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EXPERT ANALYSIS

The Federal Circuit Allows Petitioners To Submit New Evidence After The Start of an Inter Partes Review

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In June the U.S. Court of Appeals for the Federal Circuit rejected Genzyme Therapeutics Products' argument that the Patent Trial and Appeal Board's decision to invalidate two patents for the treatment of a rare genetic muscle condition violated the Administrative Procedure Act. *Genzyme Therapeutic Prods. v. BioMarin Pharm.*, Nos. 2015-1720 and 2015-1721, 2016 WL 3254734 (Fed. Cir. June 14, 2016).

Genzyme said the PTAB should not have relied on facts and arguments that were not set forth in the initial decision to institute two inter partes review proceedings.

The Federal Circuit, however, ruled that the submission of new evidence should be expected in IPR proceedings, provided that the opposing party is given notice and an opportunity to respond.

The IPR is a relatively new administrative proceeding Congress authorized in 2012 through the Leahy-Smith America Invents Act. Genzyme, a subsidiary of the French pharmaceutical giant Sanofi, is a direct competitor of BioMarin Pharmaceutical Inc. in the market for the treatment of genetic disorders.

PATENTS FOR REVIEW

The patents at issue in the IPR were U.S. Patent Nos. 7,351,410 and 7,655,226. The patents are owned by Genzyme, and they treat Pompe disease with injections of human acid a-glucosidase. Pompe disease is a genetic condition associated with a deficiency or absence of the lysosomal enzyme acid a-glucosidase, also known as GAA. GAA breaks down glycogen into glucose.

A person with Pompe disease has significantly reduced levels of GAA, or no GAA at all, and is unable to break down glycogen into glucose. As a result, glycogen collects in the muscles in excessive amounts.

The most serious form of Pompe disease typically causes death from heart failure within a year, according to the National Institutes of Health.

Research efforts focused on treating the disease through enzyme replacement therapy. By injecting patients with GAA from other sources, experts hoped they could counteract the effects of harmful glycogen buildup.

These efforts failed because the injected enzyme was predominantly taken up by the patient's liver, reducing glycogen levels there but not in the skeletal or heart muscles — where it does the most harm.

Researchers theorized that the failure of early experiments could be overcome by modifying the injected GAA to include mannose-6-phosphate, or M-6-P. M-6-P promotes GAA uptake in heart

and skeletal muscle cells containing M-6-P receptors, including cells that failed to take up GAA in prior treatment attempts.

Another problem that needed to be solved was how to manufacture human GAA for injection into patients with Pompe disease.

The solution: Animals such as mice and other mammals could have their genomes altered to produce human GAA that researchers could extract.

Finally, researchers faced the challenge of developing a dosing schedule.

A factor bearing on the dosing schedule was the half-life for GAA. That half-life was known to be six to nine days, suggesting a relatively long dosage interval for recombinant GAA of once per week or once every other week.

By 1997 research had progressed far enough that the Food and Drug Administration approved Duke University's application for "orphan drug" designation for a new therapy for Pompe disease based on the injection of a recombinant form of GAA.

THE IPR PROCEEDINGS

In 2016 BioMarin filed petitions requesting IPR proceedings for the '410 and '226 patents.

The PTAB found that a person of ordinary skill would have been motivated to pursue the clinical development of the therapy disclosed in one of the references.

For the '410 patent, the PTAB instituted an IPR on two grounds: the combination of the Duke press release and two references known as Barton and van der Ploeg '88; and the combination of a reference known as Reuser with Barton and van der Ploeg '88.

For the '226 patent, the board instituted review of claims 1 and 3 for obviousness based on the Duke press release, Reuser and a reference known as van Hove. The PTAB also instituted an IPR of claims 4 through 6 of the '226 patent for obviousness based on the Duke press release, Reuser, Barton and van der Ploeg '88.

In patent owner responses filed in both IPRs, Genzyme argued that because all of the combinations of references described in vivo experiments, a person of ordinary skill would not find those experiments predictive of results in a human patient.

Because the board did not institute the IPRs based on any references that included in vivo data from studies on live animals, Genzyme argued that BioMarin should not be permitted to use any of the prior art showing successful in vivo tests to demonstrate obviousness.

