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Federal Circuit Friday

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In *Eli Lilly v. Hospira* (August 9), the Federal Circuit provided useful analysis and guidance regarding literal infringement and the tangential exception to prosecution history estoppel.

Background.

Pemetrexed is an antifolate enzyme inhibitor used for treating cancer. It inhibits synthesis of the nucleotide building blocks of DNA and RNA, and thereby slows cell growth and division. Lilly discovered that pemetrexed can cause severe side effects leading to infection, nausea, rashes, and even death, and developed a method for alleviating those side effects that involves administering folic acid and vitamin B12 before administering pemetrexed.

Lilly initially attempted to get broad patent claims on its method, including a *two*-step method of administering an "antifolate" (a genus, of which pemetrexed is a species) in combination with a "methylmalonic acid lowering agent" (a genus, of which vitamin B12 is a species). This broad original claim made no reference to administering folic acid. The examiner rejected that claim as anticipated by a prior art research paper authored by Arsenyan and, in response, Lilly narrowed the claim to "pemetrexed disodium" and asserted that the amendment overcame the anticipation rejection because Arsenyan disclosed methotrexate[1] as the antifolate rather than pemetrexed disodium. The examiner agreed and withdrew the anticipation rejection.

It was in a continuation application that Lilly sought and obtained claims to the *three*-step method of administering folic acid and vitamin B12 and then administering pemetrexed that is at issue in this case. Lilly carried the parent application's narrowing to pemetrexed disodium through to the claims of the child patent, and the issues on appeal to the Federal Circuit related to the scope of the phrase "pemetrexed disodium" and the scope of prosecution history estoppel arising from the narrowing amendment in the parent from "antifolate" to "pemetrexed disodium."

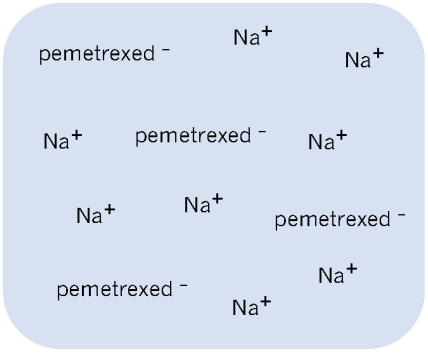
Literal Infringement.

Defendant Hospira sought to market pemetrexed ditromethamine, an alternate salt form of pemetrexed, for use in a method involving administering folic acid and vitamin B12 before administering the pemetrexed.

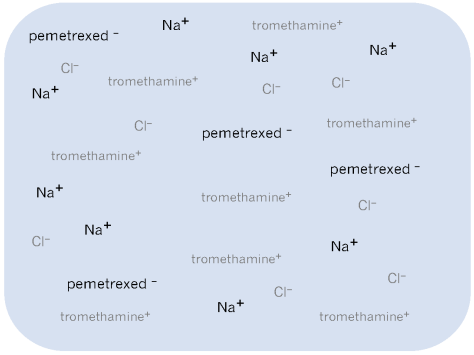
The infringement issue was not simply whether pemetrexed ditromethamine is literally the same as pemetrexed disodium (it isn't). The district court construed the claim phrase "administration of pemetrexed disodium" to mean "liquid administration of pemetrexed disodium," which "is accomplished by dissolving the solid compound pemetrexed disodium into solution." Hospira's method involved dissolving pemetrexed ditromethamine in saline for administration, and Lilly argued that the liquid form of Hospira's product infringed because it includes both pemetrexed anions (from the pemetrexed ditromethamine) and sodium cations (from the saline).

The district court agreed with Lilly but the Federal Circuit reversed, explaining that a "solution of pemetrexed and chloride anions and tromethamine and sodium cations cannot be deemed pemetrexed disodium simply because some assortment of the ions in the solution consists of pemetrexed and two

[1] Methotrexate is an older generation antifolate, in use since 1947. Pemetrexed is a newer generation antifolate, developed in 2004.



Lilly's claimed pemetrexed disodium solution



Hospira's pemetrexed ditromethamine + saline solution

sodium cations." In particular, "[o]nce diluted, the salt's crystalline structure dissolves, and the individual ions dissociate[,] . . . pemetrexed disodium no longer exists once dissolved in solution, and, as a corollary, a different salt of pemetrexed dissolved in saline is not pemetrexed disodium."

