United States Court of Appeals for the Federal Circuit

UCB, INC., UCB BIOPHARMA SPRL, RESEARCH CORPORATION TECHNOLOGIES, INC., HARRIS FRC CORPORATION,
Plaintiffs-Appellees

v.

ACCORD HEALTHCARE, INC., INTAS PHARMACEUTICALS LTD., MYLAN PHARMACEUTICALS INC., MYLAN INC., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LIMITED, AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., BRECKENRIDGE PHARMACEUTICAL, INC., SUN PHARMA GLOBAL FZE, SUN PHARMACEUTICAL INDUSTRIES, LTD., WATSON LABORATORIES, INC. - FLORIDA, NKA ACTAVIS LABORATORIES FL, INC., WATSON PHARMA, INC., NKA ACTAVIS PHARMA, INC., MSN LABORATORIES PVT. LTD., ALEMBIC PHARMACEUTICALS LTD., APOTEX CORP., APOTEX INC.,
Defendants-Appellants

ALEMBIC PHARMA LIMITED, ACTAVIS, INC., NKA ALLERGAN FINANCE, LLC,
Defendants

2016-2610, 2016-2683, 2016-2685, 2016-2698, 2016-2710, 2017-1001

Appeals from the United States District Court for the District of Delaware in Nos. 1:13-cv-01206-LPS, 1:13-cv-01207-LPS, 1:13-cv-01208-LPS, 1:13-cv-01209-LPS, 1:13-cv-01210-LPS, 1:13-cv-01211-LPS, 1:13-cv-01212-LPS, 1:13-cv-01213-LPS, 1:13-cv-01214-LPS, 1:13-cv-01215-LPS, 1:13-cv-01216-LPS, 1:13-cv-01218-LPS, 1:13-cv-01219-LPS, 1:13-cv-01220-LPS, 1:14-cv-00834-LPS, Chief Judge Leonard P. Stark.

Decided: May 23, 2018

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Before PROST, *Chief Judge*, BRYSON and STOLL, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* STOLL.

Dissenting opinion filed by *Chief Judge* PROST.

STOLL, *Circuit Judge*.

This case arises under the Hatch-Waxman Act. Appellees UCB, Inc.; UCB BioPharma SPRL; Research Corp. Technologies, Inc.; and Harris FRC Corp. (collectively, "UCB") own and/or license U.S. Patent No. RE38,551. The '551 patent covers lacosamide, an anti-epileptic drug, which treats epilepsy and other central nervous system disorders. UCB holds New Drug Applications ("NDAs") that cover its lacosamide anti-epileptic drug approved by the Food and Drug Administration ("FDA") and marketed under the tradename Vimpat®. The '551 patent is listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* ("Orange Book") as covering Vimpat®.

Appellants are generic drug manufacturers who filed Abbreviated New Drug Applications ("ANDAs"), seeking approval for generic versions of Vimpat®. Pursuant to the governing Hatch-Waxman provisions, Appellants certified in their ANDAs that the '551 patent is invalid, unenforceable, or that their proposed generic lacosamide products will not infringe the '551 patent. Consequently, UCB sued Appellants for patent infringement in the United States District Court for the District of Delaware. Appellants stipulated to infringement of claims 9, 10, and 13 of the '551 patent but maintained that these claims are invalid for obviousness-type double patenting, obviousness, and anticipation.

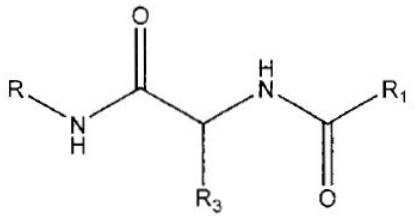
Following a bench trial, the district court made exhaustive fact findings based on the trial evidence and concluded that the asserted claims of the '551 patent are not invalid. Appellants appeal that decision, arguing that the district court misapplied the legal standards for obviousness-type double patenting, obviousness, and anticipation, and that the prior art anticipates and/or renders the '551 patent obvious.

As explained more fully below, we hold that the district court applied the correct legal standards in its obviousness-type double patenting, obviousness, and anticipation analyses. And because we discern no clear error in its underlying fact findings, we affirm the district court's ultimate conclusion that the asserted claims are not invalid.

BACKGROUND

A.

The '551 patent discloses and claims lacosamide, the active ingredient in Vimpat®. Lacosamide belongs to a class of compounds known as functionalized amino acids ("FAAs") having the following general structure:



The R, R_1, and R_3 positions are variables, representing the many different chemical groups that can be placed at each position resulting in a vast number of possible FAA compounds. These groups may be aromatic, heteroaromatic, or nonaromatic. Aromatic groups have a two-dimensional structure, typically organized into rings, such as benzene. Heteroaromatic groups, such as oxygen

or nitrogen, are also aromatic but contain at least one heteroatom, i.e., any atom other than carbon. Nonaromatic groups have three-dimensional structures and are not organized into rings.

As disclosed in the '551 patent, lacosamide is the R-enantiomer of N-benzyl-2-acetamido-3-methoxypropionamide. *See* '551 patent col. 3 ll. 65–67, col. 38 ll. 9–40. Enantiomers, a type of stereoisomers, are compounds that have the same chemical structure—i.e., the same atoms are connected to each other in the same way—but differ in orientation in three-dimensional space. These orientations are designated as either "R" or "S." A 50-50 mixture of two enantiomers is known as a "racemate" or "racemic mixture."

For its R, R_1, and R_3 positions, lacosamide has an unsubstituted benzyl at R, an unsubstituted methyl at R_1, and a nonaromatic methoxymethyl at R_3. The specification teaches that "the R stereoisomer is unexpectedly more potent than the corresponding S stereoisomer and the racemic mixture." *Id*. col. 23 ll. 31–33.

As of the March 1996 effective filing date of the '551 patent, no FAA had been approved as an anti-epileptic drug nor had any FAA advanced to clinical trials. Also, prior to the '551 patent, there was no public disclosure of pharmacological efficacy or safety data to support the use of any FAA as an anti-epileptic or anti-convulsant drug. To date, Vimpat® remains the only approved FAA for the treatment of epilepsy.

The development of FAAs as anticonvulsants began in the 1980s with the inventor of the '551 patent, Dr. Kohn. In 1985, Dr. Kohn first disclosed the anticonvulsant activity of a compound identified as "AAB," which provided the proof of concept for the use of FAAs as anti-epileptic drugs. In 1987, Dr. Kohn published a paper ("Kohn 1987"), which disclosed the anticonvulsant activity of different structural analogs of the parent AAB com-

pound. Kohn 1987 reported results of different groups at each of the different R positions of the general FAA chemical structure. Kohn 1987 showed that the placement of an aromatic group at the R_3 position showed improved anticonvulsant activity. Relevant to the issues here, the compounds studied in Kohn 1987 used an unsubstituted benzyl at R and an unsubstituted methyl at R_1. A substituted molecule replaces one of the hydrogen atoms of the parent molecule with another atom or structure.

