United States Court of Appeals for the Federal Circuit

CYTIVA BIOPROCESS R&D AB,
Appellant

v.

JSR CORP., JSR LIFE SCIENCES, LLC,
Cross-Appellants

2023-2074, 2023-2075, 2023-2191, 2023-2192, 2023-2193, 2023-2194, 2023-2239, 2023-2252, 2023-2253, 2023-2255

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2022-00036, IPR2022-00041, IPR2022-00042, IPR2022-00043, IPR2022-00044, IPR2022-00045.

Decided: December 4, 2024

DAVID M. KRINSKY, Williams & Connolly LLP, Washington, DC, argued for appellant. Also represented by ANDREW LEON HOFFMAN.

ERIC WILLIAM DITTMANN, Paul Hastings LLP, New York, NY, argued for cross-appellants. Also represented by ISAAC S. ASHKENAZI, KRYSTINA L. HO, CARL J. MINNITI, III; PHILLIP W. CITROEN, STEPHEN BLAKE KINNAIRD, NAVEEN MODI, MICHAEL WOLFE, Washington, DC; HIROYUKI HAGIWARA, Tokyo, Japan.

Before PROST, TARANTO, and HUGHES, *Circuit Judges*.

PROST, *Circuit Judge*.

In this consolidated appeal, Cytiva BioProcess R&D AB ("Cytiva") appeals the final written decisions from six inter partes reviews ("IPRs"), determining that 79 claims of the three challenged patents are unpatentable. JSR Corp. and JSR Life Sciences, LLC (collectively, "JSR") cross appeal the final written decisions in four of these IPRs, which held the remaining four challenged claims not unpatentable. We affirm the Patent Trial and Appeal Board's ("Board") determination that claims 1–7, 10–20, 23–26 of the '765 patent,[1] claims 1–3, 5–7, 10–16, 18–20, 23–30 of the '142 patent,[2] and claims 1–10, 12–14, 16–28, 30–32, and 34–37 of the '007 patent[3] are unpatentable (i.e., the 79 claims the Board held are unpatentable), and we reverse the Board's determination that claims 4 and 17 of the '142 patent[4] and claims 11 and 29 of the '007 patent are not unpatentable.

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[1] U.S. Patent No. 10,213,765.

[2] U.S. Patent No. 10,343,142.

[3] U.S. Patent No. 10,875,007.

[4] JSR's briefing suggests that the cross-appeal claims include claim 7 instead of claim 17 of the '142 patent. *E.g.*, Cross-Appellant's Br. 58 n.12. Because the Board found claims 4 and 17 not unpatentable, because claims 4 and 17 mirror each other (and claim 7 is substantively different), and because the limitation disputed here appears in claims 4 and 17 (and not claim 7), we interpret JSR's dispute to apply to claims 4 and 17 of the '142 patent.

BACKGROUND

I

JSR filed six IPRs challenging claims 1–7, 10–20, and 23–26 of the '765 patent[5]; claims 1–7, 10–20, and 23–30 of the '142 patent[6]; and claims 1–14, 16–32, and 34–37 of the '007 patent.[7] Each of the challenged patents generally relates to chromatography matrices and processes for isolating target compounds using those matrices.

A

Chromatography is the process of separating components in a mixture, which can be accomplished through a variety of separation methods. The challenged patents relate to a certain type of chromatography called affinity chromatography. In affinity chromatography, a biomolecule is separated from a mixture using molecular binding. This is done by creating a chromatography matrix (a solid support attached to a ligand), where the ligand selected has a high affinity for binding to the target biomolecule (e.g., a protein or antibody).[8] The following

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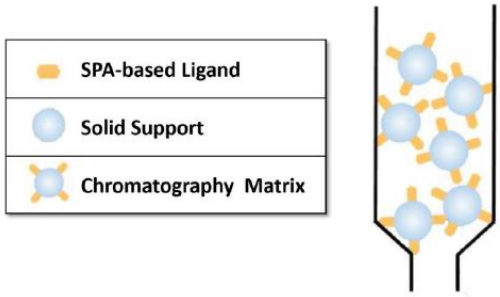
[5] *JSR Corp. v. Cytiva BioProcess R&D AB*, IPR2022-00036 and IPR2022-00043, Final Written Decision (P.T.A.B. Apr. 19, 2023), J.A. 1–54; s*ee also* J.A. 177–230.

[6] *JSR Corp. v. Cytiva BioProcess R&D AB*, IPR2022-00041 and IPR2022-00044, Final Written Decision (P.T.A.B. May 18, 2023), J.A. 55–115; *see also* J.A. 231–91.

[7] *JSR Corp. v. Cytiva BioProcess R&D AB*, IPR2022-00042 and IPR2022-00045, Final Written Decision (P.T.A.B. May 18, 2023), J.A. 116–76; *see also* J.A. 292–352.

