UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS GENE THERAPIES, INC. &
NOVARTIS PHARMACEUTICALS CORPORATION,
Petitioner

v.

GENZYME CORPORATION,
Patent Owner.

Case: IPR2023-01044
Patent No. 10,429,288

PATENT OWNER'S REQUEST FOR REHEARING BY THE DIRECTOR

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Patent Owner, Genzyme, respectfully requests Director Review of the Board's Decision in Paper 10, "Granting Institution of *Inter Partes* Review" ("Decision"). 37 C.F.R. § 42.71(c)-(d).

I. Introduction

Director Review is warranted because the Board applied an "erroneous conclusion[] of law" and made "erroneous findings of material fact" by relying on a defunct version of Rule § 42.108(c) rescinded three years ago to improperly view the "testimonial evidence … in the light most favorable to the petitioner." Decision, 25 (quoting former Rule 37 C.F.R. § 42.108(c)); Revised Interim Director Review Process at § 2.b. (Sep. 18, 2023).[1] The text of Rule § 42.108(c) the Board relied on for its analysis of each Ground was eliminated, so Petitioners are no longer entitled to this presumption. PTAB Rules of Practice, 85 FR 79120, 79122 (Dec. 9, 2020) ("Eliminating the Presumption at Institution Favoring Petitioner as to Testimonial Evidence"). The rule change responded to comments "that the practice to view testimonial evidence in the light most favorable to the petitioner…conflicts with the decision of Congress to place the burden of proof on

[1] On January 17, 2024, the Board instituted IPR2023-01045 ("IPR1045"), also challenging the '288 patent, and made a similar error. *See* IPR1045, Paper 10. Patent Owner is concurrently filing for Director Review in that proceeding.

the petitioner" to which the Office responded that it "agrees it is inconsistent with the statutory framework to view testimonial evidence in the light most favorable to petitioners." *Id.* at 79125 (citing 35 U.S.C. § 314(a)). Thus, under the currently applicable rule, the Board must evaluate "any testimonial evidence submitted with a patent owner's preliminary response" and account for it "as part of the totality of the evidence." *Id.* at 79122. By improperly evaluating the evidence "in the light most favorable to petitioner" (Decision, 25, 39), the Board acted inconsistently with 35 U.S.C. § 314(a) by discounting Patent Owner's evidence demonstrating the Petition's failure to establish a reasonable likelihood that the challenged claims were unpatentable. 37 C.F.R. § 42.71(d). When properly considered without a 'thumb on the scale' in favor of Petitioner, Patent Owner's evidence demonstrates that the Petition failed to meet its burden for institution. Accordingly, the Board's Decision should be vacated, and institution denied.

II. The Board Based Institution on an Erroneous Application of a Presumption Favoring Petitioner Eliminated from Rule § 42.108(c)

The Board incorrectly applied a version of 37 C.F.R. § 42.108(c) that was outdated since a December 9, 2020 rule change. Application of this improper presumption favoring Petitioner led the Board to overlook critical evidence and discount Patent Owner's evidentiary showings that the Petition failed to establish a reasonable likelihood that the challenged claims were unpatentable. As a result of this error, the Board premised its Decision on each Ground on the now-defunct

presumption favoring Petitioner. *See* Decision, 24-25 (Ground 1), 31 (Ground 2), 33 (Ground 3, claim 1), 39 (Ground 3, claim 2). Currently applicable Rule § 42.108(c) requires that "any testimonial evidence submitted with a patent owner's preliminary response will be taken into account as part of the totality of the evidence." *Id.* at 79122. Proper weighing of the evidence under the current rule should have resulted in a denial of institution. In 2020, Rule § 42.108(c) was revised "to ***delete*** the phrase 'but ***a genuine issue of material fact created by such testimonial evidence will be viewed in the light most favorable to the petitioner*** solely for purposes of deciding whether to institute [a] review.'" 85 FR at 79122. This change intentionally "***eliminated the presumption*** that a genuine issue of material fact created by the patent owner's testimonial evidence filed with a preliminary response will be viewed in the light most favorable to the petitioner for purposes of deciding whether to institute a review." *Id.* at 79120; *see also id.* at 79122; *Sani-Tech West, Inc. v. Meissner Filtration Prods., Inc.*, No. IPR2022-01123, Paper 9 at 4-5 (PTAB Jul. 6, 2023).