In 1988, Dr. Kohn also reported data on the racemate and individual enantiomers of AAB and APB (a similar compound to AAB except that it contained a phenyl group at R_3). This data showed that the R enantiomers of AAB and APB were 10 times more potent than their S enantiomers. In 1990, this was confirmed by Dr. Kohn in a study ("Kohn 1990") in which he concluded "that the anticonvulsant activity [of AAB and APB] resided primarily in the *R* stereoisomers." J.A. 3240. In this study, Dr. Kohn also kept the R and R_1 positions constant as benzyl and methyl, respectively, while testing the effect of different substituents at the R_3 position.

Finally, in 1991, Dr. Kohn evaluated "compound 3l," a racemate ("Kohn 1991"). Compound 3l contained a methoxyamino group at R_3 and exhibited superior anticonvulsant properties. Notably, like lacosamide, compound 3l contained a nonaromatic group at R_3. Compound 3l had instability problems, however, which were of concern for pharmaceutical formulations.

In addition to Dr. Kohn's own publications, his research was disclosed in a 1987 thesis completed by his graduate student, Philippe LeGall ("LeGall"). LeGall focused on 15 new FAAs and their potential anticonvulsant activities. Relevant here, LeGall disclosed compound 107e. Compound 107e is the racemate of the lacosamide compound claimed in the '551 patent, meaning that instead of the isolated R-enantiomer (lacosamide) claimed

in the '551 patent, compound 107e is a mixture of both the R and S enantiomers. In the study, compound 107e belonged to a class of compounds called "polar analogues" of a parent compound 68a. Similar to lacosamide, LeGall replaced the R_3 position in compound 107e with a nonaromatic methoxymethyl group.

LeGall discloses and provides anticonvulsant efficacy data for all 15 compounds except for compound 107e. The class of compounds to which compound 107e belonged all contained nonaromatic groups, and as a class, these compounds showed little to no potency, resulting in ED_{50} values ranging from above 100 mg/kg to above 300 mg/kg.[1] By comparison, LeGall reported that other proven anticonvulsants had ED_{50} values of 14.0, 18.7, 20.1, and 61.0 mg/kg, and some other FAAs had ED_{50} values of 51.0 and 62.0 mg/kg. Despite not disclosing any pharmacological data for compound 107e, LeGall speculated that because of its structural similarities to compound 86b in the study, which had an ED_{50} of 62, compound 107e "may have good anticonvulsant activity." J.A. 5001, 5050. LeGall concluded that the most active compounds studied had heteroaromatic groups in the R_3 position whereas compound 107e had a nonaromatic group.

Dr. Kohn's research led to the filing of U.S. Patent No. 5,378,729 in 1991, which is prior art to the '551 patent. The '729 patent issued to Dr. Kohn in 1995 and discloses a genus of FAAs. Its specification explains that the claimed compounds exhibit "central nervous system (CNS) activity which are useful in the treatment of epi-

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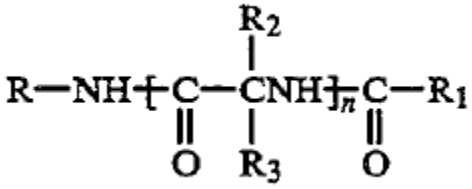
[1] Anticonvulsant activity, i.e., efficacy, is determined based on ED_{50}, which in LeGall represents the dose at which half of the animals tested did not have a convulsion. A lower ED_{50} value represents higher potency. Conversely, a higher ED_{50} value represents lower potency.

lepsy and other CNS disorders." '729 patent col. 1 ll. 30–33. The compounds of the '729 patent share the following general formula:



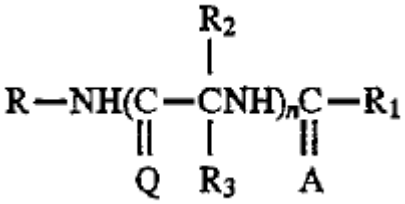
Id. at col. 1 ll. 37–43. The '729 patent lists many different compounds and groups that can be placed at each R position, which the district court found could form millions of possible compounds. Important to the issues here, the '729 patent teaches that "[t]he preferred values of R is aryl lower alkyl, especially benzyl" and "[t]he most preferred R_1 group is methyl." *Id.* at col. 5 ll. 17–19. For the R_3 position, the '729 patent lists a number of preferred heterocyclics and alkyl and lower alkoxy groups but does not list methoxymethyl. *Id.* at col. 6 ll. 13–31.

The '729 patent also discloses Table 1 containing pharmacological data for 54 FAAs. None of the compounds listed in Table 1 are lacosamide, compound 107e disclosed in LeGall, or any FAA compound with a methoxymethyl group at R_3. All of the compounds listed in Table 1 of the '729 patent have a methyl at R_1 and 49 of them have an unsubstituted benzyl at R, all with varying potency, ranging from 3.3 mg/kg to over 300 mg/kg. Of the top ten compounds with the most potency (i.e., lowest ED_{50}), eight had heteroaromatic groups at R_3 and two had nitrogen-based groups. Unlike lacosamide, none of the most potent compounds in Table 1 had a nonaromatic group at R_3. The four compounds with nonaromatic groups at R_3 showed moderate to weak potency.

U.S. Patent No. 5,654,301 is a continuation-in-part of the '729 patent and was filed in 1993. The '301 patent is

not prior art to the '551 patent. Appellants rely on the '301 patent only for their argument that the '551 patent is invalid for obviousness-type double patenting. Like its parent '729 patent, the '301 patent claims compounds of a general structure and recites several different groups that can be placed at the R and R_1 positions. The relevant claims at issue for purposes of double patenting are claims 39–47 of the '301 patent, which are reproduced below:

39. A compound of the formula



or the pharmaceutically acceptable salts thereof wherein

R is aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl or lower cycloalkyl lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;

R_1 is hydrogen or lower alkyl and R_1 is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;

A and Q are both O;

one of R_2 and R_3 is hydrogen and the other is lower alkyl which is substituted with an electron donating group or a electron withdrawing group and n is 1–4.

> 40. The compound according to claim 39 wherein one of R_2 and R_3 is hydrogen and the other is lower alkyl substituted with an electron donating group.
>
> 41. The compound according to claim 40 wherein one of R_2 and R_3 is alkyl substituted with an electron donating group wherein alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl or hexyl.
>
> 42. The compound according to claim 41 wherein one of R_2 and R_3 is methyl substituted with an electron donating group.
>
> 43. The compound according to claim 42 wherein the electron donating group is lower alkoxy.
>
> 44. The compound according to claim 43 wherein lower alkoxy is methoxy.
>
> 45. The compound according to any one of claims 39–44 wherein n is 1.
>
> 46. An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claim 37–42 and a pharmaceutical carrier therefor.
>
> 47. A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of any one of claims 39–44.

'301 patent col. 93 l. 3 – col. 94 l. 21.

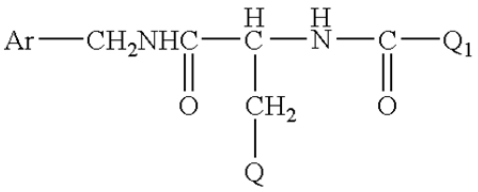
Independent claim 39 permits a large number of groups at R, R_1, and R_3, where each group can comprise a large number of substituents and can be either unsubstituted or substituted. Hence, the district court found that claim 39 could be thousands, if not millions, of possible group combinations. Although the specification does list

some of the most preferred groups, the list also contains generic categories of substituents, creating a large scope of possible groups. Although lacosamide is not specifically disclosed in the '301 patent, it is undisputed that lacosamide falls within the broad genus of claim 39 of the '301 patent.