[8] While affinity chromatography may be used to isolate a variety of molecules, the challenged patents use affinity chromatography to isolate certain antibodies. For this reason, our discussion of affinity chromatography focuses on the isolation of antibodies rather than other types of molecules. Human antibodies are called

figure illustrates these parts of the chromatography matrix inside a chromatography column:



Cross-Appellants' Br. 6 (citing J.A. 2966).

Once the chromatography matrices are prepared, affinity chromatography generally isolates the target antibody through the following steps: First, the chromatography matrices are "packed into a chromatography column." *Id.* (citing J.A. 2967–70). Next, "a fluid containing the target antibody is loaded into the column." *Id.* (citing J.A. 2970–71). The ligands in the chromatography matrices then selectively bind to the target antibody in the mixture—i.e., when the mixture is poured into the column with the matrices, the antibody attaches to the ligand, while the impurities do not. Next, a washing step removes the unbound impurities from the column, leaving behind the antibodies bound to the matrices. Finally, a solution is poured into the column in an elution step, which breaks the bond between the ligand and the target antibody, thereby isolating the antibodies. The following figure illustrates these steps:

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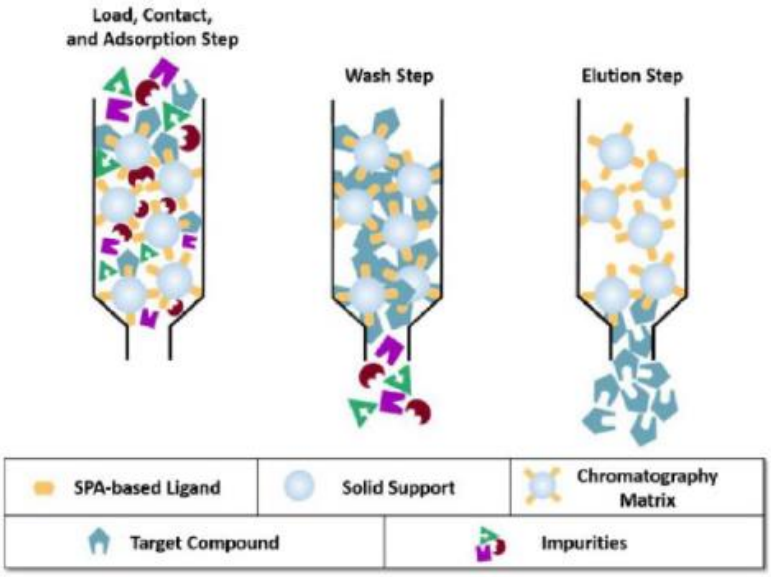
immunoglobulins, of which one type is immunoglobulin G ("IgG"). Here, we use the terms antibodies and immunoglobulins interchangeably.



Cross-Appellants' Br. 7 (citing J.A. 2970–71). When the process is complete, the columns are cleaned to remove contaminants in the column. This procedure "typically entails running an alkaline solution over the column, [and] is called cleaning-in-place ('CIP')." *Id.*

Each of the patents here relates to chromatography matrices comprising a ligand made from Protein A (also called SPA) found in the bacterium staphylococcus aureus. SPA has been the target of research in the field of chromatography for decades due to its specific binding properties to immunoglobulins. *See, e.g.*, J.A. 3896–3902. Protein A has "five highly homologous" natural domains: Domains A, B, C, D, and E. J.A. 3815; '765 patent col. 2 ll. 54–59. As early as the 1980s, researchers and scientists had designed a synthetic SPA domain, referred to as Domain Z, derived from a genetically altered Domain B. J.A. 3898.

"Because CIP involves high-alkaline conditions, which can degrade proteins, increased ligand stability in alkaline environments is desirable." Cross-Appellants' Br. 8 (citing

J.A. 2972–73; J.A. 371; J.A. 3840–41). Thus, mutations to SPA that improve ligand stability in alkaline environments are also desirable—i.e., because they reduce the risk of protein degradation when using CIP. Since at least the 1980s, the amino acid sequence asparagine-glycine, found in each of the SPA domains, has been known to be sensitive to alkaline environments. J.A. 3898. Additionally, "[s]ubstituting the glycine at position 29 for alanine, also called a 'G29A' modification, has been known since the 1980s to promote alkaline stability by avoiding this problematic asparagine-glycine connection." Cross-Appellants' Br. 8 (citing J.A. 2974–77; J.A. 3901; J.A. 3816). Scientists made the G29A substitution when creating Domain Z from Domain B, J.A. 3898; this modification "improve[d] the domain's alkaline stability." Appellant's Br. 11 (citing J.A. 3911).