Rulemaking comments noted the "presumption in favor of the petitioner is biased towards institution and discourages patent owners from submitting conflicting testimonial evidence with a preliminary response." 85 FR at 79125. The Office "agree[d] that any presumption in favor of institution is inappropriate" and that "a patent owner might not be inclined to submit pre-institution testimony

that might, under the presumption, create an issue of material fact." *Id.* The applicable rule "removes any bias or appearance of bias in favor of petitioner, and provides a balanced approach to ensure that all testimonial evidence submitted by the parties is fairly considered." *Id*. The Board's improper application of the presumption, however, deprived Patent Owner of fair consideration the rule change was intended to provide.

Further, the Office observed that "having a presumption in favor of the petitioner at the institution stage for one class of evidence may lead to ***results that are inconsistent with this statutory*** scheme…the Office has an interest in ensuring that testimonial evidence is treated ***similarly to other evidence for purposes of institution and consistently*** with the statutory scheme" that places the burden on petitioner. 85 FR at 79122 (emphasis added). Under current Rule § 42.108(c), the Board therefore must "weigh the strengths and weaknesses of the testimony for purposes of institution," which it failed to do here. *Id.*; *see also Sani-Tech*, No. IPR2022-01123, Paper 9 at 5 (The Board "must evaluate all information presented in both the Petition and the Patent Owner Preliminary Response, as well as any supporting evidence, including any testimonial evidence.")

III. Application of the Improper Rule Led the Board to Overlook Fatal Deficiencies in Petitioner's Proof of Unpatentability Grounds

The Decision did not treat Petitioner's and Patent Owner's evidence "similarly…and consistently" as required. 85 FR at 79122. The Board explicitly

based its institution decision for Grounds 1-3 on the premise that the testimonial evidence provided with Patent Owner's Preliminary Response "create[d] genuine issues of material fact" (*e.g.*, Decision, 24) and that these "genuine issue[s] of material fact" should be resolved "in the ***light most favorable to Petitioner***." Decision, 25, 39 (citing Rule § 42.108(c)) (emphasis added); *see also id.* at 31, 33. However, Revision of Rule § 42.108(c) specifically eliminated this presumption. The Board should have evaluated the totality of the evidence without favoring Petitioner. *Supra* § II. As required, this request identifies "the place where each matter was previously addressed" in Patent Owner's papers (*see* 37 C.F.R. § 42.71(c)) to highlight the Petition's failures to establish a reasonable likelihood of demonstrating unpatentability under the proper "totality of the evidence" standard.

A. The Board Discounted Evidence Exposing Failures of Proof for the Petition's Ground 1 Anticipation Argument

The Petition contended that Le Bec anticipated claim 1, including by disclosing Element 1(c), which recites "integrating the area under each peak in the C(s) distribution to determine the relative concentration of each peak, wherein each peak represents a species of [rAAV] particle." Decision at 19-21. The Board acknowledged that the Patent Owner's Preliminary Response ("POPR") and supporting testimonial evidence raised two significant concerns regarding deficiencies in Ground 1, but discounted those concerns, "determin[ing] that the information presented by Patent Owner ***creates genuine issues of material fact***

about whether a person of ordinary skill in the art would have interpreted Le Bec to disclose [the peak integration element]." Decision, 23-25. Rather than weigh the evidence, as required by applicable Rule § 42.108(c), the Board improperly viewed this factual dispute "in the light most favorable to Petitioner… determin[ing] only that Petitioners' evidence is sufficient for institution." Decision, 25.

The Decision did what the Office cautioned against by improperly giving heightened, but unwarranted, deference to Petitioner's evidence, and thereby rendering an institution decision inconsistent with the requirements of 35 U.S.C. § 314(a). By evaluating the evidence in the light most favorable to Petitioner, the Decision did not adequately address the Petition's failures of proof.

The POPR, supported by testimonial evidence, spotlighted holes in the Petition's evidence that rendered it unable to meet its burden—holes that Petitioner cannot later plug through supplementing its evidence. POPR, 30 (citing *In re Magnum Oil Tools Int'l Ltd.,* 829 F.3d 1364, 1381 (Fed. Cir. 2016); PTAB Consolidated Trial Practice Guide (Nov. 2019), 73). Petitioner was required to wholly make its case in its Petition, but fell short, and this cannot be remedied by additional arguments by Petitioner. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.,* 821 F.3d 1359, 1369 (Fed. Cir. 2016) (quoting 37 C.F.R. § 42.23(b)) ("All arguments for the relief requested in a motion must be made in the motion.")

