No. 20-2106

IN THE

United States Court of Appeals for the Federal Circuit

ADAPT PHARMA OPERATIONS LIMITED, ADAPT PHARMA, INC., ADAPT PHARMA LIMITED, OPIANT PHARMACEUTICALS, INC.,

Plaintiffs-Appellants,

v.

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES, LTD.,

Defendants-Appellees.

On Appeal from the United States District Court for the District of New Jersey
Hon. Brian R. Martinotti
Case No. 2:16-cv-7721

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April 9, 2021

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number	**20-2106**
Short Case Caption	**Adapt Pharma Operations v. Teva Pharmaceuticals USA, Inc.**
Filing Party/Entity	**Adapt Pharma Ltd.; Adapt Pharma Operations Ltd.; Adapt Pharma, Inc.**

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 04/09/2021

Signature: **/s/ Catherine E. Stetson**

Name: **Catherine E. Stetson**

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☐ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
See attached	See attached	See attached

☑ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☑ Additional pages attached

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☑ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

Adapt Pharma Operations v. Teva Pharmaceuticals USA, Inc.
Fed. Cir. No. 20-2106
Certificate of Interest Supplement

1. Represented Entities	**2. Real Party in Interest**
Adapt Pharma Ltd.	Emergent BioSolutions Ireland Ltd.
Adapt Pharma Operations Ltd.	Emergent Operations Ireland Ltd.
Adapt Pharma Inc.	Emergent Devices Inc.

3. Parent Corporations and Stockholders:

Emergent Operations Ireland Ltd. (formerly known as Adapt Pharma Operations Ltd.) is a wholly owned subsidiary of Emergent BioSolutions Ireland Ltd. (formerly known as Adapt Pharma Ltd.), which is a wholly owned subsidiary of Emergent Acquisition Ltd., which is a wholly owned subsidiary of Emergent International Inc., which is a wholly owned subsidiary of Emergent BioSolutions Inc.

Emergent Devices Inc. (formerly known as Adapt Pharma Inc.) is a wholly owned subsidiary of Emergent BioSolutions Inc.

Emergent BioSolutions Inc. is a publicly held company, and no publicly held company owns ten percent or more of Emergent BioSolutions Inc.'s stock.

4. Legal Representatives:

The following law firms, partners, and associates have (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities but have not yet entered an appearance in this court.

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- Anthony Sheh

- Kevin Hoagland-Hanson
- Youlin Yuan
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- Quinn Emanuel Uquhart & Sullivan LLP
- Williams & Connolly LLP

5. Related Cases:

The following case has been stayed pending the outcome of these proceedings: *Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals*, No. 2:18-cv-05752 (D.N.J.).

Some of the patents-in-suit are also involved in the following matters before the U.S. Patent and Trademark Office:

- IPR2019-00685
- IPR2019-00688
- IPR2019-00694

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number **2020-2106**

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Filing Party/Entity **Opiant Pharmaceuticals, Inc.**

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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 04/09/2021

Signature: **/s/ Jessica Tyrus Mackay**

Name: **Jessica Tyrus Mackay**

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Opiant Pharmaceuticals, Inc.		

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☐ None/Not Applicable ☑ Additional pages attached

Please see Exhibit A.		

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☐ None/Not Applicable ☑ Additional pages attached

Please see Exhibit B.		

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☑ None/Not Applicable ☐ Additional pages attached

Exhibit A – 4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

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Exhibit B – 5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

Nalox-1 Pharmaceuticals, LLC v. Adapt Pharma Operations Ltd., and Opiant Pharmaceuticals, Inc., No. IPR2019-00685

Nalox-1 Pharmaceuticals, LLC v. Adapt Pharma Operations Ltd., and Opiant Pharmaceuticals, Inc., No. IPR2019-00688

Nalox-1 Pharmaceuticals, LLC v. Adapt Pharma Operations Ltd., and Opiant Pharmaceuticals, Inc., No. IPR2019-00694

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REPLY BRIEF FOR APPELLANTS

INTRODUCTION

The District Court's judgment of obviousness rests on multiple legal errors, each reflecting the hindsight-based reasoning that this Court's precedents warn against. The District Court failed to identify the necessary motivation to combine the many elements of Adapt's invention. The court rejected a clear teach away by applying the wrong legal framework. And at Teva's behest, the court impermissibly

shifted the burden to *Adapt* to establish objective indicia of nonobviousness. Each of these was an independent, and independently dispositive, legal error.

In defending the judgment, Teva follows the standard appellee's post-trial playbook: argue the facts. But this approach works only if the facts are the issue on appeal. This appeal raises *legal* errors, so Teva's approach is nonresponsive.

Teva's failure to engage on the law is particularly striking as to the teach-away issue. Though Adapt explained that the District Court applied the wrong legal standard when assessing the critical prior art reference, Teva never acknowledges that argument, much less the proper standard. Examining the same reference under the correct legal standard, the Patent Trial and Appeal Board (PTAB) determined that it taught away from a component of the claimed invention. Teva's attempts to distinguish the PTAB's right decision from this wrong one are meritless.

