United States Court of Appeals for the Federal Circuit

MODERNATX, INC., FKA MODERNA THERAPEUTICS, INC.,
Appellant

v.

ARBUTUS BIOPHARMA CORPORATION,
Appellee

2020-2329

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2019-00554.

Decided: December 1, 2021

AMY K. WIGMORE, Wilmer Cutler Pickering Hale and Dorr LLP, Washington, DC, argued for appellant. Also represented by MARK CHRISTOPHER FLEMING, ANASTASIA GREENBERG, KATHERINE P. KIECKHAFER, MADELEINE C. LAUPHEIMER, EMILY R. WHELAN, Boston, MA.

DAVID I. BERL, Williams & Connolly LLP, Washington, DC, argued for appellee. Also represented by THOMAS S. FLETCHER, JESSICA PALMER RYEN; SONJA ROCHELLE GERRARD, STEVEN WILLIAM PARMELEE, MICHAEL T.

ROSATO, Wilson Sonsini Goodrich & Rosati, Seattle, WA; LORA MARIE GREEN, RICHARD TORCZON, Washington, DC.

Before LOURIE, O'MALLEY, and STOLL, *Circuit Judges*.

LOURIE, *Circuit Judge*.

ModernaTx, Inc. ("Moderna") appeals from the decision of the U.S. Patent and Trademark Office Patent Trial and Appeal Board (the "Board") holding that the claims of U.S. Patent 8,058,069 ("'069 patent") are not unpatentable as obvious. *See Moderna Therapeutics, Inc. v. Protiva Biotherapeutics, Inc.*, IPR2019-00554, 2020 WL 4237232 (July 23, 2020) ("*Board Decision*"). For the reasons provided below, we affirm.

BACKGROUND

I. The '069 Patent

Arbutus owns the '069 patent directed to "stable nucleic acid-lipid particles (SNALP) comprising a nucleic acid (such as one or more interfering RNA), methods of making the SNALP, and methods of delivering and/or administering the SNALP." '069 patent at Abstract. The '069 patent, which issued on November 15, 2011, claims priority from a provisional application filed on April 15, 2008.

As described in the '069 patent, RNA interference ("RNAi") is a biological process in which recognition of double-stranded RNA "leads to posttranscriptional suppression of gene expression." *Id.* at col. 1 ll. 28–31. That biological process is mediated by small interfering RNA ("siRNA"), "which induces specific degradation of mRNA through complementary base pairing." *Id.* at col. 1 ll. 31–34. The '069 patent recognized that RNAi provided "a potential new approach to downregulate or silence the transcription and translation of a gene of interest." *Id.* at col. 1 ll. 41–43.

A "safe and effective nucleic acid delivery system is required for RNAi to be therapeutically useful." *Id.* at col. 1 ll. 52–53. The delivery system "should be small" and "should remain intact in the circulation for an extended period of time in order to achieve delivery to affected tissues." *Id.* at col. 2 ll. 27–31. This requires a "highly stable, serum-resistant nucleic acid-containing particle that does not interact with cells and other components of the vascular compartment." *Id.* at col. 2 ll. 31–34. The particle should also "readily interact with target cells at a disease site in order to facilitate intracellular delivery of a desired nucleic acid." *Id.* at col. 2 ll. 34–36. The '069 patent thus recognized that there remained "a strong need in the art for novel and more efficient methods and compositions for introducing nucleic acids such as siRNA into cells." *Id.* at col. 2 ll. 55–57.

The '069 patent describes the invention as "novel, serum-stable lipid particles comprising one or more active agents or therapeutic agents, methods of making the lipid particles, and methods of delivering and/or administering the lipid particles (e.g., for the treatment of a disease or disorder)." *Id.* at col. 2 l. 65–col. 3 l. 2. The lipid particles are comprised of one or more cationic lipids, one or more non-cationic lipids, and one or more conjugated lipids. *See id.* at col. 3 ll. 11–20. As described in the patent, "[t]he present invention is based, in part, upon the surprising discovery that lipid particles comprising from about 50 mol % to about 85 mol % of a cationic lipid, from about 13 mol % to about 49.5 mol % of a non-cationic lipid, and from about 0.5 mol % to about 2 mol % of a lipid conjugate provide advantages when used for the in vitro or in vivo delivery of an active agent, such as a therapeutic nucleic acid (e.g., an interfering RNA)." *Id.* at col. 5 ll. 44–51. The '069 patent further states that the stable nucleic acid-lipid particles "advantageously impart increased activity of the encapsulated nucleic acid (e.g., an interfering RNA such as siRNA) and improved tolerability of the formulations in vivo, resulting in a significant increase in the therapeutic index"

as compared to prior art nucleic acid-lipid particle compositions. *Id.* at col. 5 ll. 51–58. And the particles are "stable in circulation, e.g., resistant to degradation by nucleases in serum and are substantially non-toxic" to humans. *Id.* at col. 5 ll. 58–61.