Claim 45, which depends from claim 44, recites that R_3 is a methoxymethyl group, which is the substituent at R_3 in lacosamide and claimed in the '551 patent. Claim 45 does not recite the molecules at R and R_1, however. As stated above, claim 45 depends from claim 39, which recites a genus of groups that can be located at R and R_1.

B.

The asserted '551 patent discloses and claims lacosamide, a species of the genus disclosed in the '729 and '301 patents. The claims of the '551 patent at issue in this case are claims 9, 10, and 13, which are reproduced below along with the claims from which they depend.

> 1. A compound in the R configuration having the formula:
>
> R
>
> 
>
> wherein
>
> Ar is phenyl which is unsubstituted or substituted with at least one halo group;
>
> Q is lower alkoxy, and
>
> Q_1 is methyl.

> 8. The compound according to claim 1 which is (R) N-Benzyl 2-Acetamido-3-methoxypropionamide.
>
> 9. The compound according to claim 8 which contains at least 90% (w/w) R stereoisomer.
>
> 10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1–9 and a pharmaceutical carrier therefor.
>
> 11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1–9.
>
> 12. The method according to claim 11 wherein the animal is a mammal.
>
> 13. The method according to claim 12 wherein the mammal is a human.

Claim 9 recites the lacosamide compound with 90% or greater purity. For its R positions, lacosamide has an unsubstituted benzyl at R, an unsubstituted methyl at R_1, and a nonaromatic methoxymethyl group at R_3.[2]

C.

Before the district court, Appellants asserted that claims 9, 10, and 13 of the '551 patent are invalid for obviousness-type double patenting, alleging that they are

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[2] As shown in the formula of claim 1, the '551 patent uses "Ar", "Q", and "Q_1" to designate the location of substituent groups corresponding to the "R", "R_1", and "R_3" positions in the asserted art. For ease of comparison, we use the R, R_1, and R_3 designations in discussing corresponding substituents in lacosamide.

not patentably distinct from claims 44–47 of the '301 patent. Appellants argued that the compound described in the asserted claims of the '551 patent is merely an obvious species of the genus claimed in the '301 patent.

Following a bench trial, the district court found that the differences between claim 45 of the '301 patent and the asserted claims of the '551 patent rendered the claims patentably distinct. *See UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 530–36 (D. Del. 2016) ("*District Court Opinion*"). Relying on, among other things, the lack of supporting efficacy data investigating the impact of placing an unsubstituted benzyl and methyl at R and R_1, the district court concluded that it would not have been obvious to a person of ordinary skill in the art to make lacosamide by placing an unsubstituted benzyl at R or an unsubstituted methyl at R_1 in combination with methoxymethyl at R_3. *Id.*

Appellants also asserted that LeGall's disclosure of the racemic mixture compound 107e alone, or in combination with the '729 patent's disclosure of the genus of FAAs and Kohn 1991's disclosure of compound 3l rendered the asserted claims of the '551 patent obvious. *Id.* at 540. The district court applied a lead compound analysis and concluded that, as of March 1996, a skilled artisan would not have selected any FAA, let alone compound 107e (LeGall) or compound 3l (Kohn 1991), as a lead compound. *Id.* at 542–43. The district court based this finding on the complete lack of data to support that these compounds were effective and Kohn 1991's disclosure that nonaromatic compounds were generally disfavored. *Id.*

Finally, Appellants asserted that the '551 patent was anticipated by LeGall's disclosure of the racemic mixture of compound 107e, which necessarily discloses the enantiomers of that mixture, including the R enantiomer (lacosamide). *Id.* at 544. Relying on our decision in *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir.

2008), the district court held that LeGall does not anticipate the asserted claims because, while it discloses the racemic mixture compound 107e, it does not explicitly disclose the R-enantiomer or its characteristics. *Id.*

Appellants appeal the district court's fact findings and conclusions on double patenting, obviousness, and anticipation. Invalidity under any of these three theories must be established by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011). Thus, in order to prevail on appeal, Appellants must show that the district court clearly erred in failing to find clear and convincing evidence of invalidity. We have jurisdiction pursuant to 28 U.S.C. § 1295 (a)(1).

I

OBVIOUSNESS-TYPE DOUBLE PATENTING

We first address Appellants' argument that the district court erred in holding that the asserted claims of the '551 patent are not invalid for obviousness-type double patenting.

By statute, only a single patent may issue for the same invention. *See* 35 U.S.C. § 101 ("Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain *a* patent therefor . . . .") (emphasis added); *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997) ("[Section 101] thus permits only one patent to be obtained for a single invention, and the phrase 'same invention' refers to an invention drawn to substantially identical subject matter.").

Nonstatutory double patenting, however, is a judicially-created doctrine, which "prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent." *Id.* at 965. It "prevent[s] the extension of the term of a patent, even where an express statutory basis for the rejection is

missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012) (quoting *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985)) (alteration in original).

The obviousness-type double patenting analysis involves two steps: "First, the court 'construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences.' Second, the court 'determines whether those differences render the claims patentably distinct.'" *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (quoting *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010)). The second part of this analysis is analogous to the obviousness inquiry under 35 U.S.C. § 103 in the sense that if an earlier claim renders obvious or anticipates a later claim, the later claim is not patentably distinct and is thus invalid for obviousness-type double patenting. *Id.* at 1378–79. In chemical cases, the double patenting inquiry is not whether a person of ordinary skill in the art would select the earlier compound as a lead compound, but rather whether the later compound would have been an obvious or anticipated modification of the earlier compound. *Otsuka*, 678 F.3d at 1297. Unlike in an obviousness analysis, the underlying patent in the double patenting analysis need not be prior art to the later claim. *See id.*

We review the district court's ultimate legal conclusion of obviousness-type double patenting de novo and review its underlying fact findings for clear error. *AbbVie*, 764 F.3d at 1372. "A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made." *Otsuka*, 678 F.3d at 1290.

A.

Before the district court, the parties disagreed as to the correct legal test for obviousness-type double patenting. Appellants argued that only the differences between claims 44–47 of the '301 patent and claims 9, 10, and 13 of the asserted '551 patent are to be considered. UCB argued that the claims as a whole should be considered, including the commonalities between the claims and whether a person of ordinary skill in the art would have been motivated to also modify any of those commonalities when modifying the differences between the claims. Specifically, UCB argued that the court should consider whether the commonly shared R_3 methoxymethyl group in the '301 and '551 patents would have been substituted with another substituent when considering which substituents to place at the R and R_1 positions. The district court adopted Appellants' theory, but held that the asserted claims are not invalid for obviousness-type double patenting under either theory.