Teva's attempts to rehabilitate the District Court's motivation-to-combine analysis fare no better. Teva primarily resorts to cases that help determine whether a claim is obvious where a person of ordinary skill in the art (POSA) could arrive at the claim by taking a reference's known set of inputs and shifting the range of values for those inputs. Those cases are not useful where, as here, the inventor had to choose *which* inputs to include, from among a dizzying array of options, in multiple references. The District Court apparently agreed, as it declined to rely on these cases even after Teva cited them extensively below. Teva has little else to say on the

motivation to combine. For all its quotations from the District Court's opinion, Teva fails to identify the missing link: a specific reason to pluck the specific ingredients and amounts, from among countless possibilities, and fashion them into the particular, claimed invention.

Teva now acknowledges that it is legal error for a court to place the burden on the patentee when examining the objective indicia of nonobviousness. Teva fails to mention that its briefs below asked the court to do just that. The District Court's opinion confirms it accepted Teva's invitation, which led it to discount compelling indicia that these claims were not obvious.

These are all legal problems with the District Court's analysis—not disputes about the facts. With the correct legal frameworks in place, and without the bias of hindsight, Teva did not clear the high threshold of proving Adapt's patents invalid by clear and convincing evidence. The judgment should be reversed.

ARGUMENT

I. The District Court Did Not Apply This Court's Teach-Away Standard.

A reference teaches away when a POSA "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path" of the inventor. *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018) (internal quotation marks omitted). This Court has long employed that legal standard. *See DePuy Spine, Inc. v. Medtronic*

Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009); *In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

Applied here, that legal standard compels a conclusion that Adapt's invention is not obvious. The *only* reference that tested and reported on the stability of naloxone formulations with the preservative benzalkonium chloride (BZK) claimed in Adapt's invention, *taught away* from using BZK because the data showed that BZK degraded naloxone.

Wyse studied 13 different naloxone formulations to test different preservatives' suitability. He stated that BZK was not "acceptable . . . due to increased observed degradation." Appx6894. That degradation was observed in formulations with *both* BZK and the chelator EDTA, two excipients in the claimed invention. *Id.* Thus, as the District Court recognized, "Wyse's preliminary study concluded that BZK was not suitable for use as a preservative with naloxone and instead recommended . . . benzyl alcohol and paraben preservatives." Appx44.

A POSA reading Wyse—the only prior art that tested the stability of naloxone formulations with BZK, or BZK *and* EDTA—"would be discouraged from following the path," *DePuy Spine*, 567 F.3d at 1327 (internal quotation marks omitted), that Wyse tested, found unstable, and expressly recommended against. Wyse's findings "deter any investigation into" BZK and "naturally discourage" a POSA from combining BZK with naloxone. *United States v. Adams*, 383 U.S. 39,

52 (1966). Indeed, Wyse showed that BZK did not perform as a preservative should—it decreased, rather than increased, stability. *See DePuy Spine,* 567 F.3d at 1326 ("An inference of nonobviousness is especially strong" if the reference "undermine[s] the very reason" a POSA would include the element). As the PTAB concluded when rejecting an obviousness challenge to these same claims, a POSA would "have given significant weight[ ] to the only naloxone formulation stability data"—Wyse—which discouraged using BZK as a preservative. *Nalox-1 Pharms., LLC v. Adapt Pharma Operations Ltd.*, No. IPR2019-00688, 2020 WL 4920198, at *7 (P.T.A.B. Aug. 21, 2020).

Teva does not engage with the cases that establish this Court's teach-away analysis. *See* Resp. Br. 43–48. Neither did the District Court. *See* Appx64–67. That is why Teva does not argue that the District Court applied the proper framework; it can't. Instead, Teva invokes an inapplicable standard of review, misreads this Court's teach-away precedents, and downplays the significance of the PTAB's rejection of the same obviousness challenge Teva raised here.

A. By not applying this Court's teach-away precedents, the District Court erred as a matter of law.

Teva first argues (at 44) that "[w]hether the prior art teaches away is a question of fact." But the error in the District Court's obviousness conclusion lies in its failure to apply the correct legal framework. *See* Opening Br. 23. This Court reviews that issue de novo, *id.*, and it has reversed factfinders who do not apply the established

teach-away framework. *See, e.g.*, *Polaris*, 882 F.3d at 1070 (directing the PTAB to apply "the framework that our caselaw *has* articulated"—"whether [prior art]'s teachings 'criticize, discredit, or otherwise discourage' " the invention (quoting *DePuy Spine*, 567 F.3d at 1327)).

The District Court got the inquiry backwards. Rather than ask whether a POSA "would be discouraged from following the path set out in the reference," *id.* at 1069 (quoting *DePuy Spine*, 567 F.3d at 1327), it dissected Wyse looking for any reason a POSA might have used BZK *despite* Wyse's unambiguous warning that it degraded naloxone. *See, e.g.*, Appx65 (reasoning that BZK is "commonly used" in intranasal formulations); *id.* (reasoning that two earlier references, Davies and Kerr, "did not express any concerns" about BZK); Appx67 (reasoning that Wyse did not study BZK further after reviewing preliminary testing data). That was error. Once a court finds itself asking whether a POSA would have to "ignore" "known disadvantages," the teach away is clear. *Adams*, 383 U.S. at 51–52.