In essence, the Federal Circuit held that to infringe the claim under the district court's claim construction (which was not part of this appeal), it must be pemetrexed *disodium* that is dissolved in liquid, not pemetrexed *ditromethamine* – *i.e.,* "liquid administration of pemetrexed disodium . . . is accomplished by dissolving the solid compound pemetrexed disodium into solution." In short, dissolving pemetrexed ditromethamine into solution is not literally the same as dissolving pemetrexed disodium into solution.

Lilly's literal infringement argument was creative and a great shot-on-goal, but it didn't quite work. Lilly probably didn't mind too much because it won nevertheless on doctrine of equivalents.

Doctrine of Equivalents - Tangential Exception.

Prosecution history estoppel imposes an important and powerful limitation on the doctrine of equivalents – "[p]rosecution history estoppel prevents a patentee from recapturing under the doctrine of equivalents subject matter surrendered during prosecution to obtain a patent."[2]

The issue was whether Lilly had surrendered pemetrexed salts other than the disodium salt during prosecution and was attempting unfairly to recapture those other salts in its infringement case against Hospira. There was no dispute that Lilly narrowed a pending claim in the parent application from "antifolate" to "pemetrexed disodium" and asserted that the narrowing avoided anticipation because the prior art at issue, Arsenyan, disclosed methotrexate rather than pemetrexed disodium. Indeed, "Lilly [did] not dispute that the amendment in question was both narrowing and made for a substantial reason relating to patentability." However, Lilly argued that the narrowing amendment was made for a reason "tangential" to the equivalent in question.[3] Specifically, Lilly asserted that it made the narrowing amendment "to distinguish pemetrexed from antifolates generally and that the different salt type is a

[2] *Cross Medical Products v. Medtronic Sofamor Danik*, 480 F.3d 1335, 1341 (Fed. Cir. 2007).

[3] In general, there are three exceptions that prevent application of prosecution history estoppel: (i) that the alleged equivalent could not reasonably have been described at the time the amendment was made; (ii) that the alleged equivalent was tangential to the purpose of the amendment; and (iii) that the alleged equivalent was not foreseeable and thus not claimable at the time of the amendment, *See, e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.,* 344 F.3d 1359, 1369 (Fed. Cir. 2003) (en banc).

merely tangential change with no consequence for pemetrexed's administration or mechanism of action within the body."

The Federal Circuit agreed, explaining that "[t]angential means 'touching lightly or in the most tenuous way'" and that "the particular type of salt to which pemetrexed is complexed relates only tenuously to the reason for the narrowing amendment, which was to avoid Arsenyan." The court held that "Lilly's amendment was merely tangential to pemetrexed ditromethamine because the prosecution history, in view of the '209 patent itself, strongly indicates that the reason for the amendment was not to cede other, functionally identical, pemetrexed salts."

The result may appear to be incorrect because the Federal Circuit basically rescued Lilly from a drafting blunder (*i.e.,* over-narrowing a claim to avoid the prior art), but there were several factors indicating that Lilly was likely on the correct side of the issue:

- "[T]he tangential exception only exists because applicants over-narrow their claims during prosecution," which means that a drafting error necessarily occurs in every case where a patentee is saved by the tangential exception.
- Although "[a]mendments are not construed to cede only that which is necessary to overcome the prior art" and the court will not "speculat[e] whether an amendment was necessary," the tangential exception looks at the reason for a narrowing amendment, which "cannot be determined without reference to the context in which it was made, including the prior art that might have given rise to the amendment in the first place."
- The claim at issue in the parent prosecution was a broader *two*-step method (antifolate + methylmalonic acid lowering agent) rather than the narrower *three*-step method at issue here (pemetrexed disodium + folic acid + vitamin B12), which means that the context for the narrowing amendment was very different.
- "Lilly's burden was to show that pemetrexed ditromethamine was 'peripheral, or not directly relevant,' to its amendment," not that it was *unable* to draft a claim that covered pemetrexed ditromethamine.