United States Court of Appeals for the Federal Circuit

CUMBERLAND PHARMACEUTICALS INC.,
Plaintiff-Appellee

v.

MYLAN INSTITUTIONAL LLC, MYLAN INC.,
Defendants-Appellants

2016-1155, 2016-1259

Appeals from the United States District Court for the Northern District of Illinois in No. 1:12-cv-03846, Judge Rebecca R. Pallmeyer.

Decided: January 26, 2017

LAURA POLLARD MASUROVSKY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for plaintiff-appellee. Also represented by DANIELLE ANDREA DUSZCZYSZYN, MARK J. FELDSTEIN, JASON LEE ROMRELL.

NICOLE W. STAFFORD, Wilson, Sonsini, Goodrich & Rosati, PC, Austin, TX, argued for defendants-appellants. Also represented by ROBERT DELAFIELD; ADAM WILLIAM BURROWBRIDGE, Washington, DC; ELHAM FIROUZI STEINER, San Diego, CA; NANCY L. ZHANG, Palo Alto, CA.

Before MOORE, REYNA, and TARANTO, *Circuit Judges.*

TARANTO, *Circuit Judge*.

Cumberland Pharmaceuticals, Inc. owns U.S. Patent No. 8,399,445, which describes and claims acetylcysteine compositions substantially free of chelating agents. It is listed in the Food and Drug Administration's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) as covering Cumberland's chelating-agent-free formulation of Acetadote®, an intravenous antidote for overdoses of acetaminophen. When Mylan Institutional LLC filed an abbreviated new drug application to market its own chelating-agent-free acetylcysteine formulation, Cumberland brought this patent-infringement action in the Northern District of Illinois against Mylan Institutional LLC and Mylan Inc. (hereafter "Mylan," individually or jointly). Mylan stipulated to infringement but asserted invalidity on two grounds: derivation of the claimed invention from someone at the FDA and obviousness. The district court rejected both challenges after a bench trial. In particular, the court found that Mylan proved neither (1) that anyone at the FDA conceived of the claimed invention before the patent-named inventor nor (2) that there was a reasonable expectation that the claimed formulations, without any chelating agents, would succeed. *Cumberland Pharm., Inc. v. Mylan Institutional LLC*, 137 F. Supp. 3d 1108, 1121–22, 1127 (N.D. Ill. 2015). We affirm.

I

A

At the priority date relevant here (August 24, 2005), acetylcysteine was known in the art as an antidote for acetaminophen overdoses. '445 patent, col. 1, lines 20–34. It also was known to have a stability problem: heavy metal ions, whether inherent in the formulation or found

as contaminants, catalyze the oxidation of acetylcysteine in solution, causing it to degrade. *Id.*, col. 1, lines 39–40; *see Cumberland*, 137 F. Supp. 3d at 1112 n.2. A prior-art response to the stability problem was to include edetate disodium (EDTA or edetate) in an acetylcysteine formulation. '445 patent, col. 1, line 45, through col. 2, line 4. EDTA, a chelating agent, surrounds and binds to heavy metal ions, preventing them from acting as catalysts that oxidize acetylcysteine. *Id.* Such EDTA-containing formulations of acetylcysteine were considered safe, despite potential negative side effects. *Id.*, col. 2, lines 14–27.

Cumberland's '445 patent declares: "It has been surprisingly found that an aqueous composition containing acetylcysteine, sterilized water, and a pH-adjusting agent, is stable without the addition of a chelating agent." *Id.*, col. 2, lines 48–50. The patent claims such compositions. Every claim in the patent requires a "stable" composition that is "free of chelating agents," *id.*, col. 9, line 16, through col. 10, line 53, and the district court construed the term to mean "[l]acking one or more chelating agents," *Cumberland*, 137 F. Supp. 3d at 1112.