B. A single reference can teach away from the claimed invention.

Teva next argues that what matters is what "the prior art as a whole" said about BZK. Resp. Br. 45–46 (internal quotation marks omitted). Its position appears to be that because Wyse is just *one* reference, and a number of *other* references didn't report adverse results (because they didn't study the interaction of BZK and naloxone), the majority rules. But a single reference can, of course,

"criticize, discredit, or otherwise discourage investigation" sufficiently to teach away. *DePuy Spine*, 567 F.3d at 1327 (internal quotation marks omitted). That is especially true where, as here, no other reference speaks to the question Wyse does: whether BZK used alongside naloxone risks degradation of that active ingredient. Wyse specifically "expresses concern for failure" of BZK in a naloxone formulation after testing the effects of BZK on degradation. That is sufficient to be a teach away. *Id.* (affirming teach away based on one reference).

In any event, Teva is wrong that examining the prior art "as a whole" changes the outcome. Evaluating how a POSA would read a reference against other prior art is about quality, not quantity. "[T]he nature of the teaching is highly relevant, and must be weighed in substance." *In re Gurley*, 27 F.3d at 553. If any prior art references are "conflicting," a court asks whether a later-in-time reference has a "discrediting effect" on earlier references. *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991); *see also Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). There is no "conflict" here: No other reference—not one—*tested* the effects of BZK on *stability* in a formulation *with naloxone*. Appx3971–3972 (Smyth).[1]

[1] Teva's reliance (at 46) on *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286 (Fed. Cir. 2013) is odd. There, the trial court found a patent *not* obvious because (among other things) "certain aspects of the prior art taught away from the claimed invention." *Id.* at 1293. This Court reversed because, among other reasons, the district court had not considered "what, if any, impacts these aspects . . . would have on the clear

But in any case, the specificity of the Wyse reference—which contains data showing that BZK degrades the stability of naloxone formulations, including formulations with EDTA—means that Wyse necessarily "discredit[s]," *In re Young*, 927 F.2d at 591, generic suggestions that BZK might be used as a preservative. Teva argues that BZK was well known. Resp. Br. 43. It was. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305–06 (Fed. Cir. 2015) (addressing whether prior art taught away from BZK in eyedrop formulation, even where other formulations used BZK). But that doesn't mean a reference can't teach away from BZK's use in a particular setting. *See id.* (affirming conclusion that the prior art taught away from BZK in the claimed eyedrop formulation); *see also DePuy Spine*, 567 F.3d at 1328 (finding that one reference taught away from "the backdrop of the collective teachings" because it "warn[ed] against" alternatives those teachings disclosed). If anything, BZK's use as a preservative in *some* settings only confirms that Wyse's discouragement of using BZK in *this* setting because of the potential for degradation of naloxone would stand out to a POSA.

Teva also argues that the Davies and Kerr references "used BZK with no reported problems." Resp. Br. 12. "Used" is a stretch, given that Davies merely "describes" a naloxone formulation with BZK. Appx3950 (Smyth); Appx11508;

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motivation to combine" contained in another reference, and "did not find that the prior art as a whole taught away from the invention." *Id.* Here, in contrast, Adapt argued below, and argues on appeal, exactly what the *Allergan* Court found lacking.

see also Appx11511–11524. And "no reported problems" is misleading, given that neither Davies nor Kerr tested the stability of naloxone formulations with BZK and thus neither could have reported any stability problems. Appx3950 (Smyth); Appx3971–3972 (Smyth); Appx11508. Teva's expert Dr. Smyth agreed that when tested, the Kerr formulation was "found to cause degradants to appear," Appx3974, and recognized that stability is an important consideration that formulators would be interested in, Appx3973. For these reasons, neither reference could overcome Wyse's specific, data-supported teach away, particularly because Wyse's data is more recent than the Davies and Kerr references.

Taken "as a whole," Resp. Br. 45 (internal quotation marks omitted), that prior art "in no way overshadows" Wyse's specific "warning," based on empirical data, "against" combining BZK with naloxone. *DePuy Spine*, 567 F.3d at 1327.

C. Applying this Court's teach-away precedents correctly, the PTAB declined to invalidate Adapt's patents.

The PTAB rejected an obviousness challenge to Adapt's patents based on the same arguments Teva has raised. Resp. Br. 47–48. The PTAB found that a POSA "would have taken into consideration, and indeed, would have given significant weight, to the only naloxone formulation stability data disclosed in Wyse." *Nalox*, 2020 WL 4920198, at *7. And it rejected the rationale the District Court implicitly adopted, Appx66—that Wyse would only teach away from BZK if it conclusively showed that BZK was "incompatible with naloxone"—because that "overstates the

standard for evaluating whether a reference teaches away." *Nalox*, 2020 WL 4920198, at *8 (internal quotation marks omitted).