Although the Board summarized certain arguments and testimony from the POPR, it did *not* properly weigh the evidence against the Petition when it resolved "genuine issue[s] of material fact in the light most favorable to Petitioner." Decision, 25, 39. The Board overlooked uncontroverted evidence in the POPR establishing why Le Bec does not disclose "integrating the area under each peak in the C(s) distribution to determine the relative concentration of each peak, wherein each peak represents a species of [rAAV] particle." This missing disclosure meant that Le Bec could not possibly meet "each and every limitation" of claim 1. *SRI Int'l, Inc. v. Cisco Sys., Inc.,* 930 F.3d 1295, 1306 (Fed. Cir. 2019).

1. The Board Failed to Credit Uncontroverted Evidence that Le Bec Does Not Provide Concentrations for Certain Peaks

The Decision notes Patent Owner's arguments and supporting testimony, including its "contention that Petitioner 'fails to identify where Le Bec discloses integrating and determining the area of specific peaks in its distribution, particularly those relating to partial and fragmented genome species, for example at 77S and 90S.'" Decision at 24 (citing POPR at 33, 35). But in declining to weigh Patent Owner's evidence against Petitioners' evidence, the Board did not address this deficiency in its discussion. Decision, 23-24. The POPR and supporting testimony demonstrate that Le Bec fails to disclose "integrating the area under" at least two peaks in its C(s) distributions, such that Le Bec alone fails to disclose this element of claim 1. POPR, 35, 38, 40, 43. The "Petition is understandably silent on

Le Bec's lack of disclosure of concentrations for each peak in its C(s) distributions," including the peaks at 77S and 90S. POPR, 33. Thus, "Patent Owner correctly identified a deficiency in Petitioner's…challenges" overlooked by the Board through its improper application of Rule § 42.108(c). *Sani-Tech West,* No. IPR2022-01123, Paper 9 at 6.

2. The Board Overlooked Evidence that Le Bec's Disclosure of SEDFIT Does Not Meet Claim Element 1(c)

The Board acknowledged the testimony of Patent Owner's expert, Dr. Jeffrey C. Hansen, that "the POSA would not have considered Le Bec to have provided…that the area under ***each peak*** was converted to concentrations by applying the extinction coefficients for the rAAV species corresponding to each peak." Decision, 24 (quoting Ex. 2001 ¶ 97). But the Board "credit[ed] the testimony of Dr. Berkowitz that 'the SEDFIT software referenced in Le Bec and available prior to January 2015 calculated relative concentrations by integrating the area under the peaks….'" Decision 25 n.3 (quoting Ex. 1020 ¶ 83). By crediting Dr. Berkowitz's testimony, the Board overlooked at least three deficiencies in the Petitioners' anticipation arguments the POPR identified.

First, the fact that "users [of SEDFIT] ***could*** determine relative concentrations by integrating areas under the curve" (POPR, 42), does not overcome the fact neither the Petitioner nor Dr. Berkowitz provides any evidence that Le Bec disclosed concentrations for certain peaks, including those at 77S and

90S. POPR, 35. Thus, there is no evidence in the record supporting the Petition's conclusion that Le Bec used SEDFIT software for "integrating the area under ***each peak*** in the C(s) distribution to determine the relative concentration of ***each peak***…." POPR, 32-33.

Second, the Board overlooked Patent Owner's argument that while SEDFIT may measure the relative areas of peaks, the relative areas do not correspond to relative concentrations of the rAAV species when using absorbance spectroscopy. Claim Element 1(c) recites "determin[ing] the relative ***concentration*** of each peak," which could not be done merely by determining peak area. Patent Owner explained that "the POSA would have understood that to determine concentration from AUC peaks obtained via absorbance spectroscopy at 276 nm, the method that Le Bec employs…an extinction coefficient would have been required for each peak." POPR, 42-43 (citing Ex. 2001, ¶ 110). "The Petition and Berkowitz Declaration fail to identify how Le Bec's absorbance-based method determines the concentration[s] of" the rAAV species represented by peaks at 77S or 90S "when it fails to provide those concentrations…or the extinction coefficient at 276 nm required to have determined those concentrations." *Id.* (citing Ex. 2001, ¶ 110).