B

The facts central to the dispute over the '445 patent's validity date from 2002, when the FDA was considering Cumberland's application for permission to market the original EDTA-containing formulation of Acetadote®, a formulation previously approved in other countries. On December 10, 2002, the FDA sent Cumberland a letter, in which the FDA gave Cumberland the following instructions (among others): "[2c.] Provide scientific and regulatory justification for the inclusion of Edetate as a component in the drug product. In addition, provide a description of the pharmacological properties for Edetate in this drug product." J.A. 12837. Six days later, representatives of the FDA and Cumberland spoke by telephone. Notes of the call state: "Regarding item 2(c), the

Division explained that data should be provided to support any justification for the inclusion of Edetate, since a non-trivial amount is included in the formulation." J.A. 12899.

On December 20, 2002, Cumberland formally responded to the FDA in a letter written by Leo Pavliv, who was the Cumberland official responsible for Acetadote® and who is the named inventor on the '445 patent.[1] The letter explained that EDTA was included to stabilize the formulation and stated: "If no or lower concentrations of edetate are capable of ensuring product stability, lowering or removing edetate would raise questions of how the safety and efficacy of the product would be effected." J.A. 14783. Mr. Pavliv ultimately testified at trial that, shortly after writing this letter, he had the idea of testing the stability of an acetylcysteine formulation without EDTA.

On March 5, 2003, Cumberland asked the FDA to schedule a call for further discussion of its December 20, 2002 response. With respect to question 2c, Cumberland proposed to discuss the following: "Cumberland believes the use of Edetate as a component in the drug product is justified both from a scientific as well as a regulatory point of view. Does FDA agree?" J.A. 11343. There is no written record of the occurrence or content of the requested call. At trial, however, Mr. Pavliv testified that the call took place; that FDA representatives indicated on the call that they were not prepared to say whether they considered EDTA's inclusion justified; and that Mr. Pavliv then stated his idea to perform a stability study. Accord-

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[1] Although the letter is signed by Amy Rock of Cumberland's department of regulatory affairs, both Mr. Pavliv and Dr. Rock testified that it was Mr. Pavliv who drafted the December 20th response and Cumberland's Acetadote® correspondence to the FDA more generally. *See Cumberland*, 137 F. Supp. 3d at 1114 n.3.

ing to Mr. Pavliv, at least one FDA representative on the call approved of his idea to do a study and asked him to put the proposal in writing.

Cumberland did so in a July 21, 2003 letter, stating: "As requested by FDA, upon product approval [*i.e.*, upon FDA approval of the EDTA-containing formulation], Cumberland Pharmaceuticals intends to initiate studies to determine the impact on product stability of both decreasing and completely removing edetate disodium from the formulation." J.A. 14916. The FDA issued its Chemistry Review of the EDTA-containing formulation on January 9, 2004. That document states: "The sponsor reported that, as requested by the FDA upon drug approval, an independent study will be initiated to determine the impact on drug product stability of both decreasing and completely removing the amount of edetate sodium." J.A. 12968; *see id.* at 12969 (referring twice more to Cumberland's commitment to a post-approval study). The FDA approved the EDTA-containing product on January 23, 2004, J.A. 11334–37, with the approval letter reminding Cumberland of its commitment to "evaluate the potential benefit of Edetate disodium on the stability of the drug product," the study to "include a comparison of the current concentration of Edetate to a formulation with a lower concentration and no concentration of Edetate." *Id.* at 11336.

Cumberland then arranged by contract for testing to be done by Bioniche Pharma Group, "Mylan's predecessor company." *Cumberland*, 137 F. Supp. 3d at 1116. The protocol, proposed by Mr. Pavliv and approved by the FDA without change, included testing a formulation that turned out to be the claimed invention, *i.e.*, a formulation

containing neither EDTA nor any other chelating agent.[2] On November 18, 2004, three months into the study, Mr. Pavliv received encouraging stability data. On August 24, 2005, having received further encouraging stability data (for a longer period), Cumberland filed its application for what became U.S. Patent No. 8,148,356, the parent of the '445 patent at issue here.

