Sanofi-Synthelabo v. Apotex Inc.

No. 07-1438, Fed. Cir. (Newman,* Lourie, Bryson)

Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement.

On December 12, 2008, the Federal Circuit affirmed the district court's judgment that U.S. Patent No. 4,847,265, which related to the blood clot preventative drug clopidogrel bisulfate sold by Sanofi as Plavix®, was not invalid. Apotex's abbreviated new drug application to generic clopidogrel bisulfate contained a Paragraph IV certification based solely on invalidity of the '265 patent in view of U.S. Patent No. 4,529,596 and Canadian Patent No. 1,194,875. The Federal Circuit stated:

> This appeal [focuses on the] patentability of [the] dextrorotatory isomer [claimed in the '265 patent] in view of its known racemate described in earlier Sanofi patents . . . . Enantiomers are spatial isomers, also called stereoisomers, [that] have the same chemical formula and the same chemical structure, but differ in their orientation in three-dimensional space. . . . Enantiomers are identified and distinguished by their optical characteristics [where one] enantiomer will rotate plane-polarized light to the right (and thus is called the dextrorotatory or d- or (+) isomer), and the other rotates plane-polarized light to the left (called the levorotatory or l- or (-) isomer). . . . Enantiomers generally are formed in equal amounts, to produce what is called a racemate. . . .
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> To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" [Apotex] argues that it is entitled to a presumption of enablement because the asserted references are patents, which are presumed to be enabling because they are presumed valid. Apotex argues that the presumption should be particularly strong here, because the prior art patents belong to Sanofi. Thus Apotex argues that the general statements in the reference patents concerning enantiomers are presumptively enabling of the separate enantiomers of PCR 4099. Apotex [argued that] a person of ordinary skill in this field would know all of the existing techniques for separating stereoisomers, and would presumptively succeed in this particular separation. Apotex points out that the method that was eventually used by Sanofi was a well-known method, even if it involved some experimentation.
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> Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement. The factors relevant to whether experimentation is undue [include] the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology. . . . The district court found that these references contain no description of how to separate the enantiomers of PCR 4099, and that

> "[d]iscovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art." [We] discern no clear error in [this] finding. . . .
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> [T]he expert witnesses for both sides agreed that a person of ordinary skill in this field in the mid-1980s would have known that enantiomers can exhibit different biological activities. However, the experts also agreed that it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested. The experts agreed that no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity. The experts agreed that weak stereoselectivity of biological properties is more common than strong stereoselectivity, and that absolute stereoselectivity is rare. [T]he district court found that a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity. [The district court also] observed that in 1987 there were at least ten techniques that had been used to separate enantiomers, and that they all required experimentation to determine whether they could be successful for a particular compound, including choices of reagents, solvents, concentrations, temperature, and a variety of other conditions. . . . The court described the separation as a "paradigm of trial and error," and found that "neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration." The court found that Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR 4099, before separating the enantiomers, also weighed against finding that separation would have been obvious.
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> We discern no error in the district court's findings that, on the state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity. The totality of these findings, and the correct application of law, well support the district court's conclusion that invalidity had not been established by clear and convincing evidence.