Keywords: **lead compound, obvious-to-try, inherency, reasonable expectation of success**

General: **A lead compound analysis is not required to determine that a chemical composition is obvious. An inherent property of an otherwise obvious chemical composition is not patentable.**

CYTIVA BIOPROCESS R&D AB v. JSR CORP.
United States Court of Appeals for the Federal Circuit
No. 23-2074
Decided December 4, 2024

I. Facts

Cytiva is the owner of the three patents at issue in this case (U.S. 10,213,765, U.S. 10,343,142, and U.S. 10,875,007.). JSR filed six IPRs challenging all the claims of these patents.

A. Technical Background.

The patents are part of the same family and generally relate to affinity chromatography. Affinity chromatography is a chemical process for isolating antibodies. It is performed according to the following ordered steps:

(1) Chromatography matrices are attached to a ligand.
(2) The chromatography matrices are packed into a column.
(3) A fluid that contains antibodies is poured into the column.
(4) The ligands of the chromatography matrices bind to the antibodies.
(5) The column is washed to separate the chromatography matrices from impurities in the fluid.
(6) The antibodies are isolated by pouring a solution into the column to break the bond between the ligand and the antibodies.
(7) The column is cleaned in place (CIP) with an alkaline solution to remove any remaining impurities.

JSR's patents relate to chromatography matrices with ligands made from Protein A (SPA). SPA is known to bind to certain antibodies and occurs naturally in five similar structures referred to as Domains A, B, C, D, and E. Scientists have also manufactured Domain Z by genetically altering Domain B.

The CIP step is known to degrade ligands. Specifically, amino acids found in each of the SPA domains, are sensitive to the alkaline that is used to clean the columns. Therefore, when scientists mutated Domain Z, they altered a part of the SPA structure to increase its durability to amino acids. This mutation is referred to as the G29A modification (modifying alanine for glycine at the 29th position in the Domain Z structure).

Cytiva's patents relate to chromatography matrix ligands that apply the G29A modification to Domain C. The patents also include various dependent claims relating to the ability

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of the Domain C ligands to bind to certain portions of the antibodies. Indeed, some of the challenged claims discuss binding to the Fab part of the antibodies. Initially, it is worth noting that antibodies are made up of an Fc region and Fab region. The Fab region may separate from the antibody and become a Fab fragment.

B. Patent Trial and Appeal Board Holding.

The Board found 79 of the 83 challenged claims unpatentable. The Board determined that it would have been obvious to apply the G29A mutation to Domain C ligands based on express suggestions in the prior art. The Board, conversely, found that four process claims were not unpatentable. In doing so, the Board reached divergent results with respect to parallel claim language.

Patent Claim	Language	Board Determination
Claims 4, 17 of '765	The chromatography matrix of claim 1, wherein the ligand is capable of binding to the Fab part of an antibody	Unpatentable
Claims 4, 17 of '142 & Claims 11, 29 of '007	The process of claim 1, wherein the ligand binds to the Fab part of an antibody.	Patentable

The Board held that the Fab binding limitation in the composition claims was an inherent property and was, therefore, unpatentable. But the process claims were patentable because JSR failed to show a reasonable expectation of success regarding the modified ligand binding to the Fab part of the antibody. The parties cross-appealed.

C. Arguments on Appeal.

Cytiva first argued that all of the claims in the challenged patents were patentable. Specifically, Cytiva argued that the Board erred by failing to assess whether a person of ordinary skill in the art would have selected Domain C as a lead compound over Domains B and Z. This argument is bifurcated. Cytiva argued that (a) the Board erred by failing to conduct the 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.

Cytiva separately argued that the Board erred regarding claims 4 and 17 of the '765 patent because "the Board failed to account for the unexpected Fab-binding property recited in those claims."

JSR argued that claims 4 and 17 of the '142 patent and claims 11 and 29 of the '007 patent were indistinguishable from the claims 4 and 17 of '765 patent and should have been deemed unpatentable.

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II. Issues

(1) Is a lead compound analysis a prerequisite for a determination that composition claims are obvious?
(2) Does a claim limitation that merely recites an inherent property of an otherwise obvious combination require an additional analysis that demonstrates that a person of ordinary skill in the art would have a reasonable expectation of success achieving the inherent property?

III. Discussion.

The Federal Circuit affirmed in part and reversed in part. All of Cytiva's claims were unpatentable.

A. Lead Compound Analysis.

The lead compound analysis is a generally applicable test to assist courts in assessing obviousness for chemical compounds. It can be viewed as a two-part inquiry. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) At the first step of the analysis, 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 is described as 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." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). At the second prong of the analysis, the court determines whether the prior art supplied 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 1291.