We agree with Appellants that the obviousness-type double patenting inquiry requires consideration of the differences between the claims in the reference '301 patent and the '551 patent. As we stated above, the focus of the double patenting analysis entails determining the *differences* between the compounds claimed in the reference and asserted patents and then "determin[ing] whether those *differences* render the claims patentably distinct." *AbbVie*, 764 F.3d at 1374 (emphasis added). In this case, both claims recite a methoxymethyl group at R_3. Thus, the double patenting analysis requires determining whether the claims' differences, i.e., unsubstituted benzyl and methyl at R and R_1, would have been obvious to one of skill in the art.

At the same time, as we explained in *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368 (Fed. Cir. 2012), "those differences [between the claims] cannot be

considered in isolation—the claims must be considered as a whole." *Id.* at 1377. Indeed, "just as § 103(a) requires asking whether the claimed subject matter 'as a whole' would have been obvious to one of skill in the art, so too must the subject matter of the [asserted claims] be considered 'as a whole' to determine whether the [reference patent] would have made those claims obvious for purposes of obviousness-type double patenting." *Id.* at 1377 (quoting *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278 (Fed. Cir. 1992)). Thus, the district court did not err by focusing its double patenting analysis on the claims' differences, as well as the claims as a whole.

B.

We turn next to the district court's double patenting analysis. Appellants assert that claims 9, 10, and 13 of the '551 patent are not patentably distinct from claims 44–47 of the '301 patent and are thus invalid for obviousness-type double patenting. Because these claims only have a common methoxymethyl group at the R_3 position, the question before us is whether a person of ordinary skill in the art, starting with claim 45 of the '301 patent, would have been motivated to place an unsubstituted benzyl at R and an unsubstituted methyl at R_1 in combination with the methoxymethyl group at R_3 with a reasonable expectation of success. We acknowledge that this is a close case, but because we discern no clear error in the district court's underlying fact finding that there would have been no reasonable expectation of success in placing an unsubstituted benzyl and methyl in the claimed combination, we agree with the district court that the asserted claims of the '551 patent are patentably distinct from the '301 patent.

The differences between claim 45 of the '301 patent and claim 9 of the '551 patent are that: (1) unlike claim 45 of the '301 patent, claim 9 of the '551 patent requires the

R-enantiomer with 90% or greater purity; (2) while claim 45 of the '301 patent allows for any substituted or unsubstituted "aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl, or lower cycloalkyl lower alkyl," at R, the '551 patent requires an unsubstituted benzyl at R; and (3) while claim 45 of the '301 patent allows R_1 to be a substituted or unsubstituted hydrogen or lower alkyl with at least one electron withdrawing or donating group, the '551 patent requires R_1 to be an unsubstituted methyl. *Compare* '301 patent col. 93 l. 3 – col. 94 l. 15, *with* '557 patent col. 38 ll. 8–39.

Focusing on these differences, the district court found that as of the priority date, a person of ordinary skill in the art would not have had a reasonable expectation that placing an unsubstituted benzyl at R or an unsubstituted methyl at R_1 with a methoxymethyl group at R_3 would have yielded an efficacious anticonvulsant FAA. The district court recognized that in the context of drug development, "'predictability is a vital consideration in the obviousness analysis,' including obviousness-type double patenting." *District Court Opinion*, 201 F. Supp. 3d at 531 (quoting *Otsuka*, 678 F.3d at 1298). We agree that proving that a claim is invalid for obviousness-type double patenting "requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound *with a reasonable expectation of success*." *Eli Lilly*, 689 F.3d at 1378 (emphasis added) (quoting *Otsuka*, 678 F.3d at 1297); *see also Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). Here, the district court, relying on the prior art and expert evidence, found no reasonable expectation of success. That is a fact finding that we review for clear error following a bench trial. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). We

hold that the district court's fact finding of no reasonable expectation of success is sufficiently supported by the evidence presented at trial and is not clearly erroneous. We are not left with "the definite and firm conviction that a mistake has been made." *Otsuka*, 678 F.3d at 1290. We are satisfied that the district court did not clearly err.

As the district court found, by the priority date, there was little to no data from which a person of ordinary skill in the art could have formed reasonable expectations about the effect of placing an unsubstituted benzyl at R and an unsubstituted methyl at R_1 in combination with a methoxymethyl group at R_3. Out of all the work performed by Dr. Kohn and others, not a single reference disclosed any anticonvulsant data for any compound comprising a methoxymethyl group at R_3 let alone lacosamide. And most of the FAAs studied prior to the priority date only experimented with modifying the substituents at the R_3 position while holding constant the unsubstituted benzyls at R and unsubstituted methyls at R_1. *See District Court Opinion*, 201 F. Supp. 3d at 504, 531. Thus, the district court reasonably found that the prior art data studying FAAs did not provide sufficient insight into the effectiveness of placing benzyl and methyl at those positions relative to other substituents that could have been placed at the R and R_1 positions. *Id.* at 531. This finding was supported by Dr. Roush, who explained that the prior art was silent as to what role benzyl and methyl played in the activity of the FAAs studied in the prior art. The district court buttressed its finding with the data disclosed in the '729 patent showing that compounds with benzyl and methyl at R and R_1 with different R_3 groups had a varying range of effectiveness. *Id.* (citing '729 patent at Table 1). Thus, the trial evidence supports the district court's finding that there was no prior art that would have provided a person of ordinary skill reason to believe that unsubstituted benzyl and methyl would have been successful with a methoxymethyl group. Because

these findings are supported by expert testimony and the record, we conclude that they are not clearly erroneous. *See Eli Lilly*, 689 F.3d at 1378 (affirming the district court's obviousness-type double patenting determination based on its fact finding of no reasonable expectation of success); *see also Amgen*, 580 F.3d at 1362–63 (affirming the district court's judgment as a matter of law that the asserted claims were not invalid for obviousness-type double patenting where the trial evidence supported a finding of no reasonable expectation of success).

The dissent states that the district court erred by not considering LeGall in its primary double-patenting analysis. Dissent Op. at 10. We disagree with the dissent's characterization of the district court's opinion. The district court's fact findings regarding LeGall spanned thirteen paragraphs. *District Court Opinion*, 201 F. Supp. 3d at 508–09. In what the dissent characterizes as the district court's "primary" double patenting analysis, the district court also relied on Dr. Roush's expert testimony specifically discussing LeGall. That portion of Dr. Roush's testimony explained that because R and R_1 were held constant in the compounds studied in LeGall, one could not tell what role benzyl and methyl had in the activity of the compounds disclosed. *Id.* at 531–32 (citing Roush Tr. 681–82). Moreover, in its analysis under UCB's proffered alternative double patenting test, the district court rejected Appellants' argument that the claims of the '551 patent are indistinguishable from the discussion of compound 107e in LeGall. *Id.* at 535–536. The district court explained that LeGall's reference to compound 107e lacks any data or discussion that would have motivated a person of ordinary skill in the art to use a nonaromatic compound such as a methoxymethyl at R_3. *Id.* at 535–36. Thus, far from ignoring LeGall, as the dissent suggests, the district court squarely considered and addressed LeGall in its double patenting analysis.