The '069 patent contains 22 claims. Claim 1, the only independent claim, recites:

> 1. A nucleic acid-lipid particle comprising:
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> (a) nucleic acid;
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> (b) a cationic lipid comprising from 50 mol % to 65 mol % of the total lipid present in the particle;
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> (c) a non-cationic lipid comprising a mixture of a phospholipid and cholesterol or a derivative thereof, wherein the phospholipid comprises from 4 mol % to 10 mol % of the total lipid present in the particle and the cholesterol or derivative thereof comprises from 30 mol % to 40 mol % of the total lipid present in the particle; and
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> (d) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle.

Id. at col. 91 ll. 24–35. The dependent claims, which contain all of these same limitations, do not raise separate issues. As the parties have not argued them separately, we will not deal with them separately.

II. *Inter Partes* Review of the '069 Patent

Moderna petitioned for *inter partes* review of the '069 patent. In its petition, Moderna asserted three grounds challenging all claims of the '069 patent. In the first

ground, Moderna alleged that all claims of the '069 patent would have been anticipated by and/or obvious over International Pat. Publ. WO 2005/007196 ("the '196 PCT") or U.S. Pat. Publ. 2006/0134189 ("the '189 publication"). In the second ground, Moderna alleged that all claims of the '069 patent would have been obvious over a combination of the '196 PCT, the '189 publication, Lin,[1] and Ahmad.[2] In the third ground, Moderna alleged that all claims of the '069 patent were anticipated by U.S. Pat. Publ. 2006/0240554 ("the '554 publication"), and alternatively that the claims would have been obvious over the '554 publication.

Relevant to this appeal, Moderna's arguments based on the '196 PCT and the '189 publication centered on alleged overlapping ranges of components. Moderna contended that all of the ranges for the components in the claimed nucleic acid-lipid particle were disclosed or taught by the prior art, and that a presumption of obviousness should therefore apply under our precedent.

For three of the four lipid components in the claimed nucleic acid-lipid particle—the cationic lipid, the cholesterol portion of the non-cationic lipid, and the conjugated lipid—Moderna pointed to expressly disclosed ranges in the prior art. For example, the prior art discloses a range of 2–60 mol % for the cationic lipid, *see* '196 PCT at ¶ 88; '189 publication at ¶ 152, which overlaps with the claimed range "from 50 mol % to 65 mol % of the total lipid present

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[1] Alison J. Lin, et al., Three-Dimensional Imaging of Lipid Gene-Carriers: Membrane Charge Density Controls Universal Transfection Behavior in Lamellar Cationic Liposome-DNA Complexes, 84 Biophysical J. 3307–16 (2003).

[2] Ayesha Ahmad, et al., New Multivalent Cationic Lipids Reveal Bell Curve for Transfection Efficiency Versus Membrane Charge Density: Lipid-DNA Complexes for Gene Delivery, 7 J. Gene Med. 739–48 (2005).

in the particle." '069 patent at col. 91 ll. 26–27. Similarly, the prior art discloses ranges of 0.5–25 mol % and 0.5–20 mol % for the conjugated lipid, *see* '196 PCT at ¶¶ 92–93; '189 publication at ¶ 152, which overlap with the claimed range "from 0.5 mol % to 2 mol %." '069 patent at col. 91 ll. 33–35. And for the cholesterol portion of the non-cationic lipid, the prior art discloses ranges of 20–45 mol % and 20–55 mol %, *see* '196 PCT at ¶ 91; '189 publication at ¶ 152, which overlap with the claimed range "from 30 mol % to 40 mol %." '069 patent at col. 91 ll. 31–32.

