

Valeant Pharmaceuticals Int'l Inc. et al. v. Mylan Pharm. Inc.
(U.S. Court of Appeals for the Federal Circuit, 2018, 18-2097)

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Case summary

The case concerns the analysis of obviousness, when the prior art teaches structurally and functionally similar chemical compounds, proving a definite range and variables for a solution of stability. The Appeal Court held that prior art ranges for solutions of structurally and functionally similar compounds that overlap with a claimed range can establish a *prima facie* case of obviousness. If one of the predictable solutions leads to an anticipated success, the outcome was obvious to try. The Court also held that there is no requirement that for a variable to be obvious to try, it must be the first variable a person of skill would alter.

The facts

Valeant owns U.S. Patent 8,552,025 (the '025 patent'), which claims stable methylnaltrexone pharmaceutical preparations and its injectable solution. According to the '025 patent' specification, methylnaltrexone, an opioid antagonist, can be useful for reducing the side effects of opioids but is unstable in aqueous (water) solution. The inventors discovered, however, that the pharmaceutical preparation becomes stable when the pH of a methylnaltrexone solution is adjusted, optimally to between 3.0 and 3.5. Claim 1 and Claim 8 of the '025 patent' are relevant for this dispute. Claim 1 recites:

A stable pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation comprises a pH between about 3.0 and about 4.0.

Claim 8 recites

“[t]he pharmaceutical preparation of claim 1, wherein the preparation is stable to storage for 24 months at about room temperature.”

Claim 8 recites the same preparation as claim 1, but with a stated result of 24 months stability.

A competitor, Mylan, submitted a request for an approval from the U.S. Food and Drug Administration to market a generic version of Valeant's drug. Valeant responded by bringing suit against Mylan in the District of New Jersey, alleging that Mylan's proposed product would infringe the '025 patent.' Mylan maintained that Claim 8 was invalid as obvious over solutions of similar anti-opioids. The district court ruled Claim 8 was not obvious to try and Mylan appealed.

The legal issues

The Appeal Court stated that the sole issue in this appeal, i.e., obviousness, is a question of law, supported by the underlying questions of fact. The Court restated the established jurisprudence that the analysis of obviousness considers the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and any secondary considerations. Before the district court, Mylan argued that Claim 8 would have been obvious in view of three references:

1. U.S. Patent 5,866,154 (Bahal), entitled “Stabilized Naloxone Formulations” that teaches a naloxone composition with a pH of 3 to 3.5;
2. U.S. Patent 2003/0229111 (Oshlack) that teaches a naltrexone composition with a pH of about 3 to about 5 and about 4, and
3. A journal article that discloses a naltrexone formulation with a pH of 3.5 that fell to 3.2 over 90 days.¹

Relying on these references, Mylan argued that a person of skill in the art would have been motivated to prepare and would have arrived at the preparation of Claim 8 via routine optimization of pH. The references each taught pH ranges that overlapped with the “about 3 to about 4” range in Claim 8. Although the references deal with naloxone and naltrexone, in Mylan’s view, however, they still established a *prima facie* case of obviousness because naloxone and naltrexone were structurally and functionally similar to methylnaltrexone. Mylan also argued that the pH range in the claim would have been obvious to try.

The district court disagreed, rejecting Mylan’s arguments, first because none of the references taught methylnaltrexone formulations. Overlapping ranges establish a *prima facie* case of obviousness when the only difference between the prior art is the range of a particular variable. Secondly, the court recognized that adjusting pH was only one variable among a number of others, hence, not obvious to try. Thirdly it asserted, the claimed pH range would not have been obvious to try because the quantity of number ranges between pH 3 and 7 were ‘infinite, not finite.’

The Court of Appeals first stated its decision in previous cases that recognises that a *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap with the ranges disclosed in the prior art. It explained that selecting a narrow range from *within* a somewhat broader range disclosed in a prior art reference is no less obvious than identifying a range that simply *overlaps* a disclosed range. Here, the pH range recited in Claim 8 clearly overlaps with the pH range in the record art, but none of the references disclose the same drug as the one claimed. The question is whether prior art ranges for solutions of structurally and functionally similar compounds that overlap with a claimed range can establish a *prima facie* case of obviousness. The Court conclude that they can and, in this case, do.