In its reply, BioMarin responded to Genzyme's arguments by citing two additional prior art references describing in vivo studies, referred to as van der Ploeg '91 and Kikuchi.

Van der Ploeg '91 found that the addition of M-6-P to GAA led to significantly increased uptake of GAA in mouse heart and skeletal muscle tissue.

Kikuchi found that GAA deficiencies in Japanese quail suffering from symptoms similar to the symptoms of Pompe disease could be successfully treated with intravenous injections of GAA modified with M-6-P.

In its final decision, the PTAB held that the challenged claims of the '410 patent would have been obvious. *BioMarin Pharm. v. Genzyme Therapeutic Prods,* IPR2013-00534, 2015 WL 1009195 (P.T.A.B. Feb. 23, 2014).

The board also found the '226 patent was invalid as obvious. *BioMarin Pharm. v. Genzyme Therapeutic Prods.*, IPR2013-00537, 2014 WL 2527798 (P.T.A.B. Feb. 24, 2014).

The board noted that Reuser disclosed every claim limitation other than a biweekly dosing schedule and that the claimed dosing schedule would have been arrived at by routine optimization.

For claim 6 of the '226 patent, directed to reducing heart muscle symptoms, the PTAB found that an effective treatment for Pompe disease would treat that condition as well.

The board also found that a person of ordinary skill would have been motivated to pursue the clinical development of the therapy disclosed in Reuser.

It explained that by Dec. 7, 1998, "all that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range, and its corresponding dosing schedule, would have been safe and effective for the treatment of human patients."

By the 1998 priority date, the board found, the field related to the development of an enzyme replacement therapy for Pompe disease had matured to the point that it was recognized that GAA had to be modified with M-6-P. It further found that in vivo studies had been performed in which GAA containing M-6-P had been intravenously administered to mice and Japanese quail.

The PTAB concluded that a person of ordinary skill in the art would have had a reasonable expectation of success and no more than routine processes were needed to achieve the results recited in the disputed claims.

APA REQUIREMENTS

On appeal, Genzyme argued that the PTAB violated the requirements of the APA because it relied on facts and legal arguments that were not set forth in the initial institution decisions.

Therefore, according to Genzyme, it was denied notice of the issues to be considered by the PTAB and an opportunity to address the facts and legal arguments used by the board to determine patentability.

The Federal Circuit disagreed. It noted that in an IPR, the APA requires the PTO to provide a patent owner with timely notice of matters of fact and law asserted against the patent as well as an opportunity to respond with facts and arguments.

The Federal Circuit in *Belden v. Berk–Tek LLC*, 805 F.3d 1064 (Fed. Cir. 2015), said the notice and opportunity-to-be-heard provisions of the APA have been construed to mean that "an agency may not change theories in midstream without giving respondents reasonable notice of the change" and "the opportunity to present argument under the new theory."

In this case, the board did not "change theories in midstream," much less deny Genzyme notice of any such change. The board's final written decisions were based on the same combinations of references that were set forth in its institutional decisions.

Thus, the Federal Circuit held that Genzyme could not convincingly argue that it lacked notice of the specific combinations of references that the board relied on in finding the claims invalid.

"The principal thrust of Genzyme's APA challenge is that the board cited references in its final written decisions that were not specifically included in the combinations of prior art on which the board instituted review," the Federal Circuit said.

In particular, Genzyme objected to the PTAB's citation of two references dealing with in vivo testing: the Kikuchi and van der Ploeg '91 references.

However, the Federal Circuit said the introduction of new evidence in the course of a trial is to be expected in IPR trial proceedings, as long as the opposing party is given notice of the evidence and an opportunity to respond to it.

The Federal Circuit explained:

> Genzyme's argument that the institution decision must refer to every bit of evidence that is relied on by the board in its final written decision reflects a misunderstanding of the role of the institution decision in IPR proceedings before the board. There is no requirement, either in the board's regulations, in the APA, or as a matter of due process, for the institution decision to anticipate and set forth every legal or factual issue that might arise in the course of the trial. ... Because the institution decision comes at the outset of the proceedings and the patentee is not obligated to respond before the

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> board makes its institution decision, it is hardly surprising that the board cannot predict all the legal or factual questions that the parties may raise during the litigation.

