when later issued in the continuation, that lack the first patent's express narrowing limitation.

We therefore affirm the district court's ruling that the scope of the claims of the '800 patent should not be limited so as to exclude polysorbate surfactants.

III

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

AFFIRMED