The "presence or absence of a reasonable expectation of success is . . . a question of fact," *Par Pharm.*, 773 F.3d at 1196, and after considering the prior art and expert testimony presented at trial, the district court found no reasonable expectation of success. We cannot reweigh the evidence, make credibility findings, or find facts. The district court, relying on LeGall and crediting expert testimony, made extensive fact findings regarding the LeGall Thesis. As the district court found, LeGall discloses no data whatsoever for compound 107e or any compound with a methoxymethyl group at the R_3 position. *District Court Opinion*, 201 F. Supp. 3d at 508. In fact, the data LeGall did disclose for similar polar analogue compounds showed little to no potency. *Id.* The district court acknowledged that LeGall speculated that compound 107e "may" have good anticonvulsant activity based on its structural similarity to another compound. *Id.* at 509. Dr. Roush testified, however, that a person of ordinary skill in the art looking to LeGall would have had no interest in pursuing that compound and that a person of ordinary skill would not have had a reasonable likelihood of success in pursuing an FAA with a methoxymethyl group at R_3 as an anticonvulsant drug. The district court did not clearly err in crediting this testimony.

Appellants argue that the '729 patent's disclosure that benzyl is "especially preferred" and that methyl is "most preferred" for this genus of compounds itself renders the asserted claims obvious. We disagree. The '729 patent describes other possible variants as "preferred compounds," "preferred embodiments," or preferred groups for each position, indicating a large variety of possible compounds. *See* '729 patent cols. 5–10. As we held in *Eli Lilly*, complex compounds like the FAAs disclosed in the '729 patent provide for many opportunities for modification. As the district court found here, there was no indication that out of the millions of possible choices, an unsubstituted benzyl at R and an unsubstituted methyl at

R_1 would have been selected in combination with a methoxymethyl group at R_3 to arrive at lacosamide. *See Eli Lilly*, 689 F.3d at 1378. Because the district court did not clearly err in finding that there was no motivation to modify the '301 patent's claims to arrive at lacosamide or a reasonable expectation of success in doing so, we uphold the district court's conclusion that claims 9, 10, and 13 of the '551 patent are not invalid for obviousness-type double patenting.

Appellants also argue that the district court erred by requiring them to prove that benzyl and methyl were the "best" substituents from which to choose. This is a mischaracterization of the district court's decision. The district court merely quoted Dr. Roush's expert testimony that in the prior art "[t]here is no data to say whether benzyl is best or something else would be the best." *District Court Opinion*, 201 F. Supp. 3d at 532 (quoting Dr. Roush's trial testimony). In context, however, it is clear that the district court merely relied on this testimony to support its finding that the prior art data demonstrated a range of effectiveness such that the effectiveness of prior art compounds could not be attributed to benzyl. We do not read the district court's opinion to have required Appellants to prove that benzyl was the best selection.

Appellants further argue that lacosamide falls within the broad scope of claim 45 of the '301 patent, and is thus presumed enabled. Appellants argue that this presumption establishes a reasonable expectation of success as a matter of law. We disagree. Appellants do not cite any authority for the proposition that the presumption of an enabled genus of compounds precludes the district court from finding that there was no reasonable expectation of success of creating a species falling within that genus. Moreover, such a result would have a chilling effect on genus claiming in the chemical arts as there would be

double patenting in all chemical compound cases where a parent patent claims a genus.

Because we hold that the district court's finding regarding no reasonable expectation of success was not clearly erroneous, we are compelled to affirm the district court's conclusion that the asserted claims of the '551 patent are not invalid for obviousness-type double patenting.[3] Also, for this reason, we need not reach the district court's findings regarding secondary considerations and Appellants' argument that the district court failed to find a nexus between the asserted secondary considerations and lacosamide.

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[3] We note that the USPTO instituted an ex parte reexamination and inter partes review of the '551 patent. While this appeal was pending, the USPTO issued its final written decision in the inter partes review, concluding that the petitioner failed to demonstrate that claims 1–13 of the '551 patent would have been obvious over certain prior art, including Kohn 1991 and the '729 patent. *See Argentum Pharm. LLC v. Research Corp. Techs., Inc.*, IPR2016-00204, 2017 WL 1096590 (PTAB Mar. 22, 2017). The USPTO also recently concluded its reexamination proceeding and confirmed that claims 9, 10, and 13 are not unpatentable for obviousness-type double patenting over the '301 patent, Kohn 1991, and the '729 patent.

The dissent contends that the USPTO did not consider the LeGall Thesis in its reexamination. Dissent Op. 11 n.3. We note, however, that the USPTO did consider LeGall and determined that LeGall was not prior art because it was not publically accessible before the priority date. *See Argentum Pharm.*, IPR2016-00204, Paper No. 19 at 12 (PTAB May 23, 2016); *District Court Opinion*, 201 F.3d at 523.

II

OBVIOUSNESS

Next, we address obviousness. We review the district court's ultimate determination that the asserted claims of the '551 patent would not have been obvious de novo and review its underlying fact findings for clear error. *Otsuka*, 678 F.3d at 1290.

Appellants assert that claim 9 of the '551 patent would have been obvious based on LeGall's disclosure of compound 107e as a racemic mixture. Appellants further assert that LeGall alone, or in combination with the '729 patent and Kohn 1991, render claim 9 obvious. Applying a lead compound analysis, the district court concluded that a person of ordinary skill in the art would not have selected any FAA, let alone the compounds disclosed in LeGall and Kohn 1991, as lead compounds in the lead compound analysis. Relying on our decision in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007), Appellants argue that the district court erred by using a lead compound analysis because this case merely involves purification (not structural modification) of a known compound. We disagree.

"In cases involving the patentability of a new chemical compound, *prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds." *Otsuka*, 678 F.3d at 1291. We have held that to demonstrate that a new chemical compound would have been prima facie obvious over a particular prior art compound based on a lead compound analysis, the court follows a two-part inquiry. First, "the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* Second, the court determines "whether

the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* at 1292. A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Id.* at 1291 (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

Appellants argue, however, that this court has never required a lead compound analysis in chemical purification cases. Appellants further cite *Aventis*, where we addressed whether the pure 5(S) stereoisomer of ramipril, in a form substantially free of other isomers, would have been obvious over the prior art disclosing its racemic mixture. *Aventis*, 499 F.3d at 1300. There, we held that the "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Id.* at 1301. We stated further that where a claimed composition is a purified form of a mixture that existed in the prior art and "if the prior art would provide a person of ordinary skill in the art with *reason to believe* [it had desirable properties], the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified." *Id.* (emphasis added).

Appellants argue that because *Aventis* did not apply a lead compound analysis, no such analysis is required in this case. We agree. A lead compound analysis is not required in analyzing obviousness of a chemical compound when, in the inventing process, there was no lead compound. An inventor may not have tried to improve a compound known to have desirable properties. *See, e.g.*, *Otsuka*, 678 F.3d at 1291 ("New compounds may be

created from theoretical considerations rather than from attempts to improve on prior art compounds."). And an obviousness rejection by an examiner, or a challenge in court, may be based on the closest prior art, which may not have been a lead compound that the inventor had in mind.

We are not aware of any authority holding that a lead compound analysis is or is not required in cases involving purifying mixtures. *Aventis* simply required proving that a person of ordinary skill in the art would have been motivated to purify a mixture of compounds based on some known desirable property. *See Aventis*, 499 F.3d at 1301 (holding that "if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture").