B

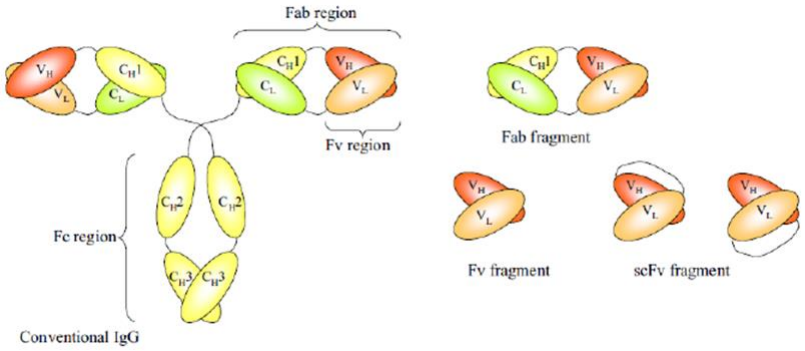
The independent claims of the challenged patents recite making the same G29A modification to Domain C of SPA as had already been made to Domain B in the prior art. For example, claim 1 of the '765 patent recites the following, where SEQ ID NO. 1 is the amino acid sequence for Domain C:

> 1. A chromatography matrix comprising:
>
> a solid support; and
>
> a ligand coupled to the solid support, the ligand comprising at least two polypeptides,
>
> wherein the amino acid sequence of each polypeptide comprises at least 55 contiguous amino acids of a modified SEQ ID NO. 1, and
>
> wherein the modified SEQ ID NO. 1 has an alanine (A) instead of glycine (G) at a

> position corresponding to position 29 of SEQ ID NO. 1.

'765 patent claim 1 (composition claim). Claim 1 of the '142 patent and claim 1 of the '007 patent recite a process for isolating a target compound with this chromatography matrix. *See* '142 patent claim 1 (process claim); '007 patent claim 1 (process claim).

In addition to the Domain C G29A mutation, the challenged patents also claim certain antibody binding properties. Antibodies are made up of different regions, including an Fc region and a Fab region. "Fab regions separated from antibodies are known as 'Fab fragments' . . . ." Appellant's Br. 7 (citing J.A. 5802; J.A. 5874–79; J.A. 6254). "Antigens can bind to either the whole antibody or a fragment of an antibody." Cross-Appellants' Br. 5 (citing J.A. 5802–03). The following figure illustrates the different regions of an antibody:



Cross-Appellants' Br. 64 (citing J.A. 5802).

Certain challenged dependent claims recite binding "to the Fab part of an antibody." For example, claim 4 of the '765 patent recites: "The chromatography matrix of claim 1, wherein the ligand is capable of binding to the Fab part of an antibody." *See also* '765 patent claim 17. Claim 4 of the '142 patent and claim 11 of the '007 patent both recite: "The process of claim 1, wherein the ligand binds to the Fab

part of an antibody." *See also* '142 patent claim 17; '007 patent claim 29.

II

The Board, in its final written decisions, found all challenged claims unpatentable as obvious in view of Linhult,[9] Abrahmsén,[10] and Hober[11] except for claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent, which the Board found were not unpatentable. *See* J.A. 52–53; J.A. 112–13; J.A. 173–75.[12] In holding most of the challenged claims unpatentable, the Board first determined it would have been obvious to make the G29A mutation to Domain C based on express suggestions in the prior art. With respect to certain dependent claims, which claim the chromatography matrices' capability of binding or process of binding to the "Fab part of an antibody," the Board reached divergent results. The Board determined that the Fab-binding composition claims (i.e., claims 4 and 17 of the '765 patent) are unpatentable because they claimed an inherent property. But with respect to the parallel process claims (i.e., claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent), the Board

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[9] M. Linhult et al., *Improving the Tolerance of a Protein A Analogue to Repeated Alkaline Exposures Using a Bypass Mutagenesis Approach*, PROTEINS: Structure, Function, and Bioinformatics, 55:407–16 (2004) ("Linhult"); J.A. 3815–24.

[10] U.S. Patent No. 5,143,844 ("Abrahmsén"); J.A. 3825–38.

[11] PCT App. No. WO 03/080655 ("Hober"); J.A. 3839–92.

[12] The substance of the final written decisions in each of the six IPRs is substantively similar. Therefore, we rely primarily on the Board's Decision in IPR2022-00036 to illustrate the Board's factual findings or legal reasoning, except where otherwise specified.

determined that the claims were not shown to have been unpatentable because even though Fab-binding was an inherent property, JSR had failed to show a reasonable expectation of success. The Board's different results were based, at least in part, on limiting the meaning of "Fab part of an antibody" to Fab fragments.

Cytiva timely appealed, and JSR timely cross-appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

"Obviousness is a question of law that we review de novo, but the Board's underlying findings of fact are reviewed for substantial evidence. Substantial evidence means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1136 (Fed. Cir. 2019) (cleaned up).

