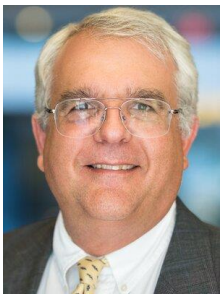
Lessons From Fed. Circ. Ruling On Lung Disease Patent

By **Paul Stewart** (January 31, 2023)



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The U.S. Court of Appeals for the Federal Circuit's Dec. 22, 2022, Genentech Inc. v. Sandoz Inc. decision includes two separate and interesting holdings involving patents claiming methods of varying doses of a specific medication in response to adverse side effects.

First, the court held that one set of patents was invalid for obviousness, in part because the practice of varying doses to avoid side effects was a well-established medical practice.

Second, the court held that the remaining set of patents was not infringed by the defendant's abbreviated new drug application filing even though the defendant's proposed label encouraged performance of an infringing method.

While the case involved an ANDA filing, at least the obviousness holding should be of interest to those whose practice does not include ANDA litigation.

The case centered upon the drug pirfenidone, a known drug used to treat a certain chronic and terminal lung disease. A second drug, nintedanib, is also known for treating the same lung disease, and each of these drugs is prescribed about half the time.

The first set of patents claimed methods of administering pirfenidone to patients who exhibited a particular side effect in the liver. The claims recited various options to respond to the side effect including:

- Temporarily reducing the dose of pirfenidone and then returning to the full dose;
- Maintaining the full dose of pirfenidone;
- Reducing the dose of pirfenidone;
- Discontinuing pirfenidone for a week and then returning to the full dose; and
- Discontinuing pirfenidone for a week and then returning to a reduced dose.

After a bench trial, the U.S. District Court for the District of Delaware held that these claims were all invalid for obviousness over a medical journal article referred to as Azuma, the prior art label for the drug Pirespa, and standard medical practices. The Federal Circuit affirmed.

The Federal Circuit began its analysis with an ominous warning to the patentee:

Before reviewing the details of the district court's thorough analysis, it is worth noting our initial perception that, as the district court noted, varying doses in response to the occurrence of side effects would seem to be a well-established, hence obvious, practice. Thus, claiming it as an invention would appear to be at best a long shot.

The Federal Circuit's formal analysis of the claims did not change its view. Applying the clear error standard of review, the court upheld the district court's findings that the Azuma and Pirespa references both generally taught decreasing the dosage of pirfenidone and other drugs in response to adverse side effects, and then reescalating the dosage as tolerated by the patient.

The Federal Circuit held that these teachings rendered the claims obvious. The Federal Circuit did not expressly approve the district court's holding that standard medical practices also rendered the claims obvious, but the Federal Circuit's deep skepticism of the claims suggests this may have been a factor.

The Federal Circuit's obviousness holding is an important reminder of the role that a gut check or reality check can have in an obviousness analysis. While it is always important to conduct a formal analysis — and the Federal Circuit did so here — it is also easy to lose the forest for the trees in the details of an obviousness analysis.

This case is a reminder that the courts may take an initial look at the forest before counting branches and leaves.

The second set of patents claimed methods of avoiding adverse interactions between pirfenidone and a second drug, fluvoxamine. The claims again provided various strategies for avoiding the adverse drug interaction including:

- Discontinuing fluvoxamine; and
- Reducing the dosage of pirfenidone in several specific ways.

The issue on appeal was whether the defendant's proposed drug label induced physicians to infringe these claims. The proposed label included on its face a warning about drug interactions with fluvoxamine.

The proposed label then stated that, to avoid interaction, fluvoxamine should be discontinued or the dosage of pirfenidone should be reduced to one of the claimed dosages.

The proposed label also warned more generally that the concomitant administration of pirfenidone and fluvoxamine was not recommended at all, and that dosage reductions of pirfenidone are recommended only if fluvoxamine is the only available drug for the patient.

The district court found that this proposed label, in light of other evidence of record, was insufficient to prove direct infringement by any physician, a necessary prerequisite to any claim for induced infringement. The Federal Circuit again affirmed.

On appeal, the patentee argued that the plain language of the proposed label encourages infringement under at least some circumstances, and that this alone should be dispositive.

The Federal Circuit disagreed that the language of the proposed label was dispositive. The court acknowledged that the filing of an ANDA, without showing the manufacture, use, or sale of the accused drug, meets the jurisdictional requirement of infringement.

However, the Federal Circuit explained that this does not establish direct infringement as a predicate for a finding of induced infringement. To prove direct infringement in an ANDA case, the patentee:

> Must show that if a particular drug were put on the market, it would infringe the relevant patent. ... Determining what will, or would, happen when a product enters the market requires consideration of all the relevant evidence, including the proposed label's instructions and physician practice.

Here, the defendant presented testimony from physicians that, in their decades of treating patients for the terminal lung disease at issue here, they had never prescribed pirfenidone to a patient taking fluvoxamine.

Further, if they were to find themselves in that position, they would choose a non-infringing response, specifically prescribing nintedanib instead of pirfenidone. The Federal Circuit held the district court did not clearly err in considering this evidence of actual physician practice and concluding that there was insufficient evidence of direct infringement to find the defendant liable for induced infringement.

The Federal Circuit's noninfringement holding is significant because it shows that in ANDA litigation, the proposed label alone may not be dispositive on the issue of infringement.

Evidence of actual conduct in the marketplace may be necessary to show that direct infringement is likely to occur. This is true even where, as here, the proposed label all but recites the claimed invention.

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