

Litigation Notes

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BARR LABS PATENT INFRINGEMENT TRIALS ON YASMIN AND RAZADYNE

We read the post-trial briefs in two patent infringement cases against **Barr Laboratories** that were tried last year and are awaiting decision. One of the cases, brought by **Bayer Schering** in the U.S. District Court in New Jersey, involves Barr's ANDA on a generic version of Bayer Schering's birth control pill called Yasmin, and the other case, brought by **Johnson & Johnson's** Janssen Pharmaceutica and Ortho-McNeil Neurologics in the U.S. District court in Delaware, involves Janssen's acetylcholinesterase inhibitor called Razadyne, used for treating Alzheimer's Disease. The Yasmin trial in New Jersey ended on December 4, 2007, and the Razadyne trial in Delaware ended on May 25, 2007. We think that Barr has first-to-file status on both of these drugs.

In our analysis, Barr has the stronger position on the Yasmin case, and we think it will probably win even at the trial level, despite the fact that the case is pending in the New Jersey federal court, which is notoriously and unabashedly pro-industry in Hatch-Waxman cases. The judge in this case, Judge Peter Sheridan, is relatively new to the bench in New Jersey and therefore he perhaps has not yet become as jaded as the other judges. We expect the decision to be issued within the next few months. As for the Razadyne case, we think the decision is already overdue, and therefore we expect it to be released in the near future. On the merits, Barr again has the stronger position, but it is a closer case than the Yasmin case and it is pending in a notoriously pro-patent jurisdiction. However, the judge in that case, Judge Sue Robinson, is fairer than at least one of the other judges in that district and is capable, we think, of issuing a decision in Barr's favor.

In the Yasmin case, Bayer decided to develop a progestin called drospirenone in combination with ethinylestradiol because drospirenone negates the bloating effects of ethinylestradiol and also avoids acne as a side effect. The idea of combining drospirenone and ethinylestradiol in a birth control pill at the desired dosage had been amply described in the prior art. However, the patent examiner allowed a patent on Bayer's formulation because the medicinal chemist who developed the drug had discovered that the formulation difficulties attributed to drospirenone's acid sensitivity could be overcome by the simple expedient of *not* using an enteric coating on the tablet.

Barr's argument, simply stated, is that enteric coatings on tablets (i.e., coatings that protect a drug from stomach acid) are the exception to the rule and that a drug developer of ordinary skill would naturally gravitate to normal tablets, which are standard for birth control pills, before resorting to an enteric coating. It is obvious, says Barr, to design a drug product in the usual way, and it is the usual way that would naturally occur to a person of ordinary skill in the art.

Bayer's argument in defense of its patent covering Yasmin, U.S. Patent No. 6,787,531, is that drospirenone is poorly soluble and yet highly sensitive to acid, and that the inventor's solution to these limitations, said to be unobvious, was to micronize the compound and yet package it as an uncoated tablet. Normally, it says, micronization increases the sensitivity of a compound to acid, and in this case micronization increases the speed not only of dissolution but of degradation as well. Accordingly, it said, the logical solution to this problem would be to give the drug an enteric coating.

Explaining further, Bayer said that its lead inventor, Dr. Johannes Tack, spent five years unsuccessfully attempting to put an enteric coating on the product before one of his teams, at his direction, decided to investigate the outcome if no coating was placed on the tablets. When the tablet worked as a birth control pill, Tack was "surprised."

Bayer cites prior art as "teaching away" from the use of an uncoated tablet in this situation, and in particular it cites the so-called Nickisch article published in 1986, reporting on an in vitro study showing that drospirenone degrades in an acid environment by isomerizing into an inactive isomer. Bayer notes that Tack confirmed the Nickisch conclusion with his own in vitro study before electing to forego development of an uncoated tablet.

A fundamental fact question to be resolved by the court in this case is whether a person of ordinary skill would make the same mistake that was made by Tack in concluding that an in vitro result would conclusively foretell the in vivo result. More importantly, however, we do not believe that even a person of ordinary skill would have concluded that the Nickisch article was definitive in ruling out the use of an uncoated tablet. As it happened, Nickisch tested drospirenone at only one pH level, i.e., a pH of 1, which is the highest level of acidity that the stomach reaches, and he only tested the acid's effect on drospirenone at the end of a three-hour period.

In explaining what is wrong with the Nickisch article as a "teaching away," Barr's expert said that the rapid dissolution of the drug enables a much speedier evacuation of the drug from the stomach, which, he said, would occur in a matter of minutes. Also, he said that the in vitro conditions of the Nickisch test do not mimic the actual in vivo conditions in which the drug would be used, since the user would invariably take the drug with a liquid that would increase the pH of the stomach, thus retarding the speed of the drug's degradation. Water, for example, has pH of 7, and therefore taking the drug with water would necessarily raise the stomach's pH.