Cytiva appeals the Board's determination that claims 1–7, 10–20, 23–26 of the '765 patent, claims 1–3, 5–7, 10–16, 18–20, 23–30 of the '142 patent, and claims 1–10, 12–14, 16–28, 30–32, and 34–37 of the '007 patent are unpatentable. Cytiva first argues that the Board's determination as to all of these claims must be reversed because the Board allegedly "failed to assess whether—and JSR failed to present evidence that—[a person of ordinary skill in the art] would have selected Domain C as a lead compound over Domains B and Z." Appellant's Br. 20. Cytiva also argues that the Board erred in its determination that claims 4 and 17 of the '765 patent are unpatentable because "the Board failed to account properly for the unexpected Fab-binding property recited in those claims." *Id.* at 21. JSR cross-appeals, arguing that the Board erred in concluding that claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent were not shown to have been unpatentable.

We address each argument in turn and ultimately conclude that the Board did not err in its determination that claims 1–7, 10–20, 23–26 of the '765 patent, claims 1–3, 5–7, 10–16, 18–20, 23–30 of the '142 patent, and claims 1–10, 12–14, 16–28, 30–32, and 34–37 of the '007 patent are unpatentable. But the Board did err in its determination that claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent were not shown to have been unpatentable.

I

We start with Cytiva's arguments regarding the lead-compound analysis. Cytiva argues that (A) the Board erred by failing to conduct this lead-compound analysis and (B) a person of ordinary skill in the art would not have been motivated to pick Domain C as the lead compound. We disagree with both propositions.

"Our case law demonstrates that whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds *ordinarily* follows a two-part inquiry." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) (second emphasis added). When it applies, the lead-compound analysis typically proceeds with 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.* "A lead compound, as we have explained, 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.* (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). "The second inquiry in the analysis is 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

We first address Cytiva's argument that the Board erred by not performing a lead-compound analysis. As a preliminary matter, our case law has not suggested that lead compound analysis is *always* required. Instead, we have explained that the lead compound analysis is an ordinary or generally applicable test that assists courts in assessing obviousness for new compounds. *See id.* at 1291 (noting that the lead-compound analysis "*ordinarily* follows a two-part inquiry" (emphasis added)); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("[P]ost-*KSR*, a prima facie case of obviousness for a chemical compound still, *in general*, begins with the reasoned identification of a lead compound." (emphasis added)). The obviousness inquiry is a flexible one that eschews rigid and formalistic rules. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007) ("[O]ur cases have set forth an expansive and flexible approach.").

A lead-compound analysis is not required where the prior-art references expressly suggest the proposed modification. *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1359 (Fed. Cir. 2000) ("The express teachings in the art provide the motivation and suggestion to modify [the prior art] . . . ."). That is the situation here. Specifically, the Board found that "Linhult and Abrahmsén both expressly suggest that the glycine codon at position 29 can be mutated for an alanine codon in *any one* of the SPA IgG binding domains E, D, A, B, or C." J.A. 36 (emphasis in original). For example, Abrahmsén states: "According to still another aspect of the invention there is provided for a recombinant DNA fragment coding for any of the E D A B C domains of staphylococcal protein A, wherein the glycine codon(s) in the Asn-Gly coding constellation has been replaced by an alanine codon." J.A. 3833 col. 2 ll. 32–37. This teaching expressly discloses the proposed G29A modification to Domain C—i.e., what is claimed in the challenged patents. To require a separate justification for

starting with Domain C, when that starting point is already taught in the prior art, would lead to the erroneous "constricted analysis" that *KSR* criticized. *KSR*, 550 U.S. at 421 ("Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it.").

Cytiva argues that the Board erred by relying on *KSR*'s obvious-to-try rationale, instead of the lead-compound test. We disagree. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. . . . In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* Indeed, we have previously indicated that the obvious-to-try inquiry is similar to the lead compound inquiry—both effectively require a finite number of proposed starting points. *See Eisai*, 533 F.3d at 1359; *Takeda*, 492 F.3d at 1359; *In re Rosuvastatin Calcium Pat. Litig.*, 703 F.3d 511, 517–18 (Fed. Cir. 2012). The Board identified a design need of "finding a SPA IgG binding domain that is resistant to protein degradation." J.A. 36 (cleaned up). The Board also identified a finite number of identified, predictable solutions:

> The SPA IgG binding domains comprise a short list of 5 members: E, D, A, B, or C. Of these 5 members, the glycine at position 29 in Domain B has already been mutated to an alanine to create a Domain Z which has been shown to retain IgG binding activity. . . . Linhult and Abrahmsén show that the IgG binding domains of SPA – E, D, A, B, or C share many structural similarities. . . . There is also an express teaching in both Linhult and Abrahmsén to mutate the glycine at position 29 to an alanine in order to prevent degradation of the protein and increase stability, which supports the obviousness

> of incorporating the mutation into any IgG binding domain that has the Asn-Gly dipeptide.