The parties' dispute focused mainly on the phospholipid portion of the non-cationic lipid, for which the claims require a range "from 4 mol % to 10 mol % of the total lipid present in the particle." '069 patent at col. 91 ll. 29–31. Moderna acknowledged that the prior art does not contain any express disclosure of a range for the phospholipid in the particle. But Moderna argued that, because the total mol % of all lipids in the particle must equal 100%, based on the ranges of the other lipid components, the maximum amount and minimum amount of phospholipid can be calculated to form a range of 0–19.5 mol %. *See, e.g.*, J.A. 134. Moderna also argued that the phospholipid range would have been obtainable through routine optimization using disclosed prior art formulations as starting points. *See* J.A. 4808–09.

The Board found that Moderna failed to meet its burden with respect to its challenges based on the '196 PCT and the '189 publication. Specifically, the Board determined that:

> the teachings of the '196 PCT and '189 Publication do not anticipate or otherwise render obvious a nucleic acid-lipid particle containing each of the recited lipid components within the claimed ranges, including specifically a phospholipid range of 4–10%.

Board Decision, 2020 WL 4237232, at *11. The Board noted that Moderna had "derive[d] an overlapping phospholipid range by making certain assumptions about the other lipid components of the particle." *Id.* at *12. Therefore, the Board concluded, a presumption of obviousness due to overlapping ranges did not apply in this case when "one of the claimed ranges for one of the expressly claimed sub-components of the claimed composition is not necessarily disclosed based on broader ranges for other components disclosed in the prior art." *Id.*

The Board proceeded to list the unfounded assumptions upon which Moderna's calculation of the phospholipid range was based. The Board specifically noted that Moderna arrived at the phospholipid range of 0–19.5% by assuming that a "skilled artisan would have selected a cationic lipid amount of 60%, cholesterol in the amount 20–40%, and PEG in the amount of 0.5–20%," but Moderna failed to explain why a skilled artisan would have chosen those particular amounts. *Id.* at *13. Moreover, the Board found that the '196 PCT and the '189 publication only identify the phospholipid as an optional example of a non-cationic lipid and nothing in the references suggested that the entirety of the "broadly disclosed ranges could apply if all four claimed lipid components were to be included as part of the nucleic-acid lipid[sic] particle." *Id.*

The Board also rejected Moderna's argument that the claimed phospholipid range would have been obtainable through routine optimization based on knowledge that some phospholipid would provide structural stability but too much would inhibit release of the nucleic acid payload. *Id.* The evidence showed that stability and delivery efficiency were general considerations when designing a nucleic acid-lipid particle, but these considerations were not connected with phospholipid amounts. *Id.* Thus, the Board found, the evidence was "insufficient to establish that the claimed phospholipid range in particular was a recognized result-effective variable subject to routine optimization."

Id. at *14 (citing *E.I. Dupont De Nemours & Co. v. Synvina C.V.* , 904 F.3d 996, 1008 (Fed. Cir. 2018)).

Finally, the Board rejected Moderna's argument that certain formulations in the prior art—namely, the "2:30" and "2:40" formulations—would have served as starting points for routine optimization. The Board found that Moderna failed to sufficiently explain how or why a skilled artisan would have upwardly and downwardly adjusted the amounts of the components in those formulations to arrive at the claimed ranges. While Moderna had identified "reasons to adjust each of the lipid components individually," the Board found that the optimization argument "does not take into account the interdependence of the claimed lipid components or how the adjustments would affect the nucleic acid-lipid particle as a whole." *Id.* *15.

Moderna appealed from the Board's decision that it failed to show that the claims of the '069 patent would have been obvious over the cited prior art. Subject to the parties' dispute about Moderna's standing to pursue its appeal, which we discuss further below, we have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4).

DISCUSSION

I. Standing

Before we consider Moderna's argument on the merits of the Board's decision upholding the claims of the '069 patent, we must first determine whether Moderna has standing to pursue its appeal. After all, "no principle is more fundamental to the judiciary's proper role in our system of government than the constitutional limitation of federal-court jurisdiction to actual cases or controversies." *DaimlerChrysler Corp. v. Cuno*, 547 U.S. 332, 341–42 (2006) (quoting *Raines v. Byrd*, 521 U.S. 811, 818 (1997)).

Since the America Invents Act took effect nearly a decade ago, we have had a number of occasions to consider the question of standing in appeals from Board decisions in

IPR proceedings.[3] Our precedent generally makes clear that, as in all appeals before this court, an appellant seeking review of a Board decision in an IPR must have "(1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the [appellee], (3) that is likely to be redressed by a favorable judicial decision." *Phigenix*, 845 F.3d at 1171–72 (Fed. Cir. 2017).