Third, the Board overlooked Patent Owner's evidence that Dr. Berkowitz's own publication supported the premise "that to determine concentration of a viral particle using an absorbance-based AUC detection, the POSA ***may need to know***

the extinction coefficient for that species," for example, if detection applies UV absorbance like Le Bec. POPR, 43 (citing Ex. 1004, 17; Ex. 2001, ¶ 111) (emphasis added). Berkowitz 2007 used SEDFIT. Ex. 1020, ¶ 31 (citing Ex. 1004, 25). Thus, Berkowitz 2007 confirms that merely determining peak area alone is insufficient for determining concentration when peaks are detected by UV absorbance. By improperly applying the presumption in favor of Petitioner, the Board did not adequately consider the points described above. Evaluation of the totality of evidence, as required by current Rule § 42.108(c), reveals that Le Bec falls short of meeting Element 1(c).

B. The Board Discounted Evidence Exposing Failures of Proof for the Petition's Ground 2 and 3 Obviousness Arguments for Claim 1

The Board's evaluation of Grounds 2 and 3 was also premised on the improper presumption favoring Petitioner. Decision 30-31, 33. The Decision concluded that "[a]lthough Patent Owner's arguments, supported by the declaration of Dr. Hansen, may have merit, those arguments raise a genuine issue of material fact that we ***decline to resolve on the current record***." Decision at 31, 33 (emphasis added). But Rule § 42.108(c) mandates that the Board "take into account…the totality of the evidence." 85 FR at 79122. The Board simply did not do so here.

For Claim Element 1(c), the Board acknowledged Patent Owner's "contention that Le Bec would need to be modified to identify partial or

fragmented rAAV species, and that a 'POSA would have understood, for example, that the need to know the extinction coefficient of each rAAV species in Le Bec's disclosure presented an obstacle to determining the concentrations of rAAV peaks associated with partial or fragmented genome and extinction coefficients were not readily obtained.'" Decision, 31. But by improperly applying a presumption favoring Petitioner, the Board overlooked evidence establishing Petitioner's incontrovertible failure to carry its burden on obviousness. Petitioner's omission cannot be corrected in this proceeding. *Intelligent Bio-Sys.,* 821 F.3d at 1369.

Le Bec lacks the requisite extinction coefficients to permit concentration determinations using SEDFIT. Thus, the "POSA would not have been motivated to determine the concentration of certain peaks, including peaks at 77S and 90S… because it would not have been possible to accurately determine their concentrations without their extinction coefficients at 276 nm." POPR, 52 (citing Hansen, ¶ 119). Ignoring this evidence, the Board credited Dr. Berkowitz's testimony relying on "Le Bec's own use of the SEDFIT software" such "that relative concentrations could be determined by integrating the areas under the peaks using the SEDFIT software functionality." Decision, 30-31 (quoting Ex. 1020, ¶ 182). As explained above (*supra* § III.A.2), the fact that "users [of SEDFIT] ***could*** determine relative concentrations by integrating areas under the curve" (POPR, 42 (citing Petition, 28 (citing Ex. 1020, ¶¶27-40, 83)) fails to

establish how the POSA: (1) would have been able to apply SEDFIT to arrive at Element 1[c] (POPR, 47-48); (2) would have been motivated to apply SEDFIT to arrive at the Element 1(c) (POPR, 49-53); or (3) would have had a reasonable expectation of success in doing so (POPR, 53-55).

The Decision further overlooked Patent Owner's evidence that the "Berkowitz 2007 publication…explains that 'AUC experiments can provide accurate and useful results when appropriate steps are taken to deal with the variability in signal response (extinction coefficient) for different adenovirus species.'" POPR, 50 (quoting Ex. 1004, 17). Without the extinction coefficient of ***each rAAV species***, it is not possible to determine their concentrations because "the correlation between peak area and concentration may be different for each species." *Id.* (citing Ex. 1005, 152; Hansen, ¶¶ 117-120). For this reason, "Dr. Berkowitz 'ha[d] not attempted to apply corrections to account for extinction coefficient differences.'" *Id.* (quoting Ex. 1004, 21). Even with SEDFIT, "[w]ithout extinction coefficients, merely integrating peak area in Le Bec's C(s) distribution based on absorbance at 276 nm would not have alone provided a meaningful measure of concentration for *each* species in the distribution." *Id.* at 53 (citing Ex. 2001, ¶ 121); *see also supra* § III.A.2. The Decision overlooked that Petitioner provided no evidence for how the POSA would have overcome Le Bec's failure to provide extinction coefficients "for partial or fragmented rAAV species,

like those at 77S and 90S," without which Petitioner "cannot establish a reasonable expectation in successfully determining the relative concentrations of each peak…based on Le Bec alone." POPR, 53-54 (citing Ex. 2001, ¶¶ 122-123).