J.A. 36–37. Under these circumstances, we conclude that no lead compound analysis was required and agree with the Board that modifying Domain C with the G29A mutation would have been obvious. J.A. 37.

B

Even if a formalistic lead-compound analysis was required, we conclude that the Board's findings and application of those findings support the conclusion that any one of the five homologous domains of SPA, including Domain C, could serve as a lead compound here. *See Otsuka*, 678 F.3d at 1293 (permitting the identification of more than one lead compound).

Recall, the first step in the lead-compound inquiry is "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.* at 1291 (emphasis added). The Board answered that question affirmatively here by finding that the prior art "suggests the use of any one of the SPA IgG binding domains E, D, A, B, or C as *the starting ligand*." J.A. 37 (emphasis added). "[I]t is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Eisai*, 533 F.3d at 1357 (cleaned up). Here, the Board found that the prior art (1) expressly suggested the G29A modification in any one of the five natural SPA domains, (2) showed that the amino acid sequences of each of the five domains were homologous, and (3) "show[e]d that the IgG binding domains of SPA – E, D, A, B, or C share many structural similarities." J.A. 36–37. Based on these facts, we see no error in the Board's conclusion that any one of the five

domains, including Domain C, could serve as the starting point here.

"The second inquiry in the analysis is 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." *Otsuka*, 678 F.3d at 1292. Cytiva does not appear to dispute that, once Domain C is selected as the lead compound under step one, a person of ordinary skill in the art would have been motivated to make the G29A modification. *See* Appellant's Br. 26–34. Regardless, we conclude that the Board did not err in finding that "Abrahmsén . . . provides motivation for making [the G29A] mutation in *any one* of the IgG binding domains of E D A B C domains of SPA." J.A. 34 (emphasis in original). We see no error in the Board's finding that a skilled artisan would have been motivated to modify Domain C with the G29A mutation.

Therefore, we affirm the Board's determination that claims 1–7, 10–20, 23–26 of the '765 patent, claims 1–3, 5–7, 10–16, 18–20, 23–30 of the '142 patent, and claims 1–10, 12–14, 16–28, 30–32, and 34–37 of the '007 patent are unpatentable.

II

Cytiva separately argues that the Board erred in concluding that claims 4 and 17 of the '765 patent ("the composition claims") are unpatentable. And relatedly, JSR argues on cross-appeal that the Board erred in concluding that claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent (collectively, "the process claims") were not shown to have been unpatentable. Both the composition and process claims relate to binding to the "Fab part of an antibody." Cytiva argues, with respect to the composition claims, that the Board erred by relying on inherency to avoid consideration of whether a skilled artisan would have a reasonable expectation of success and

by relying on inherency to avoid secondary considerations. JSR, with respect to the process claims, argues that the Board misconstrued the claims to be limited to Fab fragments and that, under the proper construction, the process claims are unpatentable for the same reason as the composition claims—i.e., that they claim only the inherent feature of Fab binding.[13]

We address each of these arguments below. First, we explain that there is no material difference between the composition and process claims for the purposes of this appeal and conclude that these claims must rise or fall together. *See* Section II.A., below. Second, we conclude that the Board erred in limiting the construction of the term "Fab part of an antibody" to Fab fragments when analyzing the process claims. *See* Section II.B., below. Third, we address the parties' arguments regarding inherency and conclude, as we have before, that "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020). *See* Section II.C., below. Finally, we reject Cytiva's argument that the Board failed to properly consider the alleged unexpected results of Fab binding. *See* Section II.D., below. We therefore conclude that both the composition and process claims are unpatentable.

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[13] In its petition and on appeal, JSR raised two primary theories of unpatentability with respect to the Fab-binding claims: an inherency theory and a prior-art-obviousness theory. *See* J.A. 443–45; J.A. 521–23; J.A. 587–89; J.A. 660–62; J.A. 750–52; J.A. 819–21. Because we reverse based on JSR's inherency-based theory, we do not address the prior-art obviousness theory here.

A

We start with our conclusion that the composition and process claims should be treated the same in this appeal. The composition and process claims are nearly identical and contain no substantive distinction relevant to this appeal. While the composition claims recite that "the ligand *is capable* of binding" and the process claims recite that "the ligand *binds*," these differences are immaterial to assessing the obviousness of the claims. That is because, on the facts here, binding is not disputed. Thus, if the ligand binds, the ligand is capable of binding.