The PTAB decision thus offers a kind of control group against which to see how the District Court's misapplication of this Court's teach-away standard changes the obviousness outcome. Teva argues that the opposite outcomes before the PTAB and the District Court stem from some difference in the references before the PTAB. Resp. Br. 47. But it does not identify any difference in the record that might matter. Teva also argues that the petitioner in the PTAB proceeding identified Wyse as an invalidating reference. *Id.* at 47–48. But *why* a particular reference is offered is irrelevant to the teach-away analysis—which is why Teva cites no authority for its odd proposition. What matters is that, after examining Wyse, the PTAB ruled it teaches away from using BZK with naloxone.[2]

D. Teva's other arguments are meritless.

Teva's remaining arguments lack merit. First, Teva argues that even if Wyse did teach away from using BZK, it would not matter because Adapt did not assert patent claims "that recited stability limitations." *Id.* at 47. For this proposition Teva

[2] Adapt is not aware of another case like this one, in which the PTAB, applying the challenger-friendly preponderance of the evidence test, has upheld a patent where a district court applying the clear-and-convincing test did not. This case shows the importance of uniformly enforcing this Court's teach-away standard. Where, as here, the petitioner does not, or perhaps lacks standing to, appeal a PTAB ruling, a patent holder can face irreconcilable rulings: one of validity and one of invalidity.

relies on *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1381–82 (Fed. Cir. 2017). But *Idemitsu* holds only that "[w]hile a prior art reference may indicate that a particular combination is undesirable for its own purposes, the reference can nevertheless teach that combination if it remains suitable *for the claimed invention*." 870 F.3d at 1382 (internal quotation marks and citation omitted). The claims here easily meet that bar. They call for BZK (a preservative) and EDTA (a chelator), excipients used to *prevent* degradation. Wyse's teaching that BZK and EDTA together *degrade* naloxone is manifestly relevant to these claims and would certainly matter to a formulator. To the extent Teva suggests that a patent claim must recite its every salutary quality to "assert" that claim, that is incorrect. Neither *Idemitsu* nor any other case Teva points to requires Adapt to do so. Adapt needed to claim the elements of the formulation, and it did. *See* Opening Br. 11 (claim 9 of '747 patent claims "between about 0.005 mg and about 0.015 mg" of BZK); *see also* Appx4819 (Smyth).[3]

Teva also offers various fact-based arguments as to why Wyse did not actually teach away from using BZK, despite expressly discouraging that use. Resp. Br. 45. A POSA, however, would understand that degradation at a high BZK concentration at the very least would *permit*, rather than exclude, the inference that a lower

[3] In any event, Dr. Smyth testified that "[g]enerally," "stability is an important consideration." Appx3972. And Narcan *is* stable, an unexpected result given the inclusion of BZK in the claimed formulation. *See infra* pp. 27–28.

concentration would similarly degrade naloxone. And in those circumstances, given the problems Wyse recognized with BZK, a POSA would be particularly "discouraged" from using BZK in a product that would need to be stored for an unknown period, outside a controlled environment. *DePuy Spine*, 567 F.3d at 1327 (internal quotation marks omitted).

Finally, Teva emphasizes that Wyse's analysis of BZK was a "preliminary screening study," but that does permit ignoring Wyse's conclusion. Resp. Br. 44; *see also* Appx67 (District Court offering same reasoning). If anything, that strengthens *Adapt's* argument, not Teva's. Wyse's subsequent abandonment of BZK in favor of other preservatives underscores that his initial study results pointed away from BZK so clearly that further tests were not worth his time.

Wyse expressly and clearly teaches away from Adapt's invention. The PTAB got this issue right. The District Court should be reversed.

II. The District Court Failed To Explain Why A POSA Would Have Been Motivated To Combine The Prior Art To Arrive At Adapt's Invention.

Before deeming the patents-in-suit obvious, the District Court was required "to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The "how" of an invention is usually obvious in hindsight. That is why the obviousness inquiry requires determining *why* a POSA would have been motivated to create the invention based

on the prior art, with some reasonable expectation of success. *See, e.g.*, *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327–28 (Fed. Cir. 2012).

The District Court did not identify an adequate—indeed, any—"why." Its obviousness finding instead boils down to a conclusion that a POSA would have been "able" to reach the claimed invention. Appx86. The court relied on Teva's expert, who started with the patented claims, reverse-engineered two sets of prior art references, each containing some reference to some elements of the claims, and then looked at each element and opined that a POSA contemplating all those references and all those elements would have made the same choices as in the patented claims. *See* Opening Br. 26–29. As Adapt explained, and Teva does not dispute, those two sets of prior art references each contains a staggering number of options for a POSA developing a naloxone product. *See id.* at 29–34. Given the sheer number of possible permutations, simply "opin[ing] that the references were like separate pieces of a simple jigsaw puzzle" is not enough. *InTouch Techs., Inc. v. VGo Commc'ns, Inc.*, 751 F.3d 1327, 1349 (Fed. Cir. 2014); *see also id.* at 1351 (finding expert's testimony deficient where she "relied on the . . . patent itself as her roadmap for putting . . . pieces of a 'jigsaw puzzle' together").

Teva offers a scattershot defense of the District Court's motivation-to-combine analysis. First it summarizes the opinion below—without identifying any part that bridges the gap just discussed. Next it leans on "range law" cases, which

hold that obviousness may be presumed if a formulation falls within the ranges of a formulation in the prior art. But those cases do not apply here. Finally, Teva insists that the prior art would have led a POSA to choose a 4mg naloxone dose—relying on an unsustainable reading of the relevant prior art. Teva's defenses cannot save the District Court's legally deficient conclusion.