Under the IPR statute, there is no standing requirement for petitioners to request institution of IPR by the Board. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2143–44 (2016) ("Parties that initiate [IPRs] need not have a concrete stake in the outcome; indeed, they may lack constitutional standing."). And we recognize that where a statute grants judicial review, as the IPR statute does, *see* 35 U.S.C. § 319, the criteria of immediacy and redressability may be "relaxed." *See Momenta*, 915 F.3d at 768. But we have always maintained that a party's participation in the underlying IPR before the Board is insufficient by itself to confer standing on that party to appeal the Board's decision to this Article III court. *See Phigenix*, 845 F.3d at 1175; *see also Momenta*, 915 F.3d at 768 ("Although the statutory grant of judicial review may 'relax' the Article III criteria, judicial review of agency action remains subject to the constitutional foundation of injury-in-fact, lest the court occupy only an advisory role."); *JTEKT*, 898 F.3d at 1219 ("[T]he statute cannot be read to dispense with the Article III injury-in-fact requirement for appeal to this

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[3] *See, e.g.*, *Apple Inc. v. Qualcomm Inc.*, 992 F.3d 1378 (Fed. Cir. 2021); *Samsung Elecs. Co. v. Infobridge Pte. Ltd.*, 929 F.3d 1363 (Fed. Cir. 2019); *Momenta Pharms., Inc. v. Bristol-Myers Squibb Co.*, 915 F.3d 764 (Fed. Cir. 2019); *JTEKT Corp. v. GKN Auto. Ltd.*, 898 F.3d 1217 (Fed. Cir. 2018); *Phigenix, Inc. v. Immunogen, Inc.*, 845 F.3d 1168 (Fed. Cir. 2017); *Consumer Watchdog v. Wis. Alumni Research Found.*, 753 F.3d 1258 (Fed. Cir. 2014).

court."). Accordingly, even when an appellant is "sharply opposed to the Board's decision and the existence of [a] patent, that is not enough to make th[e] dispute justiciable." *Consumer Watchdog*, 753 F.3d at 1263. As the party seeking judicial review, Moderna "has the burden of establishing that it possesses the requisite injury." *See JTEKT*, 898 F.3d at 1220.

Moderna asserts as a basis for standing that there is a substantial risk that Arbutus will assert the '069 patent in an infringement suit targeting Moderna's COVID-19 vaccine.[4] In connection with its burden to show standing, Moderna supplemented the record with a declaration from Shaun Ryan, Moderna's Senior Vice President and Deputy General Counsel. *See* J.A. 5737–47. Mr. Ryan described Moderna's work to harness its "proprietary mRNA technology, delivery technologies, and manufacturing processes to develop its COVID-19 vaccine, mRNA-1273." J.A. 5738. Mr. Ryan further described Moderna's concrete plans as of September 2020 to release a COVID-19 vaccine, its emergency use authorization as of December 2020, and its subsequent commercial shipments of the vaccine. J.A. 5739–41.

Mr. Ryan also described, from Moderna's perspective, how Arbutus's statements and actions have created a "substantial risk that Arbutus may bring an infringement action relating to Moderna's COVID-19 vaccine." J.A. 5741. Specifically, Mr. Ryan listed a series of public statements made by Arbutus in 2017 regarding the alleged extensive scope of its patent coverage over virtually all lipid

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[4] Moderna also asserts a second basis for standing based on its current status as a licensee of the '069 patent with monetary obligations affected by the validity of the patent. For the reasons discussed in our opinion in Appeal No. 20-1184, issued today, we reject Moderna's argument that it has standing on this basis.

nanoparticle ("LNP") delivery systems. *Id.* For example, Mr. Ryan quoted a May 2017 statement from former Arbutus CEO Mark Murray in Forbes Magazine that Arbutus "invented, developed and dominate[s] the field of LNP." *Id.* Furthermore, Mr. Ryan attested that Arbutus and its affiliates "have consistently taken the position with Moderna that [Moderna] requires a license to [Arbutus's] patents, including the '069 patent." J.A. 5742. And, Mr. Ryan asserted, "Arbutus has not granted Moderna a covenant not to sue on the '069 patent." *Id.*