Cumberland gave the FDA the final results of the stability study, containing data for thirty-six months, on August 13, 2008. It then set about securing approval to market an EDTA-free version of Acetadote®. The FDA approved that product in January 2011.

C

On December 19, 2011, Mylan filed an abbreviated new drug application seeking permission to market a generic version of Cumberland's EDTA-free acetylcysteine product. Shortly thereafter, on February 27, 2012, Cumberland filed the divisional application that became the '445 patent. When the '356 patent issued on April 3, 2012, Mylan sent Cumberland a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the '356 patent was either invalid or not infringed by Mylan's proposed product.

On May 17, 2012, Cumberland sued Mylan for infringement of the '356 patent pursuant to 35 U.S.C. § 271(e)(2)(A). The '445 patent issued on March 19, 2013, and Cumberland then amended its complaint to add allegations of infringement of the '445 patent. On August 4, 2014, Mylan stipulated to infringement of claims 1–14 of the '445 patent should they be held valid and enforcea-

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[2] Although several patent claims are at issue in this case, the issues have been litigated in such a way as to make it appropriate to use the singular "invention."

ble. Cumberland withdrew its claims regarding the '356 patent on September 28, 2014.

At the bench trial, Mylan argued that (1) the '445 patent had been derived from someone at the FDA, on the theory that it was someone at the FDA, not Mr. Pavliv, who first had the idea to remove EDTA from the prior-art formulation, and (2) the invention would have been obvious in light of certain prior-art communications from the FDA. The district court held that (1) Mylan had not proved that anyone at the FDA conceived of the invention before Cumberland's inventor did, *Cumberland*, 137 F. Supp. 3d at 1121–22, and (2) there was no reasonable expectation that a formulation without any chelating agents would be successful, given the prevailing skilled-artisan view that chelating agents were necessary to prevent degradation of acetylcysteine, *id.* at 1127. The court entered a final judgment of validity and infringement on November 17, 2015. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II

"While the ultimate question of whether a patentee derived an invention from another is one of fact, the determination of whether there was a prior conception is a question of law, which is based upon subsidiary factual findings." *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993) (citations omitted). Obviousness is a question of law based on underlying questions of fact. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1290 (Fed. Cir. 2013). We review the district court's conclusions of law de novo and its findings of fact for clear error. *Id.*

A

Mylan's derivation challenge invokes the rule that an applicant is not entitled to a patent if "he did not himself

invent the subject matter sought to be patented." 35 U.S.C. § 102(f) (2006).[3] More specifically, it invokes the familiar requirement that a challenger asserting this ground show that there was a "prior conception of the claimed subject matter and communication of the conception" to the named inventor. *Price*, 988 F.2d at 1190; *see Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1313 (Fed. Cir. 2011); *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1344 (Fed. Cir. 2003); *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1576 (Fed. Cir. 1997) ("To show derivation, the party asserting invalidity must prove both prior conception of the invention by another and communication of that conception to the patentee."). The conception requirement of derivation borrows from the conception standard for prior invention. *Creative Compounds*, 651 F.3d at 1313 (relying on the conception analysis from a discussion of priority earlier in the opinion as sufficient in the discussion of derivation). Conception is keyed to the *claimed* invention: "A conception must encompass all limitations of the claimed invention." *Singh v. Brake*, 317 F.3d 1334, 1340 (Fed. Cir. 2003); *see Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1323 (Fed. Cir. 2013); *Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304 F.3d 1256,

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[3] The quoted version of 35 U.S.C. § 102 applies to this case. The application that became the '445 patent was filed on February 27, 2012, and claims priority to August 2005. The application has never contained a claim having an effective filing date on or after March 16, 2013 (the effective date of the statutory changes enacted in 2011), or a reference under 35 U.S.C. §§ 120, 121, of 365(c) to any patent or application that ever contained such a claim. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 3(n)(1), 125 Stat. 284, 293 (2011); *Fleming v. Escort Inc.*, 774 F.3d 1371, 1374 n.1 (Fed. Cir. 2014).