A. Teva, like the District Court, relies on hindsight to explain why a POSA would have arrived at the claimed invention.

The flaw in the District Court's motivation-to-combine analysis is that the court surveyed a massive universe of potential formulations from the prior art and then declared that a POSA would have been motivated to choose *this particular* invention from among all of them—the patent-law equivalent of looking out over a crowd and picking out one's friends.[4] The court "failed to provide the glue to combine these references," making its holding legally insufficient. *InTouch Techs.*, 751 F.3d at 1348.

Teva devotes most of its discussion of the motivation-to-combine issue to summarizing the District Court's opinion, reciting many facts summarized in that opinion. Resp. Br. 24–31. But the problem with the opinion is not what it found but what it left out. The District Court never—in all its pages—identifies *why* a POSA

[4] *Cf.* Patricia M. Wald, *Some Observations on the Use of Legislative History in the 1981 Supreme Court Term*, 68 Iowa L. Rev. 195, 214 (1983) ("It sometimes seems that citing legislative history is still, as my late colleague [Judge] Harold Leventhal once observed, akin to 'looking over a crowd and picking out your friends.' ").

would have been motivated to select the elements of the claimed formulation from among the massive number of possibilities disclosed in the prior art. Nor does Teva defend the District Court's failure to explain why a POSA would have reasonably expected the claimed invention would *succeed*. As Adapt explained, even setting aside the clear teach away, the District Court failed to explain why a POSA would want any preservative at all or, reading Wyse, would expect any success with a naloxone formulation with BZK—particularly in combination with EDTA. *See* Opening Br. 45. And a POSA would have had reams of clinical studies showing that a 2mg or lower dose would be effective and safe but *zero* clinical studies showing that a 4mg dose would. *See id.* at 34. An obviousness finding requires an explanation for why a POSA would have been motivated to select the claimed combination and reasonably expected it to succeed. That is missing from the District Court's opinion. *See ActiveVideo Networks*, 694 F.3d at 1327.

Like the District Court, Teva maintains (at 24–26) that a POSA would have been motivated to improve the MAD device, especially after the 2012 FDA's call to action. That does not answer the relevant question: *why* a POSA with that goal would have combined the prior art to arrive at *the claimed invention*. A general motivation to invent *something*—even a "strong motivation[ ]," Resp. Br. 26—is not enough. *See* Opening Br. 26 n.9. Indeed, others tried to answer that call to action, but only Adapt arrived at the claimed invention. *See id.* at 9–10, 49.

Similarly, and again like the District Court, Teva maintains that there was a commercial motive to invent a better naloxone formulation. *See* Resp. Br. 25–26. But market demand for a better product does not establish a motivation to combine. This Court rejected a similar argument in *ActiveVideo Networks*. The challenger there relied on testimony that a POSA would want to "build something better" because that "makes it more attractive to your customers." 694 F.3d at 1328. That was insufficient to provide a motivation to combine because it bore "no relation to any specific combination of prior art elements." *Id.* Here too, the generic motivation to bring a product to market does not answer why a POSA would have chosen to combine the same elements Adapt chose.[5]

That leaves Teva's argument that "[o]bviousness does not require that the prior art point to a single, obvious solution." Resp. Br. 32. No one disagrees. Adapt explained, Opening Br. 28, that an invention is obvious if a POSA surveying the prior art "would have thought of either combining two or more references or modifying one to achieve the patented method," *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 (Fed. Cir. 2008) (internal quotation marks omitted), and if that

[5] As a practical matter, the record does not bear out Teva's claim. If the market was clamoring for a naloxone formulation, and if the solution really was so clearly set out in the prior art, one might have expected at least one other product to come to market—presumably long before FDA held a public meeting begging for just that. None did. *See* Opening Br. 11. Indeed, none of the other companies trying to meet that demand landed on the claimed formulation. *See id.* at 9–10.

combination or modification "would yield a predictable result," *ActiveVideo Networks*, 694 F.3d at 1327. Sometimes, more than one combination would meet that test. In the same vein, no one disputes that "routine optimization" can support a finding of obviousness in certain circumstances. But this Court's cases do not allow a party seeking to invalidate a patent to bridge the gap between a massive set of potential formulations and the precise claimed invention by simply invoking "routine optimization." Opening Br. at 38–39. Teva has no response to that.

B. Teva's resort to range law is both telling and meritless.

Much of Teva's motivation-to-combine discussion relies on a line of "range law" cases that the District Court's opinion does not mention. *See* Resp. Br. 32–33, 38–42. It is telling that Teva sees a need to find a substitute for the court's legal analysis in this way. Its attempts to shore up the opinion are meritless, however. This Court's range-law precedents do not apply to this case, which likely explains why, even though Teva cited them heavily below, the District Court declined to rely on them.

Under this Court's "range-law" cases, if a prior art reference discloses ranges for the elements of a composition or formulation, an invention that simply selects values from within those ranges may be obvious. Thus, if a reference discloses a metal alloy with ranges for the percentages of each component and a patent claims that same alloy with percentages within those ranges, the claim is prima facie

obvious. *See In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003); *see also, e.g.*, *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1011 (Fed. Cir. 2018) (references disclosed "the same oxidation reaction" and temperature and pressure "conditions either identical to or overlapping with those of [the] claims"); *In re Applied Materials, Inc.*, 692 F.3d 1289, 1294–96 (Fed. Cir. 2012) (prior art disclosed "groove depth, width, and pitch" ranges overlapping with the claimed invention). In all these scenarios, "[t]he normal desire . . . to improve upon what is already generally known provides the motivation" to simply select a better composition within the disclosed range. *In re Peterson*, 315 F.3d at 1330.