We have held that an appellant "need not face 'a specific threat of infringement litigation by the patentee' to establish the requisite injury in an appeal from a final written decision in an *inter partes* review." *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1357 (Fed. Cir. 2020) (quoting *DuPont*, 904 F.3d at 1004). Instead, "it is generally sufficient for the appellant to show that it has engaged in, is engaging in, or will likely engage in 'activity that would give rise to a possible infringement suit.'" *Grit Energy Sols., LLC v. Oren Techs., LLC*, 957 F.3d 1309, 1319 (Fed. Cir. 2020) (quoting *Consumer Watchdog*, 753 F.3d at 1262). Accordingly, on the record before us, Moderna has demonstrated enough of a risk that it will be faced with an infringement suit based on the combination of its own activities in developing the COVID-19 vaccine, Arbutus's broad public statements about its extensive patent coverage in this area, and Arbutus's refusal to grant a covenant not to sue.

It also bears noting that, if we were to dismiss this appeal for lack of standing, Arbutus could sue Moderna for infringement immediately thereafter. That possibility is easy to envision based on the record, and Arbutus has done nothing to dispel it. We seek to avoid such a result, which would perversely incentivize a future similarly situated patent owner to remain silent regarding its intentions during the pendency of an appeal and wait to sue for infringement

until after the appeal has been dismissed for lack of standing.

For the foregoing reasons, we conclude that Moderna has standing to pursue its appeal based on the risk of an infringement suit, and we proceed to the merits of this appeal.

II. Nonobviousness

Moderna raises two primary challenges to the Board's obviousness analysis. First, Moderna contends that the Board erred by failing to apply a presumption of obviousness based on overlapping ranges in the prior art. Based on this first challenge, Moderna also raises a number of ancillary arguments about the Board's misplacement of various evidentiary burdens. Second, Moderna argues that the Board erred in finding that Moderna had not shown a motivation to optimize the lipid components of the prior art nucleic acid-lipid particles and that the phospholipid is a result-effective variable. We address these two challenges in turn.

Obviousness is a question of law that "lends itself to several basic factual inquiries," including the scope and content of the prior art, the level of ordinary skill in the art, and differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) (citing *Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 155 (1950)). We review the Board's legal determinations *de novo*, *In re Elsner*, 381 F.3d 1125, 1127 (Fed. Cir. 2004), and the Board's factual findings underlying those determinations for substantial evidence, *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding. *See Consol. Edison Co. of New York v. NLRB*, 305 U.S. 197, 229 (1938).

A.

Moderna contends that the Board erred when it held that Moderna had not established that a presumption of obviousness should apply based on the overlapping ranges in the prior art. Arbutus responds that the Board correctly found that Moderna had not demonstrated that the presumption should apply because the prior art does not disclose a range for the phospholipid component.

We have held that a presumption of obviousness typically exists "when the ranges of a claimed composition overlap the ranges *disclosed* in the prior art." *In re Peterson,* 315 F.3d 1325, 1329 (Fed. Cir. 2003) (emphasis added); *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) ("Where a claimed range overlaps with a range *disclosed in the prior art*, there is a presumption of obviousness." (emphasis added)). Here, it is undisputed that a range for the phospholipid is not expressly "disclosed" in the prior art. Yet, Moderna argues that the Board should have applied the presumption anyway based on Moderna's theory that a phospholipid range can be derived or calculated from the disclosures of the prior art.

The Board correctly recognized that we have never before applied the presumption of obviousness for overlapping ranges in a case in which the prior art does not contain an express disclosure of a range. *Board Decision*, 2020 WL 4237232, at *12 ("[T]he Federal Circuit has only applied the presumption where the overlapping range is expressly disclosed, not where an overlap might be assumed based on other motivating factors." (citations omitted)). It is, however, also true that we have never affirmatively decided whether or not the presumption ever *could* apply in such a case. Though the parties would have us make that decision here, it is not necessary or appropriate for us to reach that general question because this case turns on a narrower issue, specifically, Moderna's failure to show that the overlapping range is actually taught by the prior art.

Before the presumption of obviousness could be applied, Moderna would have to first show that, despite the lack of an express disclosure in the references, a person of ordinary skill would have nevertheless understood that the '196 PCT and the '189 publication teach or suggest a range for the phospholipid component that overlaps with the claimed range. Moderna has failed to make that threshold showing.