1263 (Fed. Cir. 2002); *Brown v. Barbacid*, 276 F.3d 1327, 1336 (Fed. Cir. 2002). Conception requires more than "a general goal or research plan"; it requires a "definite and permanent," "specific, settled idea," namely, the idea defined by the claim at issue. *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994); *see REG Synthetic Fuels, LLC v. Neste Oil Oyj*, 841 F.3d 954, 962 (Fed. Cir. 2016).

In inventorship disputes, "the inventors named on the issued patent are presumed to be correct" and "a person seeking to add his name 'must meet the heavy burden of proving its case by clear and convincing evidence.'" *Shum v. Intel Corp.*, 633 F.3d 1067, 1083 (Fed. Cir. 2010) (quoting *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1358 (Fed. Cir. 2004)). We apply the same approach in the derivation context here. *Amax Fly Ash Corp. v. United States*, 514 F.2d 1041, 1047–48 (Ct. Cl. 1975), cited with approval in *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 980 (Fed. Cir. 1997).

In this case, as the derivation issue was litigated, it suffices to focus on the fact that the required complete conception had to include the specific idea to remove EDTA from Acetadote® (or a similar product that met all the other '445 claim elements) and *not* add another chelating agent. It was that idea which Mylan had to show, by clear and convincing evidence, was conceived by someone at the FDA and communicated to Mr. Pavliv. *See Amax Fly Ash Corp.*, 514 F.2d at 1048.

The district court found that Mylan did not carry that burden. After considering the "surprising paucity of direct evidence," *Cumberland*, 137 F. Supp. 3d at 1120, the district court concluded that while "the evidence does not establish a precise date of conception by Pavliv," "Mylan has failed to persuade the court that anyone other than Pavliv *ever* conceived of a 'definite and permanent idea' of an EDTA-free Acetadote formulation," *id.* at

1121–22. Given the claim language requiring that the product be "free of chelating agents," '445 patent, col. 9, lines 20–21, not just EDTA, and the district court's several references to that particular claim requirement, *Cumberland*, 137 F. Supp. 3d at 1112–13 (discussing the claim limitation "free of chelating agents"); *id.* at 1123–24 (same), we think it clear that the district court's finding refers to a formulation of Acetadote® that *simply* removes EDTA, without adding another chelating agent in its place. The court thus found that Mylan did not prove that an FDA person conceived of that formulation, or communicated it to Cumberland, before Mr. Pavliv thought of it.

The evidence supports the finding. The court could properly view the FDA's December 10, 2002 letter, which simply requested justification for the inclusion of EDTA in the drug product, as not showing the prior conception needed here. J.A. 12837 ("[2(c):] Provide scientific and regulatory justification for the inclusion of Edetate as a component in the drug product. In addition, provide a description of the pharmacological properties for Edetate in this drug product."). A different view is not required by the notes of the December 16, 2002 call, which add only that the FDA wanted *data* to support the justification. J.A. 12899 ("Regarding item 2(c), the Division explained that data should be provided to support any justification for the inclusion of Edetate, since a non-trivial amount is included in the formulation."). A request for justification of the inclusion of EDTA, supported by data, is not the same as a suggestion to remove it, let alone to remove it and not replace it with another chelating agent.

Mylan argues that the request for data to support the inclusion of EDTA required Cumberland to undertake research that would have inevitably led it to the invention. That is not enough for derivation. We have held that derivation is not proved by showing conception and communication of an idea different from the claimed invention even where that idea would make the claimed

idea obvious. *Gambro Lundia*, 110 F.3d at 1577–78. We also have made clear that a "general goal or research plan" does not constitute the "definite and permanent idea" required for conception, *Burroughs Wellcome*, 40 F.3d at 1228, and that a "bare hope" of a result "never before . . . achieved" (here, the claimed "stable" compound) is not sufficient for conception, *Hitzeman v. Rutter*, 243 F.3d 1345, 1356–57 (Fed. Cir. 2001). *See Cumberland*, 137 F. Supp. 3d at 1121. The kind of general research suggestion at issue here, whatever its role in an obviousness analysis, does not establish the conception required for derivation.