The lead compound analysis may be a helpful tool in assessing patentability—but it is not always required. The Supreme Court, in *KSR Int'l Co. v. Teleflex*, rejected rigid applications of the obviousness doctrine. *See* 550 U.S. 398, 415 (2007). In particular, the lead compound analysis is not a prerequisite for assessing obviousness where the prior-art references expressly suggest the proposed modification. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1359 (Fed. Cir. 2000).

In this case, the Board found that two of the prior references expressly suggested that any of the SPA structures (Domains A, B, C, D, or E) could be modified with the G29A mutation to improve ligand durability. That is, JSR showed that the prior art taught that Domain C could be a starting point. That ends the analysis. It would be inconsistent with obviousness jurisprudence to require JSR to provide a supplemental justification showing that a chemist of ordinary skill would have selected Domain C as a lead compound. *See, e.g., KSR*, 550 U.S.at 421.

Moreover, the Supreme Court has clarified that a "design need or market pressure" and a "finite number of identified, predictable solutions," obviates a composition. *See id.* This has been referred to as the obvious-to-try inquiry. Here the Board found that there is a finite number of solutions, and a design need for modifying the SPA protein to reduce ligand degradation during cleaning phases of chromatography.

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Because the Board applied the obvious-to-try test, the lead compound analysis was not necessary in this case. But even if the lead compound analysis was required, it was satisfied here. Since the prior art suggested the use of any one of the SPA Domains E, D, A, B, or C as the starting ligand, an ordinary chemist would have selected the prior art compounds as starting points for further development. *See Otsuka,* 678 F.3d at 1291.

B. The Relationship Between Process Claims and Composition Claims.

The process and composition claims are written in parallel and, therefore, "must rise or fall together." The process claims recite that "the ligand is capable of binding" and the composition claims recite that "the ligand binds." The Court concluded that the claims must be treated the same because "if the ligand binds, the ligand is capable of binding."

The Board took a different approach. It determined that binding to the Fab part of the antibody was an inherent feature of the compound in the composition claim. But with regard to the process claims, the Board held that a person of ordinary skill in the art would need to be aware (or have a reasonable expectation of success) of the ligand binding to Fab fragments. The Board argued that this prior knowledge was required before the ordinary skill would take the step of "separating [Fab] fragments from the full antibody before the claimed process could be performed."

Neither the process nor the composition claim clarified that the ligand binds to Fab fragments. Thus, a brief claim construction analysis is required. The patents at issue share similar specifications, which state that the ligands are "capable of binding to either full antibodies via Fab-binding; or to antibody fragments which includes the variable parts also known as Fab fragments." The Board erred by limiting "Fab part" to Fab fragment and excluding the remaining Fab region of the antibody.

C. Inherency and Reasonable Expectations of Success.

The final question is whether a skilled artisan would have a reasonable expectation of success of arriving at the claimed invention. Cytiva argued that unexpected properties can cause an otherwise obvious composition to be nonobvious. *See Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354–55. JSR countered by arguing that, as a brightline rule, inherency mandates a reasonable expectation of success. *See Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020).

This case is much closer to *Hospira* than *Honeywell*. *Honeywell* related to a composition for use in air conditioning comprising an HFO refrigerant and a PAG lubricant. 865 F.3d at 1350–51. Because HFO refrigerants and PAG lubricants were both known to be unstable, the combination of the two was unexpected. Therefore, a person of skill in the art would not have been motivated to combine the two. In *Hospira*, the critical limitation was a composition comprised of certain structures that did not deteriorate by more than 2% when stored in a glass container for five months. 946 F.3d at 1327, 1332. In analyzing these two cases, the Court drew a line between

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inherent properties that require prior knowledge and inherent properties of otherwise obvious compositions. *See In re Spormann 363 F.2d 444, 448 (C.C.P.A. 1966).*

Here, both the composition and process claims recite a natural result of otherwise obvious chromatography matrices. The fact that SPA ligands bind to the Fab part of an antibody—opposed to just Fab fragments—was an obvious property of the ligands. The claims, therefore, did not require any prior knowledge and were unpatentable.

Lastly, the Board noted that this analysis should not be conflated with the secondary considerations of nonobviousness. Specifically, the reasonable expectation of success test described above is separate from the unexpected results indicia of nonobviousness.

IV. Conclusion

When reviewing chemical compound claims, patent examiners may start with the lead compound analysis, but they do not have to. Other tests, such as the obvious-to-try test, may also be a useful starting point. During prosecution, the patent applicant may benefit from steering the examiner towards the obvious-to-try test if there is an indefinite or unpredictable number of solutions to the technical problem at issue. Moreover, if the applicant is claiming an inherent property of a composition, the applicant should argue that the inherent property required prior knowledge and a chemist would, therefore, lack a reasonable expectation of success in arriving at the claimed inherent property.

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