In IPR1045, the Board "f[ound] some merit" in arguments made by Patent Owner for the integration element of claims 5-8 and 15. *See* IPR1045, Paper 10 at 26. There, the Board recognized that "the issue is not whether a [POSA] would have known how to integrate peaks, rather the issue…is whether a [POSA] would had ***reason to modify Le Bec*** to integrate the area under each peak in the C(s) distribution ***to determine the relative concentration of each species***…as required by the challenged claims." IPR1045, Paper 10 at 26 (emphasis added). This same deficiency impacts Ground 2 and 3's obviousness arguments here. As the POPR at 49 pointed out, "[e]vidence that supports, rather than negates, patentability," including Berkowitz "must be fairly considered," because the POSA has "knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *In re Dow Chem. Co.,* 837 F.2d 469, 473 (Fed. Cir. 1988). The Board's discussion of Ground 3 of IPR1045 indicates that taking the 'thumb' that is the presumption favoring Petitioner 'off the scale' favors Patent Owner's nonobviousness evidence. Thus, in crediting Petitioner's testimony while "declin[ing] to resolve on the current record" the issues raised by the POPR, the Board disregarded the failures in Petitioner's obviousness proof.

Evaluating the parties' evidence under current Rule § 42.108(c), Petitioner did not establish a reasonable likelihood of unpatentability in Grounds 2 and 3.

C. The Board Failed to Credit Evidence Exposing Failures of Proof for the Petition's Ground 3 Obviousness Arguments for Claim 2

Claim Element 2(c) recites that "the genome size of a particular species of [rAAV] particles is calculated by comparing the S value of the species to a standard curve generated by S values of [rAAV] particles comprising encapsidated AAV genomes of known nucleotide size." As the POPR explained, none of "the asserted prior art references taught or suggested the 'standard curve' recited in Element 2[c]." POPR, 59. Element 2(c) works because the "inventors surprisingly found that sedimentation coefficients were linearly related to genome mass for rAAV particles, and that unlike adenovirus particles (Ex. 1004, 31-32), the frictional coefficient appeared to remain constant." POPR, 5.

Petitioner relied on Dr. Berkowitz's testimony that "a POSA would generally expect the S-value of an rAAV particle with a variant genome to vary linearly" because "for rAAV particles differing only by their genome size, a POSA would expect any changes would be internal and not affect the frictional force of the AAV capsid shell." Ex. 1020, ¶ 213. The Board acknowledged that Petitioner's relied-upon art, Cole (Ex. 1005) and Berkowitz 2007 (Ex. 1004), contradicted Dr. Berkowitz's testimony regarding the POSA's expectation that frictional coefficients of viral particles remain the same. Decision, 38-39 (citing POPR 61-

62; *compare* Ex. 1020, ¶ 213). Nonetheless, the Board declined to address that Petitioner's own evidence conclusively undercuts its testimony. Instead, the Board again relied improperly on the superseded version of Rule § 42.108(c). Decision, 39 ("Because the conflicting testimony creates a genuine issue of material fact, we view the material fact in the light most favorable to Petitioner….").

Cole (Ex. 1005) and Berkowitz 2007 (Ex. 1004) confirm that a POSA would not have expected frictional coefficients to remain the same between distinct species of rAAV particles. Dr. Berkowitz, however, failed to cite any authority to support the contention that "a POSA would expect any changes would be internal and not affect the frictional force of the AAV capsid shell." Ex. 1020, ¶ 213. Thus, "Patent Owner correctly identified a deficiency in Petitioner's … challenges," for which Petitioner does not provide opposing evidence. *Sani-Tech West,* No. IPR2022-01123, Paper 9 at 6. Properly evaluating the evidence under the governing Rule, Petitioner failed to meet its burden for establishing a reasonable likelihood that claim 2 is unpatentable.

IV. Conclusion

For the foregoing reasons, Patent Owner respectfully requests Director Review and that the Board's Institution Decision be vacated and Institution denied.

Respectfully submitted,

Dated: January 23, 2024

/ Blaine M. Hackman /

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Counsel for Patent Owner

CERTIFICATE OF SERVICE

I certify that today in:

Novartis Gene Therapies, Inc. & Novartis Pharmaceuticals Corporation v. Genzyme Corporation, IPR2023-01044 (U.S. Patent 10,429,288)

I caused to be served a copy of:

PATENT OWNER'S REQUEST FOR REHEARING BY THE DIRECTOR

upon:

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