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Federal Circuit Patent Bulletin: *Millennium Pharm., Inc. v. Sandoz Inc.*

July 18, 2017

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."

On July 17, 2017, in *Millennium Pharm., Inc. v. Sandoz Inc.*, the U.S. Court of Appeals for the Federal Circuit (Newman,* Mayer, O'Malley) reversed-in-part, vacated-in-part and remanded-in-part the district court's judgment that certain claims of U.S. Patent No. 6,713,446, which related to lyophilized D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate for treating multiple myeloma and mantle cell lymphoma marketed as Velcade®, were invalid for obviousness under 35 U.S.C. § 103. The Federal Circuit stated:

The question is whether a person of ordinary skill, seeking to remedy the known instability and insolubility and to produce an efficacious formulation of bortezomib, would obviously produce the D-mannitol ester of bortezomib, a previously unknown compound. The prior art contains no teaching or suggestion of this new compound, or that it would form during lyophilization. Sandoz identifies no reference or combination of references that shows or suggests a reason to make the claimed compound. No reference teaches or suggests that such a new compound would have the long-sought properties of stability and solubility, and sufficiently dissociate to release bortezomib at an effective rate in the bloodstream, all critical to effective use for treating multiple myeloma.

The D-mannitol ester of bortezomib is a new compound with distinct chemical properties. We consider 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

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reasonable expectation of success." The parties agree that bortezomib is the proper lead compound for this analysis. It is not disputed that the Velcade® compound provided unexpected properties, solving the problems that accompanied bortezomib.

[T]he prior art does not teach or suggest that lyophilization of bortezomib in the presence of mannitol would produce a chemical reaction and form a new chemical compound, or provide a reason to make this specific new chemical compound, or that this new compound would solve the previously intractable problems of bortezomib formulation. Although mannitol was a known bulking agent, and lyophilization was a known method of drug formulation, nothing on the record teaches or suggests that a person of ordinary skill should have used mannitol as part of a synthetic reaction to make an ester through lyophilization. A result is obvious when it is "the natural result flowing from the operation as taught," or a "property that is necessarily present" when applying a process disclosed in the prior art. Sandoz failed to show that it was obvious to use mannitol to make an ester during lyophilization, or that the ester would solve the problems experienced with bortezomib.

Sandoz defends the district court's ruling by citing three groups of references that purportedly provide the required teaching or suggestion. The first group shows that lyophilization is a known technique to prepare pharmaceutical formulations, although no reference shows lyophilization of bortezomib. The second group shows that mannitol is a known inert bulking agent, although no reference shows mannitol as a bulking agent for bortezomib. The third group starts from the Adams Patent that states that boronic acids can form esters, although mannitol is not included in the ester-forming alcohols mentioned in the Adams Patent. None of these references, alone or in combination, suggests or teaches that the solution to the problems of creating an efficacious formulation of bortezomib lay in freeze-drying bortezomib with mannitol to form an ester having the necessary properties for stability, storage, and treatment. . . . The sole reason Sandoz provides for choosing mannitol to make a new ester of bortezomib is because mannitol is one of a relatively small number of bulking agents used in lyophilization. Sandoz provides no reason why a person of ordinary skill who is seeking to make esters of bortezomib would look to lyophilization bulking agents. . . .

The district court also clearly erred in its determination that lyophilizing bortezomib with mannitol to form an ester was a "suitable option from which the prior art did not teach away." "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Millennium offered persuasive evidence that the chemical modification of bortezomib would have been unattractive to a person of ordinary skill for fear of disturbing the chemical properties whereby bortezomib functions effectively as an anti-cancer agent; in particular, a person of ordinary skill would have noted that the ester blocks a portion of the bortezomib molecule. Without the knowledge that the D-mannitol bortezomib ester dissociates in the bloodstream at a rate of pharmaceutical efficacy, a person of ordinary skill would not have been led to create the ester. . . .

The district court also clearly erred in its consideration of inherency. "A party must . . . meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis." "The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to

render the result inherent. The district court stated that Millennium "conceded as a matter of law that the ester is the 'natural result' of freeze-drying bortezomib with mannitol." However, "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." . . .

Sandoz argues that although lyophilization in the presence of mannitol produced an unexpected result, the result was "inevitable" and thus "inherent," and thus not "inventive." However, invention is not a matter of what the inventor intended when the experiment was performed; obviousness is measured objectively in light of the prior art, as viewed by a person of ordinary skill in the field of the invention. "Those charged with determining compliance with 35 U.S.C. § 103 are required to place themselves in the minds of those of ordinary skill in the relevant art at the time the invention was made, to determine whether that which is now plainly at hand would have been obvious at such earlier time." No expert testified that they foresaw, or expected, or would have intended, the reaction between bortezomib and mannitol, or that the resulting ester would have the long-sought properties and advantages.

We conclude finally that the district court clearly erred in its examination of the objective indicia of unexpected results and long-felt need. All of the Graham factors must be considered, including the objective indicia when present, before any conclusion regarding obviousness is reached. Evidence of objective indicia "can be the most probative evidence of nonobviousness in the record," and objective indicia enable "the court to avert the trap of hindsight." These indicia cannot be set aside in the analysis of obviousness.

"Unexpected results are useful to show the improved properties provided by the claimed compositions are much greater than would have been predicted." Nonobviousness may be established when an invention "yield[ed] more than predictable results." "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."

Millennium presented expert testimony that the lyophilized mannitol ester of bortezomib yielded unexpected results as compared to bortezomib, viz., greatly improved stability, solubility, and dissolution. However, the district court ruled that bortezomib itself was not the closest prior art, and declined to consider the advantages and benefits of the Velcade® product. The district court's error stems from its determination that Millennium should have compared the glycerol bortezomib ester, for the Adams Patent included glycerol as one of ten "[p]referred . . . dihydroxy compounds" for "boronate esters." The bortezomib glycerol ester was not specifically disclosed, prepared, or tested in the Adams Patent. . . . We conclude that the district court should have treated bortezomib as the closest prior art compound, and acknowledged the unrebutted evidence that the Dmannitol ester of bortezomib exhibited unexpected results compared with bortezomib, including unexpectedly superior stability, solubility, and dissolution.

The existence of a long-felt but unsolved need that is met by the claimed invention is further objective evidence of non-obviousness. Evidence of long-felt need is "particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." The district court's conclusion that the lyophilized mannitol ester of bortezomib did not meet a long-felt need was both perfunctory and clearly erroneous. There is no dispute that there was a long-felt need

for a product to treat multiple myeloma, for treatments prior to Velcade® gave poor remission and low survival rates. Although it is agreed that bortezomib is the effective product in the body, bortezomib alone is not an available product. Sandoz offered no evidence of successful solution of the problems that had barred bortezomib from clinical approval. The district court clearly erred in attributing Velcade®'s commercial success to bortezomib alone, as bortezomib is not a viable commercial product and had been denied FDA approval because of its instability. The D-mannitol ester was responsible for Velcade®'s successful results, for the D-mannitol ester is necessary to provide the required solubility and stability.