Moderna's theory essentially proceeds as follows. The '196 PCT and the '189 publication each disclose a nucleic acid-lipid particle with four lipid components—cationic lipid, cholesterol, phospholipid, conjugated lipid. Each reference discloses a range for three out of the four lipids. It is axiomatic that the amounts of the four lipids must add to 100 mol %. Therefore, Moderna posits, it would have been a matter of simple subtraction for a person of ordinary skill in the art to derive a range for the phospholipid.

We agree with the Board and Arbutus that Moderna's theory is an oversimplification based on unfounded assumptions. One of the key flawed assumptions that Moderna makes is that the amount of each individual lipid component in the prior art nucleic acid-lipid particles can be freely manipulated and adjusted across the full scope of the disclosed ranges. As a corollary to that assumption, Moderna assumes that any lipid component of the particle can be increased as long as any other lipid component of the particle is decreased by a corresponding amount to maintain a total of 100%. These assumptions are contrary to logic and the evidence in the record.

In its petition, Moderna presented one hypothetical "scenario" in which it assumed that the prior art particle contains the maximum 60 mol % of cationic lipid and the ranges of cholesterol and conjugated lipid are selected from the range of 20–40 mol % and 0.5–25 mol %, respectively. *See* J.A. 134 (Moderna's petition for IPR, presenting a table showing a scenario in which the cationic lipid in the prior

art nucleic acid-lipid particle is set to maximum). But even that one scenario illustrates the problem with Moderna's assumptions. Moderna focuses on the minimum selection for cholesterol and conjugated lipid, which would, in fact, result in a phospholipid maximum of 19.5 mol %. But rather than acknowledge that selecting the maximums for cholesterol and conjugated lipid would result in a nonsensical negative value for the phospholipid, Moderna simply sets the phospholipid minimum to 0. Indeed, if this case were as simple as arbitrarily setting maximums and minimums for each individual component in the prior art and subtracting from 100%, it would seem that the possible range for the phospholipid component in the prior art nucleic acid-lipid particle extends from a minimum value -40 mol % (which is a meaningless negative number)[5] to a maximum value of 77.5 mol % (which is an amount inconsistent with the teachings of the prior art).[6]

As Arbutus demonstrated to the Board, this case is not that simple because the lipid components of the nucleic acid-lipid particle are interdependent, and they interact with each other unpredictably. Arbutus put forth a plethora of evidence, including evidence from the prior art references as well as expert testimony, demonstrating that the properties of nucleic acid-lipid particles depend on the particle as a whole, rather than on any one component. *See, e.g.*, J.A. 1710–14 (expert declaration citing prior art references to demonstrate the effects of varying the amounts of the lipid components on toxicity and efficacy). Thus, substantial evidence supports the Board's rejection of

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[5] -40% phospholipid = [100% total]–[60% cationic]–[55% cholesterol]–[25% conjugated]

[6] 77.5% phospholipid = [100% total]–[2% cationic]–[20% cholesterol]–[0.5% conjugated]

Moderna's premise that one could obtain a value for the amount of any one lipid component in the particle by adding up the amounts of the other three components and subtracting from 100%.

Even in cases with overlapping ranges involving multiple components, we have held that evidence that the components "interacted in an unpredictable or unexpected way could render the combination nonobvious." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012). That holding applies even more strongly here, where the assumption necessary to derive the implicit overlapping range is itself undermined by the unpredictable interactivity between the components.

It is telling that even Moderna has been unable to remain consistent in its contentions about the allegedly implied phospholipid range in the prior art. For example, Moderna argued in its petition that the phospholipid range in the '196 PCT and the '189 publication can be calculated as 0–19.5 mol %. *See* J.A. 134. In its opening brief in this court, however, Moderna acknowledged that performing its arithmetic using different inputs from the prior art references could result in ranges of 0–30 mol % or 0–80 mol %. *See* Moderna Opening Br. at 38. Although we recognize that both of those ranges would still overlap with the 4–10 mol % phospholipid range in claim 1 of the '069 patent, the possibility of calculating multiple different ranges for the phospholipid cuts against Moderna's argument that there is a clearly taught overlapping phospholipid range that compels the application of a presumption of obviousness.