The evidence dating from after December 2002 likewise does not compel a finding contrary to the district court's. In particular, even when documents go beyond discussing a study of whether EDTA's inclusion is justified and mention removing EDTA, they do not make clear either that all chelating agents were to be avoided or that even the EDTA-removal idea (whether or not a substitute was to be added) came from someone other than Mr. Pavliv. All of those documents postdate the conversation Mr. Pavliv had with FDA representatives, in which, he testified, he was the one who introduced the idea of testing an EDTA-free product.

Thus, several Cumberland documents, starting with the July 21, 2003 letter quoted above, J.A. 14916, refer to the FDA as having "requested" the study. But that language can be read as focusing on the FDA's request for a study implementing the idea already suggested by Mr. Pavliv. *See* J.A. 11263 (Cumberland's Apr. 19, 2004 proposed study protocol) ("As part of a post approval marketing commitment, the FDA requested Cumberland investigate whether EDTA has a beneficial impact on stability and if so whether the level could be reduced."); J.A. 11311 (Cumberland's Aug. 13, 2008 final report from stability study) ("The FDA expressed a potential safety concern with EDTA in the formulation and as such,

requested Cumberland investigate whether EDTA provided a stability benefit or could be reduced or removed from the product."); J.A. 11360 (Cumberland's May 10, 2011 draft clinical study protocol for EDTA-free Acetadote®) ("The FDA expressed a potential safety concern with EDTA in the formulation of Acetadote and requested that the manufacturer investigate whether EDTA provided a stability benefit or could be reduced or removed from the product."); J.A. 11693 (Cumberland's May 18, 2012 citizen petition) ("From the outset, FDA wanted Cumberland to investigate reducing or removing EDTA from Acetadote® because the agency was concerned with the safety of EDTA. The agency should not now approve an ANDA for Acetadote® that relies on the discontinued formulation that is less safe than the EDTA-free formulation that FDA specifically requested Cumberland investigate developing, and that is currently on the market.").

Indeed, the FDA's January 9, 2004 Chemistry Review, after stating that "[t]he sponsor reported that, as requested by FDA . . . , an independent study will be initiated to determine the impact on drug product stability of both decreasing and completely removing the amount of edetate sodium," J.A. 12968, adds that the study was "applicant proposed," J.A. 12969. As that document confirms, it is entirely possible for Cumberland to have first proposed the idea of studying EDTA removal, as Mr. Pavliv testified, and for the FDA to have "requested" that Cumberland actually perform that study. And, as with the December 2002 communications, none of these documents establish that the FDA specifically conceived of removing EDTA from the prior-art Acetadote® without adding any other chelating agents, as required by the claim language.

Mylan gets no further help in reversing the district court's finding from the FDA's reliance on Cumberland's commitment to perform the study in approving the EDTA-containing product in 2004. It simply does not follow from the fact that the study ultimately became a commitment

recited in the 2004 FDA approval that it was someone at the FDA who originally proposed the study, let alone conceived of the invention eventually claimed in the '445 patent. The district court could properly find that the study requirement in the Approval Letter did not specify that Cumberland must test an EDTA-free formulation of acetylcysteine without adding any other chelating agents. *Cumberland*, 137 F. Supp. 3d at 1123 ("Most importantly, the reference to Cumberland's commitment to study the removal of EDTA from Acetadote nowhere specifies that the *exact* same drug formulation without EDTA must be used."). The study requirement, in total, reads:

> Commit to evaluate the potential benefit of Edetate disodium on the stability of the drug product. The study shall include a comparison of the current concentration of Edetate to a formulation with a lower concentration and no concentration of Edetate. Generate stability data from the new proposed formulations including compatibility stability with infusion bags.