Despite the similarity of these claims, the Board held the composition claims unpatentable (claims 4 and 17 of the '765 patent) and the process claims not unpatentable (claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent). J.A. 44–49; J.A. 101–05; J.A. 162–66. But both parties, throughout these proceedings have treated the composition and process claims the same. For example, in its petitions, JSR argued for each of these claims that the limitation "binding to the Fab part of an antibody" "is an inherent property of the claimed C(G29A)-based SPA ligand." *See* J.A. 443–44; J.A. 521–22; J.A. 587–88; J.A. 660–61; J.A. 750–51; J.A. 819–20. And in its patent owner responses, Cytiva made nearly identical responses to the petition for both sets of claims. J.A. 1428–32; J.A. 1493–97; J.A. 1559–62. Even on appeal, both parties cross-reference the arguments made between the composition and process claims. *See, e.g.*, Appellant's Br. 48–49; Cross-Appellants' Br. 58.

Because the composition and process claims have no material differences, and because the parties relied on the same arguments before the Board for each of these claims, we see no basis for treating the claims differently here and for finding one set of claims unpatentable and the other not unpatentable.

B

We next address the Board's construction of "Fab part of an antibody." JSR alleges that the Board misconstrued "Fab part of an antibody" when it determined that the process claims were not shown to have been unpatentable. We interpret a claim in view of the claim language, the specification, the prosecution history, and, where relevant, extrinsic evidence. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). Here, we examine the meaning of "Fab part of an antibody" in both the process and composition claims together because the same term in different claims generally means the same thing unless context indicates otherwise. *PODS, Inc. v. Porta Stor, Inc.*, 484 F.3d 1359, 1366 (Fed. Cir. 2007).

Recall, a whole antibody has a Fab region. When that Fab region is separated from the whole antibody, it is called a Fab fragment. The specification[14] asserts that "a 'Fab-binding ligand' is capable of binding to either full antibodies via Fab-binding; or to antibody fragments which includes the variable parts also known as Fab fragments." '765 patent col. 4 ll. 39–58. Additionally, both parties agree that the "Fab part of an antibody" may refer to either the Fab portion of the full antibody or the Fab antibody fragment. Appellant's Reply Br. 49–50; Cross-Appellant's Br. 62. We therefore conclude, in line with the specification, that the term "Fab part of an antibody" may refer to either a Fab part of a full antibody or a Fab fragment.

Turning to the Board's decisions, we agree with JSR that the Board's analysis with respect to the process claims

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[14] The patents here are part of the same family and share substantively similar specifications. For simplicity, we cite only the '765 patent's specification, except where otherwise indicated.

was focused on the ligand's ability to bind to a Fab fragment. *See, e.g.*, J.A. 102 ("Petitioner needs to establish that a mutated SPA domain would reasonably bind *a Fab fragment*." (emphasis added)). Indeed, this appears to be a part of the reason for the Board's conclusion that the process claims were not unpatentable. For example, the Board explained that the composition claims were unpatentable because binding to Fab was an inherent feature of the claimed structure. J.A. 104 n.12. But with respect to the process claims, according to the Board, "isolating Fab . . . requires prior knowledge that the ligand binds Fab. . . . [T]here would be no elution of Fab because *the fragments* are not present in an IgG containing sample." *Id.* (emphasis added). The Board believed that a person of ordinary skill in the art would need to be aware that the ligand binds to Fab fragments (or have a reasonable expectation of success of binding) to take the step of separating those fragments from the full antibody before the claimed process could be performed. But because we and the parties agree that the claims are not limited to Fab fragments and instead also include the Fab part of the full antibody, the Board erred in requiring that JSR separately demonstrate that a person of ordinary skill in the art would have a motivation or prior knowledge concerning Fab *fragments* to show obviousness of the process claims.

C

Having determined that the composition claims and the process claims only contain immaterial differences relevant to the inquiry here and concluded that "Fab part of an antibody" means either a Fab fragment or the Fab part of a whole antibody, we next turn to whether a skilled artisan would have a reasonable expectation of success of arriving at the claimed invention. We conclude, as we have before, that if a limitation of a claim is inherent, "there is no question of a reasonable expectation of success in achieving it." *Hospira*, 946 F.3d at 1332.

1

A prima facie case of obviousness requires "evidence that a person of ordinary skill would have selected and combined and modified the subject matter of the references in the manner of the claimed invention, with a reasonable expectation of success." *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1271 (Fed. Cir. 2018). "The reasonable expectation of success requirement refers to the likelihood of success in combining the references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

"[I]nherency may supply a missing claim limitation in an obviousness analysis." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014). "It is long settled that in the context of obviousness, the 'mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.'" *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)); *see also In re Wiseman*, 596 F.2d 1019, 1023 (C.C.P.A. 1979) (explaining it "is not the law" that "a structure suggested by the prior art, and, hence potentially in the possession of the public, is patentable . . . because it also possesses an Inherent, but hitherto unknown, function which [patent owners] claim to have discovered); *In re Pearson*, 494 F.2d 1399, 1403 (C.C.P.A. 1974) (concluding a compound was undisputedly taught in the prior art and then determining that additional limitations that merely "set forth the intended use for, or a property inherent in, an otherwise old composition . . . do not differentiate the claimed composition from those known to the prior art").