In any event, even if a lead compound analysis is required here, we hold that the district court did not clearly err in finding that a person of ordinary skill in the art would not have selected compound 107e as a lead compound. As we have stated, the district court found that LeGall contains no data that would have led a person of ordinary skill in the art to select compound 107e among the many compounds disclosed in LeGall as a lead compound. The district court further found that the data provided in LeGall for that class of compounds showed little potency. Dr. Roush also testified that based on LeGall's disclosure, a person of ordinary skill in the art would not have been motivated to develop compound 107e. We see no clear error in the district court's factual findings based on such evidence.

We also see no clear error in the district court's fact finding that a person of ordinary skill in the art would not

have selected Kohn's 1991 compound 3l as a lead compound. Kohn's compound 3l is also a nonaromatic compound like compound 107e, and Dr. Roush testified that nonaromatic compounds were not of interest as of 1996. The district court's fact finding was also supported by additional expert testimony, which established that compound 3l had properties making it less stable and that medicinal chemists would have avoided investigating its potential use in a pharmaceutical product.

Based on this evidence, we see no clear error in the district court's fact findings and sustain its conclusion that the asserted claims of the '551 patent would not have been obvious.

III

ANTICIPATION

Finally, we address anticipation. Only Appellants Accord Healthcare, Inc. and Intas Pharmaceuticals Ltd. (the "Accord Appellants") raise anticipation on appeal. They argue that because LeGall discloses the chemical structure of the racemic compound 107e, it necessarily discloses the R-enantiomer (lacosamide) recited in claim 9 of the '551 patent.

Relying principally on our decision in *Sanofi*, 550 F.3d at 1084, the district court found claim 9 of the '551 patent not anticipated, concluding that LeGall discloses neither the R-enantiomer of compound 107e nor any of its characteristics. Anticipation is also a question of fact, which we review for clear error. *See Sanofi*, 550 F.3d at 1082.

We hold that the district court did not clearly err in finding that LeGall does not anticipate claim 9 of the '551 patent. As the district court recognized, we have held that "[t]he knowledge that enantiomers may be separated is not 'anticipation' of a specific enantiomer that has not been separated, identified, and characterized." *Id.* at 1084. We have also stated that "the novelty

of an optical isomer is not negated by the prior art disclosure of its racemate." *In re May*, 574 F.2d 1082, 1090 (CCPA 1978). Although LeGall discloses the chemical structure of the racemic compound 107e, it does not disclose its separation into individual enantiomers nor does it disclose any pharmaceutical data of the R enantiomer recited in claim 9 of the '551 patent. As the Accord Appellants point out, LeGall expressly stated that he "prepare[d] the racemic amino acid derivatives rather than the individual enantiomers," and that "[i]n each case, the functionalized amino acid racemate was prepared *rather than* the individual enantiomers." J.A. 4942; J.A. 5030 (emphasis added). Thus, we discern no clear error in the district court's finding of no anticipation.

CONCLUSION

We have considered the parties' remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm the district court's judgment that the asserted claims of the '551 patent are not anticipated, obvious, or invalid for obviousness-type double patenting.

AFFIRMED

COSTS

Costs to Appellees.

United States Court of Appeals for the Federal Circuit

UCB, INC., UCB BIOPHARMA SPRL, RESEARCH CORPORATION TECHNOLOGIES, INC., HARRIS FRC CORPORATION,
Plaintiffs-Appellees

v.

ACCORD HEALTHCARE, INC., INTAS PHARMACEUTICALS LTD., MYLAN PHARMACEUTICALS INC., MYLAN INC., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LIMITED, AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA, INC., BRECKENRIDGE PHARMACEUTICAL, INC., SUN PHARMA GLOBAL FZE, SUN PHARMACEUTICAL INDUSTRIES, LTD., WATSON LABORATORIES, INC. - FLORIDA, NKA ACTAVIS LABORATORIES FL, INC., WATSON PHARMA, INC., NKA ACTAVIS PHARMA, INC., MSN LABORATORIES PVT. LTD., ALEMBIC PHARMACEUTICALS LTD., APOTEX CORP., APOTEX INC.,
Defendants-Appellants

ALEMBIC PHARMA LIMITED, ACTAVIS, INC., NKA ALLERGAN FINANCE, LLC,
Defendants

2016-2610, 2016-2683, 2016-2685, 2016-2698, 2016-2710, 2017-1001

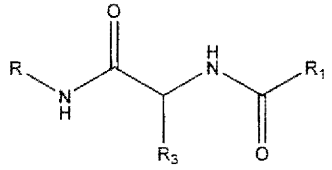
Appeals from the United States District Court for the District of Delaware in Nos. 1:13-cv-01206-LPS, 1:13-cv-01207-LPS, 1:13-cv-01208-LPS, 1:13-cv-01209-LPS, 1:13-cv-01210-LPS, 1:13-cv-01211-LPS, 1:13-cv-01212-LPS, 1:13-cv-01213-LPS, 1:13-cv-01214-LPS, 1:13-cv-01215-LPS, 1:13-cv-01216-LPS, 1:13-cv-01218-LPS, 1:13-cv-01219-LPS, 1:13-cv-01220-LPS, 1:14-cv-00834-LPS, Chief Judge Leonard P. Stark.

PROST, *Chief Judge*, dissenting.

Because I believe that the district court clearly erred when it found there would not have been a reasonable expectation of success in selecting unsubstituted benzyl for R and unsubstituted methyl for R_1, I disagree with the majority that the asserted claims of the '551 patent are patentably distinct from the reference patent claims. I therefore respectfully dissent.

I

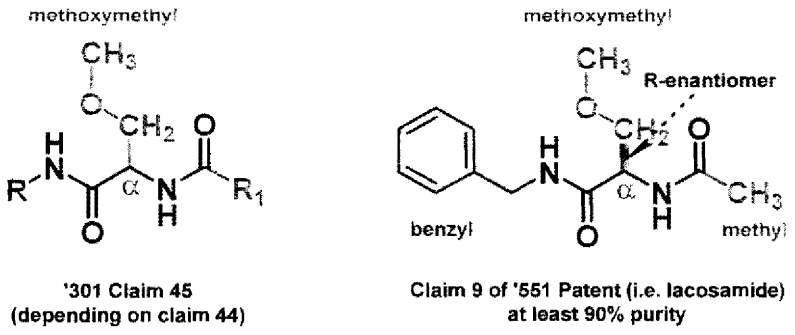
The parties focused their double-patenting presentations to the district court on whether claim 9 of the '551 patent (asserted claim) is invalid for obviousness-type double patenting over claims 44 and 45 of the '301 patent (reference claims). *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 528 (D. Del. 2016) ("*District Court Opinion*"). Reference claim 45 covers a genus of compounds known as functionalized amino acids ("FAA") having the following general structure of the formula:



Id. at 512.

In this formula, R, R_1, and R_3 are variables, meaning that different elements or compounds can be placed at each of these three sites. When claim 45 is limited to depending from claim 44, the R_3 group is defined as methoxymethyl. *Id.* The definition of R includes unsubstituted benzyl and the definition of R_1 includes unsubstituted methyl. *Id.* at 516.