J.A. 11336. As the district court explained: "'A formulation' could contain, for instance, a chelating agent other than EDTA. This composition would be free of EDTA and satisfy the study requirement, but would not be 'free of chelating agents,' . . . which every claim of the '445 patent requires." *Cumberland*, 137 F. Supp. 3d at 1123–24 (citation omitted). Consistent with this conclusion, Cumberland provided testimony that there were many possible ways to meet this commitment, including adding other chelating agents or testing without the claimed "airtight container" containing inert gas, and there was documentary evidence that it was Mr. Pavliv who came up with the precise protocol that amounted to a reduction to practice of the '445 patent's invention.

Mylan does not contend that anyone at the FDA, rather than Mr. Pavliv, drafted the study protocol that

resulted in the claimed invention (though it does point out that the protocol Mr. Pavliv chose was the same protocol used to confirm the stability of EDTA-containing Acetadote®). Instead, Mylan takes the position that the communications between the FDA and Cumberland, which all require "removing or reducing" EDTA from "*the*" formulation or "*the*" drug product, must refer to the approved EDTA-containing product; thus, according to Mylan, the study requirement is not open to an interpretation that would allow a relevant skilled artisan to do anything other than arrive at the claimed invention, free of chelating agents. But the use of the definite article need not do so much work as to direct a skilled artisan to remove EDTA, add nothing else, and test the resulting formulation in exactly the manner to lead to the invention. Indeed, Mylan's theory would appear to prove too much: Cumberland's December 20, 2002 letter referred to the effect on "*the* product" if it turned out that "no or lower concentrations of edetate are capable of ensuring product stability," and Cumberland's July 21, 2003 letter also refers to "completely removing edetate disodium from *the* formulation." J.A. 14783, 14916 (emphases added). If reference to removing EDTA from "the" formulation is enough, we do not see why Cumberland's evidence would not suffice to show that Mr. Pavliv, the author of the December 20, 2002 and July 21, 2003 letters, first conceived of the invention.

For those reasons, we affirm the district court's determination that Mylan did not clearly and convincingly show that Mr. Pavliv derived the invention of the '445 patent from someone at the FDA.

B

We also affirm the district court's rejection of Mylan's obviousness challenge. Mylan relies for this challenge on the EDTA-containing Acetadote® and its package insert—which, Mylan asserts, include or teach all of the elements

of the invention except the removal of EDTA—together with several references that allegedly bridge the gap to reach the claimed chelating-agent-free version of an acetylcysteine product. Specifically, Mylan relies on (a) the FDA's January 9, 2004 Chemistry Review and January 23, 2004 Approval Letter, each of which, it asserts, motivates removal of EDTA by stating Cumberland's commitment to study EDTA's role; and (b) U.S. Patent Pub. No. 2004/0022873 to Guilford, which describes intravenous acetylcysteine formulations for treating bioterror exposures.[4] Those contentions, we conclude, do not undermine the district court's rejection of Mylan's obviousness challenge.

"A party seeking to invalidate a patent on the basis of obviousness must demonstrate 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." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012) (internal quotation marks and citations omitted). The presence or absence of a reasonable expectation of success is a question of fact. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016); *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

"The reasonable expectation of success requirement

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[4] The parties have stipulated that the Approval Letter and package insert were publicly available no later than February 2, 2004, and that the Chemistry Review was publicly available as of October 1, 2004. J.A. 14923. The parties accept that the priority date for the '445 patent is August 24, 2005.

refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Systems*, 821 F.3d at 1367. Here, stability is an express claim requirement. The district court in this case wrote: "the court's review of the evidence supports the conclusion that persons of ordinary skill in the art would have assumed that EDTA, or some other chelating agent, was necessary to maintain stability in an acetylcysteine formulation." *Cumberland*, 137 F. Supp. 3d at 1125. It added: "Given that all prior acetylcysteine formulations contained EDTA, and given that the prior art taught that EDTA or another chelating agent was necessary to stabilize the formulation, the court rejects the argument that the Approval Letter or Chemistry Review, which contained the EDTA study commitments, would reasonably lead to a stable acetylcysteine formulation." *Id.* at 1126. Though not using the exact phrase, "reasonable expectation of success," the court thus found that the hypothetical relevant skilled artisan would not have reasonably expected a chelating-agent-free intravenous acetylcysteine formulation to succeed in being stable, a claim requirement. *Id.* at 1125.