Teva aggressively expands this narrow doctrine to suggest that any patent claiming various components in various ranges carries the same presumption of obviousness. Teva is wrong. The range-law presumption attaches only where a subsequent inventor merely tinkers with ranges of *known elements already used in combination*. The motivation to combine is already satisfied in these circumstances; all the subsequent inventor needs to do is adjust the ranges. *See id.* at 1329–30. That rationale does not apply where the POSA would have to *first* combine various prior art references to generate ranges for each of several possible elements of a claimed formulation, and *then* pick ranges for each chosen element from within the various disclosed ranges. Range law also does not apply when there is no basis to believe a POSA could simply pick from within the disclosed range and expect success. *See*

Allergan, 796 F.3d at 1305 (rejecting range-law argument where ranges in prior art were "broader" than prior range cases had countenanced, and "the claimed amounts of the two different ingredients" in the prior art ranges "could and did materially and unpredictably alter the property of the claimed formulation"). And range law does not apply where the ranges disclosed are very broad. *See, e.g.*, *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) ("[T]he disclosed range is so broad as to encompass a very large number of possible distinct compositions thus requiring nonobvious invention . . . ." (alterations and internal quotation marks omitted)).

This case is worlds apart from this Court's range precedents. *No* reference contains all of the claimed elements, as shown by Dr. Smyth's cobbling together combinations of multiple references to support his obviousness analysis. *See* Appx60–64. And the sheer number of choices a POSA would have to make to select the claimed invention from among what the prior art discloses, *see* Opening Br. 29–34, means that a run-of-the-mill desire to improve on a known combination did not provide the initial motivation to combine required here.

C. The District Court's use of Strang's reference to a 4mg naloxone dose demonstrates the flaws in its analysis.

The flaw in the District Court's motivation-to-combine analysis is particularly pronounced when it comes to the naloxone dose. Adapt explained in its opening brief that the District Court's discussion of why a POSA would have been motivated

to use a 4mg dose of intranasal naloxone—the dose claimed—was legally deficient. *Id.* at 34–36. At bottom, the court was satisfied "4mg dose" appeared somewhere in the prior art. Appx50–51. But although the prior art disclosed doses ranging from 0.5mg to 20mg, the only clinical studies of intranasal administration to overdose patients (that is, tested doses, not conjecture) recommended 2mg or less. A factual conclusion based on insufficient evidence is not a defensible factual conclusion. It is a legal deficiency. *See* Opening Br. 34–36; *InTouch Techs.*, 751 F.3d at 1351 (the "reason for combining disparate prior art references" must be "explicit" (internal quotation marks omitted)).

Teva argues that the District Court's dose explanation was sufficient because it rested on a prior determination that Teva's expert was credible. Resp. Br. 33. That conflates credibility with evidence. Adapt has never questioned the District Court's finding that Dr. Smyth was credible. Appx18; *see* Opening Br. 34, 35, 38, 40, 44, 48, 52 (citing Smyth testimony). But no matter how credible an expert witness is, his testimony is valuable only if the expert provides adequate factual support for his conclusions. *See, e.g.*, Opening Br. 34–35; *InTouch Techs.*, 751 F.3d at 1351 (witness "failed to provide the necessary articulated reasoning with some rational underpinning" (internal quotation marks omitted)).

Based on Dr. Smyth's testimony, the District Court concluded that "a POSA would have thought a 4 mg intranasal dose was safe and would have preferred a

higher initial dose of naloxone in the community setting." Appx52–57. As discussed, however, the prior art disclosed doses from 0.5mg up to 20mg. And Dr. Smyth provided no reason why a POSA would have picked 4mg over any other dose in this range, such as 3.5mg or 4.5mg. He provided no reason why a POSA would have thought any other dose in this range was unsafe. And he provided no reason why a POSA—even one who landed on a 4mg dose out of the many "preferred" doses in prior art—would have done so with a reasonable expectation of success. Appx3906 (testifying only that a POSA had "a reasonable expectation of success in arriving at an improved" intranasal product).

Teva mirrors the District Court's reliance on Strang to conclude that a POSA would have chosen a formulation with a 4mg dose. Resp. Br. 34. But as Adapt has explained, Opening Br. 15–16, 35, Strang mentions "4 mg" just twice in 73 pages. The first mention is as one of *seven* "preferred" starting points: "4 mg naloxone HCl, 6 mg naloxone HCl, 8 mg naloxone HCl, 10 mg naloxone HCl, 12 mg naloxone HCl, 14 mg naloxone HCl or 16 mg naloxone HCl . . . ." Appx6964.[6] Even so, Strang "[m]ost preferred" somewhere between 1.3 and 1.6mg naloxone—the range Strang ultimately claimed. Appx6940, 6988.

[6] Strang's "preferred" doses span 14 pages. Appx6939–6945, 6959–6965.