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Cytiva does not dispute that Fab binding in fact occurs when the other limitations are met (i.e., that the claim limitations at issue recite an inherent property). *See* Appellant's Br. 45–59. Instead, Cytiva asserts that "[t]he issue before the Board here was whether [a person of ordinary skill in the art] would have had a reasonable expectation of *combining the disclosures* of the prior art to achieve a C(G29A) ligand 'capable of binding to the Fab part of an antibody.'" Appellant's Br. 46 (emphasis added). The question we must resolve, therefore, is whether a claim limitation that merely recites an inherent property of an otherwise obvious combination requires additional analysis to demonstrate that a person of ordinary skill in the art would have a reasonable expectation of success. We conclude that this additional showing is not required.[15]

To start, reasonable expectation of success is a question about the expectation of success in "combining the references to meet the limitations of the claimed invention." *Intelligent Bio-Sys.*, 821 F.3d at 1367; *see also* Appellant's Br. 46. But for its inherency-based theory addressed here, JSR's obviousness argument concerning the "Fab binding" limitation does not rely on any combination or modification of prior-art references to arrive at the property required by that limitation. Instead, taking the obviousness of the combination of the other claim limitations as established without regard to any Fab binding property (as it has been), JSR asserts that "[t]he

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[15] Our holding today does not address the situation where a claim contains a limitation that would require prior knowledge of the inherent property. Further, a petitioner must still meet its burden to demonstrate that the claimed limitation is indeed inherent. Simply saying it is so without sufficient evidence will not demonstrate unpatentability.

natural result of th[e] [C(G29A)] modification is the capability to bind to the Fab part of an antibody." Cross-Appellants' Br. 41; *see also In re Oelrich*, 666 F.2d at 581 (inherency may be demonstrated by "the *natural result* flowing from the operation as taught would result in the performance of the questioned function" (emphasis added) (citation omitted)).

The parties each identify cases reaching back decades that purportedly support their respective positions. Cytiva relies heavily on cases that stand for the principle that "unexpected properties may cause what may appear to be an obvious composition to be nonobvious." Appellant's Br. 50 (quoting *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354–55 (Fed. Cir. 2017)); *see also id.* at 46 ("protein engineering is a notoriously unpredictable art"); *id.* at 48 ("binding . . . was unexpected"). JSR, in contrast, primarily relies on the principle that, "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." Cross-Appellants' Br. 44 (quoting *Hospira*, 946 F.3d at 1332); *see also id.* 40–45.

Both *Honeywell* and *Hospira* discuss inherency in the context of composition claims. The claims in *Honeywell* recited "a heat transfer composition for use in an air condition system compromising [an HFO refrigerant] and [a PAG lubricant]." 865 F.3d at 1350–51. There, HFO refrigerants were disfavored and known to be reactive and unstable, and PAG lubricants were also known to be unstable—i.e., both components of the composition were disfavored in the art for the intended purposes in the claim. *Id.* at 1351. Unexpectedly, however, the combination of these two components achieved a stable composition. *Id.* at 1354. Yet, the Board held the claims unpatentable, viewing the disadvantages as trade-offs and finding the combination of the two compounds were inherently stable. *Id.* at 1352. We concluded that the Board's reasoning was flawed in a number of ways, but relevant here is that the

claims in *Honeywell* did not attempt to claim the inherent result—instead, they claimed a composition that itself was not inherent, the combination of which had unexpected properties. In other words, in *Honeywell*, a person of ordinary skill in the art would not have been motivated to combine the two compounds in the first place.

Conversely, the claims in *Hospira* contained a limitation that stated the "composition when stored in the glass container for at least five months exhibits no more than about 2% decrease in the concentration of dexmedetomidine." *Hospira*, 946 F.3d at 1327, 1332. There, the claim limitation recited the stability and activity of the composition after storage—an inherent property of the claimed composition. *Id.* at 1329. After concluding the limitation was an inherent property of the otherwise obvious composition, we turned to the district court's analysis of reasonable expectation of success and determined the district court's analysis was "unnecessary" because, "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." *Id.* at 1332.

These two cases provide important guideposts between claims which require knowledge of an inherent property to arrive at the claimed invention and claims which simply claim an inherent property or result. When claims require prior knowledge of the inherent property—e.g., for motivation to combine—then a petitioner would still generally need to demonstrate a reasonable expectation of success. As explained decades ago in *In re Spormann*, unknown properties cannot be used as the basis for such a motivation. 363 F.2d 444, 448 (C.C.P.A. 1966) ("Obviousness cannot be *predicated* on what is unknown." (emphasis added)). But that situation is different from simply claiming an inherent property of an otherwise obvious composition or process—i.e., one obvious without

regard to the property at issue.[16] In this latter context, "there is no question of a reasonable expectation of success." *Hospira*, 946 F.3d at 1332. Any separate analysis on this point is unnecessary. *Id.*

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Turning to the merits, we conclude that both the composition and process claims would have been obvious. With respect to the composition claims, the claims' undisputed Fab-binding ability is dispositive. No reasonable expectation of success argument or analysis is required where the sole disputed limitation was an inherent property of the claimed composition already determined to be obvious. *See id.* As explained above, the independent claims here recite obvious chromatography matrices. The dependent composition claims recite only a natural result of the obvious composition recited in the independent claims. Therefore, the Board did not err in determining that these dependent claims would have been obvious.