As for what a person of ordinary skill in the art would do, Barr cites two prior art patents concerning formulations of drospirenone and ethinylestradiol for contraceptive use, including U.S. Patent Nos. 5,583,129 and 5,756,490, issued to Spona and Lachnit, respectively. The doses disclosed in these patents are within the claimed ranges of Bayer's '531 patent and, significantly, the patents do not mention the need for enteric coatings on the tablets. The combination of drospirenone and ethinylestradiol is also cited in a 1995 article by Oelkers and in a patent application by Gast, neither of which has any mention of the isomerization problem. Barr's argument is that a person of ordinary skill would simply follow these items of prior art and would not concern himself with a problem that did not arise.

In our analysis, the discovery that a problem of concern to the inventor alone is not really a problem after all cannot properly take obvious subject matter out of the public domain.

Regarding Razadyne, Barr's basic argument is that galantamine (the generic name) was well-known in the prior art as a cholinesterase inhibitor and was a logical candidate for treating Alzheimer's Disease once the undesirable side effects of its predecessors, physostigmine and tacrine, were recognized. The thesis behind the use of acetylcholinesterase inhibitors to treat Alzheimer's Disease was premised on the 1970s

discovery that acetylcholine levels decreased in Alzheimer's patients, and that therefore a reduction of an enzyme that breaks down acetylcholine would preserve acetylcholine for a longer period in the brain and thus enhance cortical function and retard the progress of the disease. Barr cites numerous articles describing the strategy of inhibiting acetylcholinesterase as a means of increasing the available acetylcholine in the brains of Alzheimer's Disease patients.

Barr also says that the '318 patent is very cryptic, limited to a mere two columns in which the patentee, Dr. Bonnie Davis, cites five prior art articles and then deduces that galantamine would be a desirable acetylcholinesterase inhibitor for use in treating Alzheimer's Disease. These five articles, Barr says, disclose the entire invention, and it then says that if they do not disclose the invention, then the invention itself is not enabled. Janssen cannot have it both ways, it argues. Since the prior art is the only basis for enablement of the patent, it says that either the patent makes no unobvious contribution to the art or the patent is not enabled at all.

We thought that Janssen's counterargument was pretty good, but in the end we did not find it convincing. The prior art, says Janssen, is premised on the belief that of the two types of cholinergic receptors found in the body and in the brain, acetylcholine acts on the muscarinic receptors in the brain but not on the nicotinic receptors. Nicotinic receptors are more generally associated with the peripheral system, and although they are also found in the brain, muscarinic receptors are more significant for memory and hence are regarded as more relevant to Alzheimer's Disease. The insight that Dr. Davis had, according to Janssen, was that both types of receptors were relevant to Alzheimer's Disease and that therefore an agent was required that would act on nicotinic receptors as well as on muscarinic receptors.

Barr responds by citing a prior art article by P.A. Bhasker entitled "Medical Management of Dementia," published in 1974 in a journal called *The Antiseptic*, which, says Barr, anticipates the '318 invention. According to Barr, the article suggests using galantamine for "progressive dementias," which would include Alzheimer's Disease, but Janssen got some expert testimony arguing that the Bhasker article refers only to "arrested dementias." To us, the article is not so limited, although it does provide examples of "local brain damage like tumor, head injury, infarct, etc." It also states that it is directed in general to "restoration of higher cortical function," which would include Alzheimer's. We think that a reader of ordinary skill would not eliminate Alzheimer's as one of the conditions covered by the article. In any event, the article clearly describes galantamine as an acetylcholinesterase inhibitor, and it states that "deinhibition refers to the facilitation of acetylcholine activity" thus rendering galantamine obvious in view of other articles embracing the cholinergic hypothesis.

In any event, the patent has other problems. For one thing, the patent broadly claims the use of galantamine to treat Alzheimer's even though the only contribution made by the patentee is the insight that the drug is active primarily on the nicotinic receptor system rather than on the muscarinic system. The patent itself does not even mention either nicotinic or muscarinic receptors, and therefore the sole intellectual contribution of the inventor is totally missing. Likewise, the case for specially targeting the nicotinic receptors is absent. Accordingly, even if there is a unique feature distinguishing galantamine from other acetylcholinesterase inhibitors, a medicinal chemist would never know it from the patent.

Finally, although not an argument made in court, we think there is a disconnect in the mechanism described. As we understand it, cells that make acetylcholine die relatively early in the progression of Alzheimer's Disease, leaving a so-called three-year window in which acetylcholine can provide any benefit at all. The patent does not explain how inhibition of the enzyme that breaks down acetylcholine can focus the acetylcholine itself on the nicotinic receptor system. The story, in other words, is dubious.