For the foregoing reasons, the Board correctly held that Moderna had not established that a presumption of obviousness applies based on overlapping ranges. As noted above, Moderna raises a number of ancillary arguments that are contingent on its argument that a presumption of obviousness should have applied. For example, Moderna argues that the Board improperly placed the burden on

Moderna to show a motivation to optimize the lipid components as well as to demonstrate that the phospholipid range is a result effective variable, but that those showings should have been considered subsumed within the presumption of obviousness. Because we hold that the Board did not err in its analysis of the overlapping range issue, we reject these ancillary arguments as essentially moot. Furthermore, as indicated above, all of the dependent claims are subject to this same resolution.

B.

Beyond its legal arguments contingent on the presumption of obviousness and the improper placement of the burdens, Moderna argues that, even if it did bear the burden of proof on the fact questions that underlie obviousness, it presented sufficient evidence to meet those burdens. This argument pertains, in particular, to the Board's findings with respect to the motivation to optimize result-effective variables in the prior art. Importantly, as these are fact issues, we review the Board's findings for substantial evidence. *See St. Jude Med., LLC v. Snyders Heart Valve LLC*, 977 F.3d 1232, 1238 (Fed. Cir. 2020).

It has long been established law that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955). It is also well-established that "the parameter to be optimized must have been recognized by those skilled in the art to be a 'result-effective variable.'" *In re Antoine*, 559 F.2d 618, 620 (C.C.P.A. 1977). But, more recently, we clarified that in cases with multiple result-effective variables, "[e]vidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious." *Applied Materials*, 692 F.3d at 1298.

It cannot be disputed that the general conditions for a nucleic acid-lipid particle were disclosed in the prior art.

Specifically, the '196 PCT and the '189 publication disclose particles that contain all four of the lipid components recited in the claims of the '069 patent. Moderna argues that it presented sufficient evidence that the disclosures in those references presented a starting point that would have allowed a person of ordinary skill in the art to arrive at the claimed invention through routine optimization.

Moderna relies on the previously discussed ranges as well as the 2:30 and 2:40 formulations as starting points for optimization. Those formulations have cationic lipid amounts slightly below the claimed 50–65% range and cholesterol amounts slightly above the claimed 30–40% range. According to Moderna, it presented evidence to the Board regarding the motivating factors for optimizing each lipid component in the prior art particles. For example, Lin and Ahmad would have taught a person of ordinary skill to increase the amount of cationic lipid to increase transfection efficiency. *See Moderna Opening Br.* at 47–48 (citing expert testimony, Lin, and Ahmad). Moderna also argues that it was well known that phospholipids help stabilize the particles, but too much phospholipid can inhibit transfection. *Id.* at 48 (citing expert testimony). Cholesterol was known to stabilize lipid bilayers, but keeping the cholesterol level low would be necessary to prevent it from precipitating out of the lipid layer. *Id.* at 49 (citing prior art and expert testimony). And conjugated lipid prevents particles from aggregating, but it is used in small amounts to avoid inhibiting particles from fusing with cells. *Id.*

The Board found that the evidence was insufficient to establish that the phospholipid range was a result-effective variable. However, even if we accepted Moderna's argument that the phospholipid range is a result-effective variable, we would have to conclude based on the record that the other lipid components in the prior art nucleic acid-lipid particles are result-effective variables. Then the question would be whether Moderna showed that reaching the claimed ranges for these result-effective variables would

have been achievable through routine optimization. Moderna failed to make that showing.

Moderna provided evidence of general considerations to be taken into account with respect to each individual component. But Moderna's evidence failed to address the interdependence of the claimed lipid components and how adjustments would affect the nucleic acid-lipid particle as a whole. *See Board Decision*, 2020 WL 4237232, at *15. As one example, the Board considered Moderna's general evidence that high cationic lipid amounts and low phospholipid amounts would be desirable, but the Board was unpersuaded in part because the '196 PCT and the '189 publication also suggested that lower amounts of cationic lipids and higher amounts of phospholipid would be acceptable. *See id*. Ultimately, substantial evidence—including the prior art and expert testimony—supports the Board's finding that optimizing the four interdependent lipid components in the prior art nucleic acid-lipid particles would not have been routine, and Moderna's proposed adjustments to the various lipid components are hindsight driven. *See id*. The unpredictable interactivity between the various lipid components renders the claims of the '069 nonobvious. *See Applied Materials*, 692 F.3d at 1298.

CONCLUSION

We have considered Moderna's remaining arguments but we find them unpersuasive. Accordingly, the decision of the Board is affirmed.

AFFIRMED