With respect to the process claims, we likewise conclude that the claims recite an inherent property of an otherwise obvious composition. Based on the erroneous construction we discussed above, the Board assumed that, unless a skilled artisan first had a reasonable expectation of success of Fab fragment binding, such an artisan would not have prepared the Fab fragments for elution in the chromatography process to begin with. But we disagree that the Board should have limited the claims to Fab fragments. As explained above, the term "Fab part of an

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[16] While much of our case law on inherency in the chemical and biological fields discusses composition claims, we see no reason that these same guideposts do not apply equally to claims for processes of making those compositions.

antibody" refers both to a Fab fragment and the Fab portion of the full antibody. Thus, demonstrating inherency that the ligands would bind to the Fab part of the full antibody does not require separate showing that a person of ordinary skill would first prepare Fab fragments for elution. And because the dependent process claims recite only the property of Fab binding and Fab binding under the proper construction is an undisputedly inherent property on this record, "there is no question of a reasonable expectation of success in achieving [the claimed invention]." *Hospira*, 946 F.3d at 1332. Therefore, with respect to the cross-appeal, we reverse the Board's determination that the process claims were not shown to have been unpatentable.

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Turning back to the main appeal, Cytiva argues that the Board also erred by failing to address secondary considerations—here, that "the claimed chromatography matrices unexpectedly retained their ability to bind to the Fab part of an antibody," J.A. 1434. *See* Appellant's Br. 59 ("Objective indicia of non-obviousness must be considered if present."); *id.* at 63 ("The Board's dereliction of its duty to consider objective indicia of nonobviousness here was error . . ."). But the Board did in fact address this argument. J.A. 48–49. It simply was "not persuaded by Cytiva's unexpected-results argument." J.A. 48.

Cytiva also argues that the Board conflated reasonable expectation of success with unexpected results. Appellant's Br. 62. While we agree that reasonable expectation of success and unexpected results are separate inquiries, we disagree that the Board here conflated these concepts. Instead, the Board appears to have found, based on the facts here, that the reasonable expectation of success included expecting that modifying Domain C with the G29A mutation would "*result[] in a product that binds* at least IgG." J.A. 48 (emphasis added). In other words, the

Board found that binding to an antibody was not unexpected. It is also not unusual that the reasonable-expectation-of-success and unexpected-results inquiries may contain similar underlying factual inquiries. In fact, we have previously stated that reaching different results on these two inquiries may be "internally inconsistent" in certain circumstances. *Honeywell*, 865 F.3d at 1354 (determining that the Board was inconsistent by dismissing evidence of "unpredictability and unexpected properties of the claimed combination by characterizing them as 'inherent'" on the one hand and simultaneously crediting the same evidence as persuasive of unexpected results on the other hand).

While the Board could have been more specific that Fab-binding was not unexpected, rather than explaining that antibody binding was not unexpected, we find that any error in the Board's analysis on this point is harmless because "[t]here is no requirement that the inherent characteristic of the Fab binding needed to be recognized . . . ." J.A. 48–49. In *In re Couvaras*, "Couvaras attempt[ed] to claim a mechanism of action that naturally flows from the co-administration of two known antihypertensive agents." 70 F.4th 1374, 1380 (Fed. Cir. 2023). "According to Couvaras, even if the recited mechanism of action is, effectively, inherent . . . the [result] was unexpected." *Id.* We concluded that "results that naturally flow from the administration of a given compound or mixture of compounds . . . cannot overcome a prima facie case of obviousness, even if the nature of that mechanism is unexpected." *Id.* The same analysis applies to the facts here: Having determined that the independent claims would have been obvious, the recitation of a naturally flowing property of those obvious claims "cannot overcome a prima facie case of obviousness." *Id.*

CONCLUSION

We have considered the parties' remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm the Board's determination that claims 1–7, 10–20, 23–26 of the '765 patent, claims 1–3, 5–7, 10–16, 18–20, 23–30 of the '142 patent, and claims 1–10, 12–14, 16–28, 30–32, and 34–37 of the '007 patent are unpatentable. We reverse the Board's determination that claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent are not unpatentable.

AFFIRMED-IN-PART AND REVERSED-IN-PART

COSTS

No costs.