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Federal Circuit Patent Bulletin: *Hoffmann-La Roche Inc. v. Apotex Inc.*

April 11, 2014

"The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success . . . even if the level of success may have turned out to be somewhat greater than would have been expected."

On April 11, 2014, in *Hoffmann-La Roche Inc. v. Apotex Inc.*, the U.S. Court of Appeals for the Federal Circuit (Newman, Lourie, Bryson*) affirmed the district court's summary judgment that U.S. Patents No. 7,718,634 and No. 7,410,957, which related to treating osteoporosis through the once monthly administration of ibandronate that Roche markets as Boniva®, were invalid for obviousness under 35 U.S.C. § 103(a). The Federal Circuit stated:

The issue in this case is whether it would have been obvious at the time of invention to select a once monthly oral dosing regimen of ibandronate to treat osteoporosis and to set that dose at 150 mg. A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance stemming from the inconvenience of oral bisphosphonate regimens. Fosamax®, a prior artbisphosphonate product sold by Merck & Co., was administered weekly, and several prior art references taught once monthly oral dosing of ibandronate or other bisphosphonates. . . . Roche argues that the art taught away from once monthly dosing because, according to Roche, it was widely believed as of the date of invention that a bisphosphonate regimen with a dose-free interval longer than one or two weeks would not be effective. To support that contention, Roche primarily relies on the alleged failure of its intravenous ibandronate study ("Recker") to demonstrate antifracture efficacy with quarterly dosing. Secondarily, Roche relies on a prior art article by Thomas Schnitzer ("Schnitzer") speculating that the failure of the Recker study was due to the long dose-free interval. . . .

Roche's patents do not themselves present data demonstrating antifracture efficacy for a once monthly150 mg dose. In fact, antifracture efficacy for Boniva® was demonstrated to the FDA through a "bridging study" that used BMD [(bone mineral density)] and bone turnover results—not antifracture testing—to establish the

therapeutic noninferiority of the 150 mg monthly dose relative to the previously approved 2.5 mg daily dose, for which antifracture efficacy had been demonstrated. Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success. Riis—along with other prior art that used BMD improvement as the primary efficacy marker for treating osteoporosis—established at least a reasonable expectation that once monthly dosing of ibandronate could successfully treat osteoporosis and reduce fracture risk.

Riis confirmed the total-dose concept whereby "the efficacy of ibandronate depends on the total oral dose given rather than on the dosing schedule." Riis therefore teaches that in setting the dosage level for an intermittent ibandronate regimen, one need only scale up a known-effective dose from a short-interval regimen—e.g., daily dosing—to achieve approximately the same BMD and bone-loss efficacy with a long-interval regimen. The prior art provided substantial guidance as to the total dose, within a given time period, that would produce effective results. [T]he "average change in bone mass showed positive outcome in all regions in the groups receiving ibandronate 2.5 and 5.0 mg." The 2.5 mg dose exhibited a response that was "virtually equal" to the 5mg dose, even though it contained only half the amount of ibandronate. The 2.5 mg dose was thereby deemed the "most effective dose." A person skilled in the art looking to scale to a monthly dose of oral ibandronate from a known-effective daily dose was thus faced with a very limited set of possibilities: Of the five daily doses tested in Ravn, only the 2.5and 5 mg doses "showed positive outcome in all regions." Even though the 5 mg dose did not demonstrate greater efficacy than the 2.5 mg dose, it was still deemed an equivalently effective dose so that someone scaling it to a single monthly dose of 150 mg (5 mg/day x 30 days/month) would have anticipated equivalent success in raising BMD and limiting bone turnover, based on Riis. . . .

Roche contends that findings by the FDA taught away from further development of the 5 mg daily dose (and its total-dose equivalents) because the FDA approved a 2.5 mg daily dose of ibandronate instead of a 5 mg daily dose. But the FDA never made any findings contrary to the 5 mg daily dose, because it was never asked to approve that dose. Instead, in approving the 2.5 mg daily dose, the FDA merely . . . concluded that "the 2.5 mg daily dose of ibandronate has the most favorable benefit – risk ratio and is the most appropriate dose for the prevention and treatment of postmenopausal osteoporosis." . . .

Roche argues that the district court erred by granting summary judgment of obviousness because the evidence of record showed that the 150 mg monthly dose was more effective than the 2.5 mg daily dose and that the superior effectiveness of the 150 mg monthly dose was unexpected. Roche also contends that ibandronate's nonlinear bioavailability at the 150 mg dosage level was an unexpected result. . . . While the evidence would support a finding of superior efficacy of the 150 mg monthly dose in raising BMD levels, as

compared to a 2.5 mg daily dose, that improved efficacy does not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg. The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected.

For the same reasons, the nonlinear bioavailability of ibandronate does not rebut the prima facie showing of obviousness of a once monthly dose of 150 mg. The increased level of bioavailability has not been shown to be responsible for the improved osteoporosis treatment efficacy of the 150 mg dose. . . . The evidence regarding bioavailability is therefore of little relevance to the obviousness inquiry. Accordingly, we uphold the judgment of the district court that claims 1-8 of the '634 patent and claims 1-10 of the '957 patent would have been obvious in light of the prior art and are therefore invalid.