¹ J. Paul Fawcett, et.al., *Formulation and Stability of Naltrexone Oral Liquid for Rapid Withdrawal from Methadone*, 31 *Annals of Pharmacotherapy*, 1291-95 (1997).

The Appeal Court stated that when compounds share significant structural and functional similarity, those compounds are likely to share other properties, including optimal formulation for long-term stability. Naloxone, naltrexone, and methylnaltrexone are well-known opioid antagonists that operate by binding to the body's opioid receptors without activating them. Each is an oxymorphone derivative, and the group members have remarkably similar structures. The only structural difference between these three molecules is the identity of the functional group attached to the nitrogen atom.² Because of the strong structural and functional similarity between the molecules, a person of skill could expect similar stability of the molecules at similar pH ranges in solution. Because these three molecules bear significant structural and functionality similarity, and because the prior art of record teaches pH ranges that overlap with the pH range recited in Claim 8, Mylan has at least raised a *prima facie* case of obviousness. In a such situation, the patent claimant has the burden to rebut the *prima facie* case by, for example, establishing that the claimed pH range is critical or that the prior art teaches away from the claimed invention in any respect, such as unexpected properties.

Secondly, the Appeal Court held that the district court's obvious-to-try analysis is inconsistent with precedent when the district court attempts to illustrate an infinite number of possibilities within the pH range of 3 and 4. The Appeal court stated that when 'there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp' and if 'one of these predictable solutions leads to the anticipated success, the combination was obvious to try.' The bounded range of pH presents a finite number of narrower pH ranges for a skilled artisan to try. As a matter of mathematics, there may be an infinite potential number of ranges, but only if the realities of pH values (and the limitations of commercially available pH meters) are ignored.

Finally, the Appeal Court rejected the district court's view that manipulating pH was not obvious to try because none of the references listed pH as the "first variable" that an artisan would manipulate for stability. According to the Appeal Court there is no requirement that for a variable to be obvious to try, it must be the first variable a person of skill would alter, nor for absolute predictability that the proposed pH range would yield the exact stability parameters in the claim. Moreover, it is important to note that pH is in fact the only variable in Claim 8, not one of many variables that can be experimented with. And, lacking anything in the claim that is a stabilizer, it can be presumed, if the claim is valid, that the stability for up to 24 months must be due to the nature of the compound in the solution and the claimed pH level.

Points of significance

- Prior art ranges for solutions of structurally and functionally similar compounds that overlap with a claimed range can establish a *prima facie* case of obviousness.

² Naloxone is a neutral tertiary amine. Naltrexone, also a neutral tertiary amine, has a cyclopropylmethyl group attached to the nitrogen. Methylnaltrexone, a derivative of naltrexone, is a quaternary ammonium salt and has both a cyclopropylmethyl group and a methyl group attached to its nitrogen with a positive charge.

- The court’s recognition that “[w]hen compounds share significant structural and functional similarity, those compounds are likely to share other properties including optimal formulation for long-term stability” clarifies the test of obviousness in case of structural similarities;
- Choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success is ‘obvious to try’. There is no requirement that for a variable to be obvious to try, it must be the first variable a person of skill would alter, nor for absolute predictability that the proposed pH range would yield the exact stability parameters in the claim. In this regard, the number of options within a given range shall only be assessed based on design incentives or other market forces. Even if, as a matter of mathematics, there may be an infinite potential number of ranges, the commercial and design necessities suggest the existence of a finite number of options.

Keywords: Obviousness, obvious-to-try, skilled person, skilled artisans, structural similarity, functional similarity, prima facie case of obviousness.

Decision available at: http://www.cafc.uscourts.gov/sites/default/files/opinions-orders/18-2097.Opinion.4-8-2020_1566066.pdf