Lacosamide is one species of this genus. *Id.* at 512. Lacosamide has a methoxymethyl group at R_3, *id.* at 503, unsubstituted benzyl at R, and unsubstituted methyl at R_1, *id.* at 530. Asserted claim 9 claims lacosamide. *Id.* at 502. It "fills in the variables of the claim 44/45 equation, so as to narrow the genus of claims 44 and 45 to the species of a single compound, lacosamide." *Id.* at 515. In other words, claim 9 "selects substituents for R (benzyl) and R_1 (methyl) that fall within the scope of claims 44/45." *Id.* at 516. These differences are depicted below:



Id.

II

With respect to the district court's double-patenting analysis, much like the majority, I would leave undis-

turbed nearly all of the district court's findings. To the extent, however, the district court found that a person of ordinary skill in the art would not have had a reasonable expectation of success in selecting an unsubstituted benzyl for R and an unsubstituted methyl for R_1, it clearly erred.

The obviousness-type double-patenting analysis involves determining whether the differences between the claims in the reference patent and the claims in the asserted patent render the claims patentably distinct. *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014). This part of the obviousness-type double-patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009). An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art. *Id.* at 1362. This is a question of fact, which we review for clear error following a bench trial. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014). "A factual finding is clearly erroneous if, despite some supporting evidence, 'the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007) (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)).

A

The district court found that a person of ordinary skill in the art would not have had a reasonable expectation of success in selecting an unsubstituted benzyl for R and an unsubstituted methyl for R_1. It based this finding largely on a lack of data showing the effect of placing these substituents at their respective positions. *District Court Opinion*, 201 F. Supp. 3d at 532. The court stated that

"given how unpredictable drug development is, and the high likelihood that any formulation will prove unsuccessful, the lack of data strongly contributes to the [c]ourt's finding." *Id.* (citations omitted).

Although we cannot reject the district court's finding that drug development is unpredictable, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364. In reality, "there were many tests conducted on FAAs with benzyl at R and methyl at R_1." *District Court Opinion*, 201 F. Supp. 3d at 531. And indeed, as the district court found, 75% of Dr. Kohn's experimental compounds contained benzyl at R and methyl at R_1, and most of these were unsubstituted. *Id.* As I detail below, the district court's findings of fact as to the prior art provided ample evidence showing that a person of skill in the art would have had a reasonable expectation of success in creating an FAA with anticonvulsant activity by selecting an unsubstituted benzyl for R and an unsubstituted methyl for R_1. While it is true that there may be some evidence supporting the district court's view, given the overwhelming evidence to the contrary, I am "left with the definite and firm conviction that a mistake has been committed." *Pfizer*, 480 F.3d at 1359 (quoting *U.S. Gypsum*, 333 U.S. at 395).

In 1985, Dr. Kohn published the anticonvulsant activity of his first FAA compound, AAB. *District Court Opinion*, 201 F. Supp. 3d at 505. AAB contained a benzyl at R, and a methyl at R_1. *Id.* According to Dr. Kohn, AAB demonstrated the "proof of concept" for FAAs. *Id.* Two years later, Dr. Kohn reported on the anticonvulsant activity of sixteen structural analogues of AAB. *Id.* The paper used unsubstituted benzyl at R and unsubstituted methyl at R_1 as a "reference point," and considered five possible modifications of the unsubstituted benzyl at R

and three modifications of the unsubstituted methyl at R_1. *Id.* at 506.

In Dr. Kohn's 1990 paper, he also kept "R_1 constant and R constant" as methyl and benzyl, respectively. *Id.* at 509. He reported that the most potent compound was 2g, which had benzyl at R and methyl at R_1. *Id.* Unlike lacosamide, 2g had an aromatic 2-furanyl structure at R_3. *Id.* Compound 2g "was found to be significantly more potent than APB [described in a 1988 paper], and at the time in 1990 when this paper was published this was the most potent compound in the FAA family." *Id.*

Dr. Kohn then summarized his prior FAA work in a 1991 paper. *Id.* All twenty-six compounds reported in that paper had unsubstituted benzyl at R and unsubstituted methyl at R_1 with different compounds at the R_3 group. *Id.* at 506–07. Dr. Kohn explained in this paper that "you get potent protection if you have a benzyl on one end [at R] and a methyl on the other [at R_1]." *Id.* at 506. The 1991 paper also identified compound 3l, which possessed "the best activity to date" for any FAA racemate. *Id.* at 507. Compound 3l had unsubstituted benzyl at R and unsubstituted methyl at R_1 with methoxyamino at R_3. *Id.*

Dr. Kohn continued to explore and publish data for many other compounds with different groups at R_3. *Id.* at 506. In a 1993 paper, Dr. Kohn published the results of an experiment investigating modifications of the 2-furanyl group at R_3 with other heteroaromatic groups. Once again, the "starting point" was benzyl at R and methyl at R_1. *Id.*

On this record it is clear that Dr. Kohn's extensive study of FAAs provides copious amounts of information from which a person of ordinary skill would form a reasonable expectation that the selection of an unsubstituted benzyl for R and an unsubstituted methyl for R_1 would lead to the successful creation of an FAA with anticonvul-

sant activity. Indeed, Dr. Kohn described unsubstituted benzyl for R and an unsubstituted methyl for R_1 as the "starting point" or "reference point" for nearly every experiment he published. Dr. Kohn himself explained in his 1991 paper (where all 26 compounds reported had unsubstituted benzyl at R and unsubstituted methyl at R_1) that "you get potent protection if you have a benzyl on one end [at R] and a methyl on the other [at R_1]."[1] *Id.* at 506.

The district court recognized that "there were many tests conducted on FAAs with benzyl at R and methyl at R_1." *Id.* at 531. But it dismissed the resulting data because "[m]ost of these tests kept the structures at R and R_1 constant in order to assess changes made at the R_3 position" and so "any changes (whether increases or decreases) observed in anticonvulsant behavior and/or neurotoxicity would be attributed to the structure at R_3 rather than to the benzyl at R or the methyl at R_1." *Id.* In dismissing the data resulting from these tests, the court clearly erred. Although the experiments may have been designed to assess changes made at the R_3 position, by using unsubstituted benzyl for R and an unsubstituted methyl for R_1 as the "starting point" or "reference point" for these tests, the prior art showed, without question, that those substituents would work at those positions. And not only did the prior art show that unsubstituted benzyl works at R and that unsubstituted methyl works

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[1] Additionally, I find it significant that unsubstituted benzyl and unsubstituted methyl were most often used together at R and R_1, respectively. In other words, they are presented throughout the prior art as a pair. Thus, a person of ordinary skill would not need to independently select benzyl for R and then separately select methyl for R_1, as the district court posited.

at R_1, the prior art showed that FAAs with these substituents so positioned demonstrate anticonvulsant activity.

It was clear error for the district court to require testing to provide "insight into the effectiveness of benzyl and methyl *relative* to other structures that could be placed at R and R_1." *Id.* Where the prior art teaches that the selected substituent will work, even when it is selected from thousands of compounds, an inability to predict how any one substituent will work in the composition and a need for testing will not render that selection nonobvious. *See In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) ("Although [the inventor] declared that it cannot be predicted how any candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work."); *Pfizer*, 480 F.3d at 1364.