The second time Strang mentions "4mg" is as part of a mathematical calculation meant to predict bioavailability of doses Strang did not test. Appx6983 ("estimat[ing]" that 1mg injectable naloxone should have the same bioavailability as "the range of 3 mg to 4 mg" intranasal naloxone). From that, the District Court concluded that "Strang would motivate a POSA to use a 4mg intranasal dose to match the bioavailability" of "the FDA-approved 1mg intramuscular injectable dose." Appx40. But the very next sentence demonstrates that Strang sought to match a *0.4mg* injectable dose. Appx6983 (recommending "starting amounts for naloxone administered intranasally ranging from 1.2 mg to 1.6 mg" which matched "0.4 mg IV naloxone"); *see also* Opening Br. 34–35 (explaining that prior art taught that a 2mg initial *intranasal* dose worked as well as the 0.4mg injectable dose).

Teva cannot dispute any of this. *See* Resp. Br. 34 & n.4. Instead, it parrots the District Court's statement that Strang "preferred" a 4mg dose, Appx40. Again, it is unreasonable to read Strang, which "prefer[s]" nearly every one of the many doses it discusses, as motivating a POSA to select a 4mg dose out of all the options. *See In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986) (a reference must be "considered in its entirety for what it fairly suggests"); *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) ("A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.").

The District Court, therefore, at most found that a POSA *could have* selected a 4mg naloxone dose from among a host of doses; it nowhere explains why a POSA "*would*" *have* done so. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (emphasis added and internal quotation marks omitted). Its reasoning on each of the elements of the claimed invention followed this same pattern. *See* Opening Br. 29. The District Court thus never answered the critical question when it comes to finding a motivation to combine: why a POSA would have put the references together as the claimed invention does—and would have reasonably anticipated that doing so would lead to a successful formulation. Using a passing mention in Strang to deem these patents obvious is a telltale sign of the District Court's hindsight bias.

III. The District Court Erred When Analyzing The Objective Indicia Of Nonobviousness.

When considering obviousness, "a court must not stop until *all* pieces of evidence on that issue have been fully considered and each has been given its appropriate weight." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). The District Court legally erred by accepting Teva's invitation to shift the burden to Adapt. That led the court to fail to recognize multiple hallmarks of nonobviousness in this record. These errors require reversal.

A. The District Court erroneously shifted the burden to Adapt.

Patents enjoy a statutory presumption of validity, 35 U.S.C. § 282(a), and the party challenging validity bears the burden of establishing invalidity by clear and

convincing evidence. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012). The burden always remains on the challenger, including with respect to the "objective considerations" of nonobviousness, which "guard as a check against hindsight bias." *Id.* at 1079.

The District Court did not follow this rule. After concluding the claims were "rendered obvious by the prior art," Appx59, it asked whether *Adapt* showed "any secondary considerations of nonobviousness sufficient to *overcome* Teva's prima facie case." Appx67 (emphasis added). The court erroneously imposed "a burden-shifting framework" where "none exists." *In re Cyclobenzaprine*, 676 F.3d at 1075.

It is not hard to understand why the District Court made this error: Teva asked it to. Teva argued below that "Adapt bears the burden of proof on its assertions of secondary indicia." Appx5292. Teva now recognizes that it was wrong, Resp. Br. 48–50, yet still claims that the District Court correctly followed the law.

Teva's efforts to rehabilitate the District Court's reasoning fall short. First it tries to minimize the problem as only "a sentence" in the District Court's opinion. *Id.* at 49. Not so. The court repeatedly, and expressly, confirmed that it viewed Adapt as bearing the burden. *See* Appx67 ("Adapt has failed to show any secondary considerations of nonobviousness sufficient to overcome Teva's prima facie case."); Appx88 ("Plaintiffs Fail to Show Any Secondary Considerations of Nonobviousness"); Appx89 ("Adapt's proffered indicia of nonobviousness are

insufficient to overcome Teva's strong demonstration of obviousness."); Appx90 ("Adapt has failed to establish a nexus"); Appx91 ("Adapt has [not] presented significant evidence"); Appx92 ("Adapt has failed to present significant evidence"); Appx93 ("proffered evidence . . . does not rebut Teva's"); Appx95 ("Adapt failed to present sufficient evidence").[7]

The cases Teva relies on do not help it either. *In re Cyclobenzoprine* explains that there is a difference between merely recognizing a "prima facie" case and "establishing a formal burden-shifting framework." 676 F.3d at 1076-77. The latter is "in derogation of" this Court's precedent and "Supreme Court case law." *Id.* at 1079-80. The cases Teva cites respect this rule. In *Nalpropion Pharmaceuticals, Inc. v. Actavis Laboratories FL, Inc.*, the Court recognized that "every limitation in the claims at issue" was in the prior art, but waited to determine obviousness until it examined the "objective indicia of nonobviousness." 934 F.3d 1344, 1355–56 (Fed. Cir. 2019). And in *Intercontinental Great Brands LLC v. Kellogg North America Co.*, this Court confirmed that the district court had drawn "its conclusion of obviousness only after, not before, considering the objective indicia." 869 F.3d 1336, 1345 (Fed. Cir. 2017). Contrast these cases with the decision below, which

[7] Teva misleadingly suggests that the District Court recognized that Teva bore the burden only by quoting a parenthetical in a *different* section of the District Court's opinion. *See* Resp. Br. 21 (quoting Appx79).

concluded, based solely on the "prior art," that the invention was "obvious" before requiring Adapt to rebut that premature conclusion with objective indicia. Appx59.