The Federal Circuit said the development of evidence during an IPR trial is consistent with the oppositional framework of an IPR proceeding. "The parties present their evidence up front, the patent owner offers any amendments, and the PTO simply decides whether the challenger has met his burden of proving invalidity," it explained.

The purpose of the trial is to give the parties an opportunity to construct a record by submitting evidence.

The Federal Circuit emphasized that the critical question for determining compliance with the APA and due process was whether Genzyme received "adequate notice of the issues that would be considered, and ultimately resolved, at that hearing."

The Federal Circuit explained Genzyme had not shown that the board's decisions relied on any factual or legal issues on which Genzyme was denied notice or an opportunity to be heard in the IPR.

The Federal Circuit also said Genzyme could not fairly argue it lacked notice that the board might cite Kikuchi and van der Ploeg '91 in its final written decisions, because Genzyme itself raised the issue of the in vivo studies in its patent owner responses. In those responses, it argued that Kikuchi and other in vivo studies cited in its petitions should not be considered as rebuttal evidence.

Specifically, BioMarin argued in its replies to Genzyme that the in vivo references were relevant to show the state of the art at the time of the inventions.

Thus, Genzyme had ample notice that those prior art references were potentially relevant and that the board might address them in its final written decisions.

The Federal Circuit said it was clear from the record as a whole that Genzyme had actual notice of the in vivo references and an opportunity to respond to them.

For example, Genzyme argued that the in vivo references could be used only for limited purposes.

In addition, the regulations governing IPR proceedings provide patent owners with procedural mechanisms that enable them to respond to evidence raised in the petitioner's reply or move to exclude it.

BioMarin raised the in vivo data issue in its reply, stating that the fact that BioMarin's expert, Dr. Gregory M. Pastores, testified that in vitro data was sufficient and was confirmed by in vivo data should not have prevented the board from considering these references.

In addition, the Federal Circuit explained that Genzyme could have filed a motion to exclude the in vivo references. The court further pointed out that Genzyme could have asked for leave to file a surreply, which PTAB practice allows.

Even though Genzyme had actual notice that BioMarin was relying on the in vivo references to rebut Genzyme's arguments, Genzyme failed to take advantage of its procedural options to exclude that evidence or respond to BioMarin's arguments.

Thus, the Federal Circuit said, the substance of Genzyme's argument was a challenge to the propriety of the PTAB's use — for any purpose — of a reference that was not part of the combinations submitted in the institution decisions.

However, the Federal Circuit explained that the Kikuchi and van der Ploeg '91 references were used by the board only to describe the state of the art as of Dec. 7, 1998; the board did not rely on them to establish any claim limitations used in the rejections.

According to the Federal Circuit:

> The board may consider a prior art reference to show the state of the art at the time of the invention, regardless of whether that reference was cited in the board's institution decision.

In sum, the Federal Circuit held Genzyme was not denied notice of the in vivo references or an opportunity to respond to them. And to the extent Genzyme contended that the board used those references for an improper purpose, the Federal Circuit disagreed.

PRACTICE TIP

The Genzyme decision makes it clear that an IPR petitioner can submit new evidence to support obviousness in response to a patent owner's argument in the initial response to the petition prior to institution.

The decision also makes it clear that the IPR trial record can be expected to evolve over the course of the proceeding.

The Federal Circuit stressed that Genzyme could have filed a motion to exclude the references or sought leave to file a surreply to provide a substantive response, but it did neither.

Patent owners and petitioners should carefully scrutinize filings to make sure any new evidence or argument is objected to or rebutted in a timely manner.

Irah H. Donner is an intellectual property partner at **Manatt, Phelps & Phillips** in New York. His practice focuses on the counseling, acquisition and enforcement of all forms of IP rights, with particular emphasis in the patenting of computer software and hardware-related inventions, including telecommunications, wireless and satellite communication technology, financial software and trading platforms. He is the author of "Patent Prosecution: Practice and Procedure Before the U.S. Patent Office" and "Constructing and Deconstructing Patents."