Further, if, as the district court found, all the testing focused on R_3 and a person of ordinary skill would attribute anticonvulsant behavior to R_3, once R_3 was fixed in the '301 reference patent genus, plugging in unsubstituted benzyl at R and unsubstituted methyl at R_1 (which had remained largely constant throughout the prior art testing) would be viewed simply as a trivial selection. Indeed, because the '301 claim is a genus claim, with only two variables R and R_1, a person of ordinary skill would know to select a substituent for each variable. A person of ordinary skill would certainly have a reasonable expectation of success when deciding which substituents to select if she copied the "75% of Dr. Kohn's compounds [which] contained benzyl at R and methyl at R_1, and most of these were unsubstituted." *District Court Opinion*, 201 F. Supp. 3d at 531.

In dismissing the data resulting from the many tests conducted with unsubstituted benzyl at R and unsubstituted methyl at R_1 and in relying so heavily on what it saw as a lack of data, the district court clearly erred.

B

The district court also erred when it found that the limited data that did exist at the time would not have led a person of ordinary skill to place an unsubstituted benzyl at R or an unsubstituted methyl at R_1. *Id.* at 532. Indeed, the data that were available showed that unsubstituted benzyl at R and an unsubstituted methyl at R_1 were comparable to, if not better than, any other substituents tested.

For example, Dr. Kohn, in his 1985 paper, used unsubstituted benzyl at R and unsubstituted methyl at R_1 as a "reference point," and considered five possible modifications of the unsubstituted benzyl at R and three modifications of the unsubstituted methyl at R_1. *Id.* at 506. With respect to the R position, only one of the five R modifications showed activity comparable to unsubstituted benzyl at R. *Id.* The others showed decreased activity. *Id.* For the R_1 position, each of the three modifications *decreased* anticonvulsant activity when compared to unsubstituted methyl. *Id.*

Dr. Kohn also considered, in his 1990 paper, the effect of replacing an unsubstituted benzyl at R and found that placing a fluoro-substituted benzyl at R yielded only a comparable anticonvulsant effect. *Id.* Fluoro-substituted benzyl at R did, however, provide a "far superior" protective index. *Id.* Yet, this must be balanced against Dr. Kohn's 1991 paper (where all 26 compounds reported had unsubstituted benzyl at R and unsubstituted methyl at R_1) explaining that "you get *potent protection* if you have a benzyl on one end [at R] and a methyl on the other [at R_1]." *Id.* (emphasis added).

Thus, the data that were available showed that unsubstituted benzyl at R and an unsubstituted methyl at R_1 were comparable, if not better, than any other substituents that were tested with respect to anticonvulsant activity. Despite the test that demonstrated fluoro-

substituted benzyl's "far superior" protective index, these tests provide strong evidence that a person of ordinary skill would have a reasonable expectation of success in selecting these substituents in order to create an FAA having an anticonvulsant effect. This is especially so with respect to selecting unsubstituted methyl for R_1 as it was the most successful substituent tested. Although these data might have shown that there was no guarantee that unsubstituted benzyl at R would provide the greatest protective index as compared to other possible substituents, "only a reasonable expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d at 1364.

Accordingly, the district court clearly erred when it found that the data specific to R and R_1 that did exist at the time would not have led a person of ordinary skill to place an unsubstituted benzyl at R or an unsubstituted methyl at R_1.

C

Finally, and perhaps most importantly, the district court erred when it did not consider the LeGall Thesis in its primary double-patenting analysis.[2] *See District Court Opinion*, 201 F. Supp. 3d at 530–35. For purposes of this

[2] The majority takes issue with my characterization of the district court's opinion on this point. I do not mean to imply that the district court did not make any findings of fact as to the LeGall Thesis. The court certainly did in its introductory "Findings of Fact" section. *District Court Opinion*, 201 F. Supp. 3d at 508–09. But I maintain that the district court determined in its primary double-patenting analysis that there was no reasonable expectation of success without considering the teachings of this reference. A citation to two pages of Dr. Roush's trial testimony, stripped of any reference to the LeGall Thesis, cannot cure this deficiency.

litigation, the parties agree that the LeGall Thesis constitutes a "printed publication" within the meaning of 35 U.S.C. § 102(b).[3] *Id.* at 508.

Importantly, the LeGall Thesis disclosed compound 107e which, exactly like lacosamide, has a methoxymethyl group at R_3, an unsubstituted benzyl at R, and an unsubstituted methyl at R_1. *Id.* Compound 107e is identical to lacosamide except that it contains both the R- and S-enantiomers in a mixture, rather than just the R-enantiomer. *Id.* Although he did not have data for compound 107e, LeGall hypothesized that structural similarities between compound 107e and another compound for which he did have data, 86b, suggested that compound 107e "may have good anticonvulsant activity." *Id.* at 509.

The LeGall Thesis is highly relevant to the obviousness analysis. For example, the majority concluded that "the trial evidence supports the district court's finding that there was no prior art that would have provided a person of ordinary skill reason to believe that unsubstituted benzyl and methyl would have been successful with a methoxymethyl group." Majority Op. 20. Not so. The thesis disclosed a compound having, like lacosamide, a methoxymethyl group at R_3 together with an unsubstituted benzyl at R and an unsubstituted methyl at R_1 and it provided a reasonable hypothesis, based on structural similarities to other compounds, that this compound "may have good anticonvulsant activity." *District Court Opinion*, 201 F. Supp. 3d at 509. Again, "only a reasonable

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[3] The majority, in support of its conclusion, notes that the USPTO instituted an ex parte reexamination of the '551 patent and concluded that claims 9, 10, and 13 were not unpatentable for obviousness-type double patenting over the '301 patent, Kohn 1991, and the '729 patent. Crucially, however, the USPTO did not institute trial as to grounds relying on the LeGall Thesis.

expectation of success, not a guarantee, is needed." *Pfizer*, 480 F.3d at 1364. Thus, to the extent the district court found that there was no indication in the prior art that benzyl and methyl would have been successful with a methoxymethyl group, it clearly erred.

Certainly this evidence, especially when considered along with the other evidence before the district court, would have strongly contributed to a person of ordinary skill in the art's having a reasonable expectation of success in creating an FAA with anticonvulsant activity by selecting an unsubstituted benzyl for R and an unsubstituted methyl for R_1.

* * *

Considering all of the evidence, despite some supporting evidence identified by the district court, I am "left with the definite and firm conviction" that the district court made a mistake. *Id.* at 1359 (quoting *U.S. Gypsum*, 333 U.S. at 395). Thus, I conclude that the district court clearly erred in finding that one skilled in the art would not have had a reasonable expectation of success with unsubstituted benzyl at R and unsubstituted methyl at R_1. Taking the district court's clear error together with the remainder of its fact findings, I would have concluded that claims 9, 10, and 13 of the asserted '551 patent are not patentably distinct from the reference claims. Thus, I would reverse the district court's conclusion and hold that the asserted claims of the '551 patent are invalid for obviousness-type double patenting. I therefore respectfully dissent.