B. The District Court improperly discounted multiple objective indicia of nonobviousness.

The District Court's erroneous burden-shifting framework skewed the lens through which it assessed the objective indicia. When the clear and convincing evidence burden remains with Teva, multiple considerations weigh strongly against obviousness. Teva attacks each individually, but fails to fill in the gaps in the District Court's analysis. And this factor-by-factor approach fails to give adequate weight to *all* of the indicia together as part of "the totality of the evidence," as this Court's precedents require. *In re Cyclobenzaprine*, 676 F.3d at 1083.

First, Adapt's patented formulation filled a long-felt, unmet need. Teva fails to discuss the most obvious evidence for that need: the FDA's convening an industry-wide conference seeking an effective and practical intranasal naloxone formulation. Appx6476, Appx6485. Teva focuses on the MAD device, suggesting it sufficed. Resp. Br. 52. But it elsewhere admits that the MAD device was plagued with "obvious and well-known drawbacks." *Id.* at 4. Teva next suggests that other products might have offered a solution. *Id.* at 52–54. But those products never received FDA approval, and were thus *not* safe or effective enough to fill the need.

Second, the claimed invention demonstrated unexpected results because it was unexpectedly stable and yielded a higher amount of drug in the blood

(bioavailability). On stability, its formulation was unexpectedly stable in light of Wyse's *in*stability findings. *See* Opening Br. 52–53; *supra* pp. 4–5. Teva's contrary arguments duplicate its claim that Wyse did not teach away from using BZK, and are no more persuasive in this context. *See supra* pp. 4–13. As for bioavailability, Teva ignores that although use of BZK might have been expected to yield *some* increase in blood concentration, the observed effect was far greater than one would expect based on BZK alone. *See* Opening Br. 52. Teva next claims (at 57) that Adapt's expert conceded there was "no correlation" between the observed effect on concentration in the bloodstream and "therapeutic efficacy." But the testimony Teva cites merely contrasts a performance metric called "Cmax"—which Adapt's opening brief did not discuss—with "bioavailability," which it did. Appx4289–4290 (Illum). There was no dispute that the "bioavailability" metric Adapt discusses—and that demonstrated "a 56 percent improvement over Wyse's formulation—measures "how much of the drug that you've given . . . is in the blood and can be acting in the clinical way," Appx4287 (Illum), and is considered an important measure of performance by the FDA, *see* Appx4168–69, Appx4171 (Illum); Appx4635 (Shpichuk).

Finally, the invention—particularly the 4mg dose—was initially greeted with substantial industry skepticism, but ultimately multiple competitors attempted to copy novel aspects of Adapt's claims. Teva does not dispute that the prior art

suggested concerns about withdrawal and that there was "widespread reluctance" to use a 4mg dose. Opening Br. 54; *see* Resp. Br. 55. Instead, Teva claims (at 55–56) that this skepticism is irrelevant because the invention does not ameliorate the risk of withdrawals. But what matters is that higher doses were expected to present a higher risk of withdrawal relative to lower doses. And on copying, Teva does not dispute that other companies followed Adapt's lead with respect to the dose and excipients. *See* Resp. Br. 56. Although Teva claims this evidence is irrelevant because others did not adopt the invention wholesale, *id.*, it offers no authority for the proposition that copying must be all-or-nothing. *See* Opening Br. 54–55.

Without an effective rebuttal to these objective considerations, Teva claims that the Court need not consider them because Adapt failed to challenge the District Court's conclusion that these considerations lacked a "nexus" to the inventive aspects of the claims. That is wrong.[8] For each of the four considerations discussed, Adapt identified a direct link to a novel aspect of its invention. *See* Opening Br. 49 (Adapt's combination was "effective, safe, and easy-to-use," unlike prior efforts); *id.* at 51 (unexpected results linked to "higher dose and specific concentrations of

[8] It is Teva who bears the burden to rebut a nexus. "[A] patentee is entitled to a rebuttable presumption of nexus" if it "shows that the asserted evidence is tied to a specific product and that the product *is* the invention." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (internal quotation marks omitted). There is no dispute that the evidence here is tied to Narcan, or that Narcan embodies the invention.

excipients"); *id.* at 53–54 (skepticism of higher dose); *id.* at 55 (copying involved dose and excipients). Any argument that Adapt failed to use the magic word "nexus," Resp. Br. 50–51, exalts form over substance.

CONCLUSION

For the foregoing reasons, and those in the opening brief, the District Court's judgment should be reversed.

Respectfully submitted,

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April 9, 2021

CERTIFICATE OF SERVICE

I hereby certify that on April 9, 2021, the foregoing was electronically filed through this Court's CM/ECF system, which will send a notice of filing to all registered users.

/s/ Catherine E. Stetson
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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(a)(7)(B) and Circuit Rule 32(b)(1), I hereby certify that this brief contains 6,997 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Circuit Rule 32(b)(2).

I further certify that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because the brief has been has been prepared in Times New Roman 14-point font using Microsoft Word for Office 365.

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