That finding is not clearly erroneous. Considerable evidence supports the finding that relevant skilled artisans believed that chelating agents were necessary to sequester metal contaminants and prevent oxidative degradation of acetylcysteine and that such artisans had no reasonable expectation of stability without such an agent. J.A. 14507 (U.S. Patent No. 5,700,653 to Lu, explaining how EDTA can alleviate acetylcysteine's "notorious instability in solution"); J.A. 14509 (Lu patent, referring to an experiment "carried out to confirm that, as known in the art, [acetylcysteine] in a solution of creatine kinase buffer will become unstable in the buffer solution, but that the presence of EDTA can provide some limited stability"); J.A. 8666, 8723 (Dr. Kent, expert for Mylan,

testifying that acetylcysteine's thiol groups are prone to oxidation); J.A. 9298, 9304, 9323–25 (Dr. Byrn, expert for Cumberland, testifying that a person of ordinary skill would understand that EDTA was necessary to prevent oxidation and would be concerned about removing it); *see also* J.A. 13324 (Hamlow, observing that "data show that acetylcysteine solution containing the chelating agent EDTA is well protected from oxidative degradation"). As late as 2011, Mylan's own scientists expressed concern that the removal of EDTA would make the product more vulnerable to oxidation. *E.g.*, J.A. 14346 (email noting the "risk" that "removing EDTA will open up sensitivity to heavy metals at low ppm levels in solution" and proposing experiments to determine sources and effects of heavy metals in the proposed product); J.A. 14487–88 (email to vial supplier requesting data for how much iron could leech from the glass into solution because of concern that the "product may be sensitive to oxidation"); J.A. 14562 (meeting agenda stating: "Iron in Glass may cause an issue with EDTA removal. Set up tests to confirm glass being chosen is acceptable.").

Mylan offered evidence tending to show that there is no need to chelate trace metal ions because degradation may be effectively avoided by an inert vial atmosphere together with modern manufacturing practices that leave very low levels of metal contaminants. But Mylan's evidence did not compel a finding that relevant skilled artisans would have reasonably expected success for those reasons in 2005. The district court had sufficient evidence to find otherwise. In addition to the already-cited evidence, we note the pre-2005 references indicating that even very small amounts of metal and oxygen could result in degradation. J.A. 13574 (Kasraian et al.[5] stating: "In

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[5] Kasra Kasraian et al., *Developing an Injectable Formula Containing an Oxygen-Sensitive Drug: A case*

many cases, minimizing oxygen alone is not sufficient to prevent autoxidation, because trace levels of oxygen may be enough to initiate this reaction"); J.A. 13459 (Waterman[6] stating: "Trace metals are almost ubiquitous in dosage forms, and since they are often catalysts rather than consumed, they can affect rates even at low levels").

Finally, there is no clear error in the district court's finding that Guilford did not provide either a motivation to remove EDTA or a reasonable expectation of success. *Cumberland*, 137 F. Supp. 3d at 1126. Although Guilford did not disclose a chelating agent in its formulation of acetylcysteine, it also did not publish stability data. To the extent that a person of ordinary skill could infer that the Guilford formulation was stable, there was testimony explaining that a person of ordinary skill would not expect it to remain stable as the concentration of acetylcysteine was raised to the level required by the '445 patent. *See id.*

III

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

AFFIRMED

Study of Danofloxacin Injectable, 4 Pharmaceutical Dev. & Tech. 475 (1999).

[6] Kenneth C. Waterman et al., *Stabilization of Pharmaceuticals to Oxidative Degradation*, 7 Pharmaceutical Dev. & Tech. 1 (2002).