Innovator versus Generic

Taking into account the investment made to bring a drug to market, it is in the best interests of the originator pharmaceutical company to seek patent protection for the alternative entities of the drug; failure to do so could mean not maximising the full value of the initial investment.

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Patent protection is of significant importance to both the innovative and generic pharmaceutical industry. Given the enormous investments needed to develop a new chemical entity (NCE) and bring a drug to market, protection of this investment requires identifying and protecting alternative chemical forms of the drug. Crystalline forms, enantiomers, salts and prodrugs are alternative forms that may be subject to patent protection. It has become common-place for the generic industry to also explore these alternative forms of protection on an innovative drug, thus an innovator that does not consider these possibilities takes a significant risk. This article explores the current state of the law that may provide patent protection for such alternative forms and identifies issues associated therewith.

In the US, patents are granted a term of 20 years from the date of filing of the earliest application to which the patent claims priority, or 17 years from the date of issue, depending on the whether the patent application was filed before or after 8 June 1995 (1). But effective patent protection for a marketed drug is often far less than the statutory term, due to the loss of term while the NCE is undergoing FDA review and approval. Although patenting a NCE can provide substantial patent protection, safeguarding the investment requires that patents are sought on alternative chemical forms. While such alternative protection remains a real possibility that cannot be ignored, successfully procuring and asserting this type of protection is highly fact-dependent, as the recent case law makes abundantly clear.

Crystalline Forms

Polymorphs, hydrates and semi-hydrates, as well as solvates and co-solvates, are alternative chemical forms that should always be considered after selecting a clinical NCE target compound. The last major decision by the United States Court of Appeals for the Federal Circuit addressing patents claiming crystal forms is most notable for concluding that product-by-process claims of a crystalline compound, will only infringe the claims if made by the recited process steps. The decision was, however, also instructive on claim construction issues associated with claims to crystalline compounds (2).

The facts underlying the *Abbott Labs v Sandoz Inc* decision are convoluted. The antibiotic cefdinir was first discovered and disclosed in a US patent. A later-filed patent (the '507 patent) claimed cefdinir anhydrate ('crystal A'), marketed by Abbott Laboratories as OMNICEF. The '507 patent claimed the benefit of a Japanese application that disclosed and claimed two crystalline forms of cefdinir: crystal A and the monohydrate ('crystal B'). Although the '507 patent relied on the earlier priority date of the Japanese application, applicants revised the specification to omit references and claims to 'crystal B.'

The '507 patent included product claims that required the compound to have a specific powder X-ray diffraction pattern. The patent also included product-by-process claims to crystalline cefdinir obtained by a specific process.

The patent was involved in district court cases in two jurisdictions. On appeal, the Federal Circuit affirmed both district courts' findings of non-infringement after concluding the claims' recitation of crystalline cefdinir was properly construed to mean crystal A. Moreover, the Court, *sua sponte*, took up the product-by-process claims portion of appeal *en banc*. The majority, citing jurisprudence dating back to the 1880s, expressly adopted the *Atlantic Thermoplastics* rule (3), which held that process steps in a product-by-process claim must be met to find infringement (4).

While the Federal Circuit has not addressed the patentability of crystalline forms recently, it has been a very active issue before the Board of Patent Appeals and Interferences. A review of these decisions clearly shows that both innovators and generics continue to actively seek patent protection on crystalline forms of known NCEs. For example, in *Pfrengle*, applicants sought claims to a crystalline anticholinergic compound co-promoted by Boehringer-Ingleheim and Pfizer (5). The specification disclosed that 'surprisingly' the anhydrous compound may be obtained from the monohydrate as a starting material and that the anhydrate has particular advantageous hygroscopic characteristics. The patent examiner rejected the claims as anticipated and obvious in view of prior art references. On appeal, the Board of Appeals for Patents and Interferences reversed the rejections.

Although the examiner made out a *prima facie* case of anticipation, the Board concluded the applicant met its burden of demonstrating that the claimed compound was different than the prior art compound. This was done by filing an inventor's declaration with powder X-ray diffraction data demonstrating that the

prior art compound had a different diffraction pattern than that of the claimed compound. What's more, the applicants provided a declaration showing that the claimed compound had a different dynamic vapour sorption than the prior art compound, bolstering their argument over the prior art.

The underlying facts, however, are highly determinative regarding claims to a compound relying on a specific X-ray powder diffraction pattern. In *Reddy*, the examiner rejected the claims in an application filed by Dr Reddy's Laboratory because the claimed (S)-repaglinide and prior art compounds were made by the same process (6). Here, applicants were unable to show that the claimed and prior art compounds were different, primarily because the compounds were made by the same process, and a comparison of the X-ray diffraction patterns showed they were statistically the same. Applicants argued that differences in melting points between the claimed and prior art compounds distinguished the two. The Board, however, agreed with the examiner's conclusion that differences in melting points are affected by the degree of purity of the compound and thus the proffered data was not persuasive.

Enantiomers

Like crystalline forms, enantiomers have been a fertile area of alternative patent protection. Patents on a NCE will often disclose and claim the racemate, but not specific enantiomeric forms. In view of a previously claimed racemate, patentability of a specific enantiomer will generally turn on whether the claimed form has unexpected advantageous properties and the difficulty of separating the enantiomers. An illustrative case involved clopidogrel bisulfate (PLAVIX) (7).

Sanofi obtained a patent (the '265 patent) that claimed a substantially separated hydrogen sulfate of the dextro-rotary enantiomer of the racemate. Earlier Sanofi patents disclosed and claimed the racemate. At the time the '265 patent was filed, it was known that chiral compounds have stereoisomers that might be separated, but none of the earlier Sanofi patents disclosed their separation into enantiomers.

In a patent infringement suit against Apotex, the Federal Circuit held that the enantiomer was not anticipated by prior art disclosing the racemate and stating it consisted of enantiomers. The Court held that knowledge that enantiomers may be separated is not 'anticipation' of a specific enantiomer that has not been separated, identified and characterised. Even so, defendants argued, a person of ordinary skill in the art would know how to do so. But the Federal Circuit determined that a bare statement in the prior art that enantiomers could be separated was not enabling without guidance.

The Federal Circuit also held that the claimed enantiomer was not obvious over the racemate. The degree to which different stereoisomers exhibit different levels of therapeutic activity and toxicity is unpredictable, and absolute stereoselectivity was rare. Here, the dextro-rotary compound unexpectedly provided all of the therapeutic benefit and none of the toxicity effects. Moreover, the Court held that separation of the enantiomer was neither routine nor simple, as there was no showing that a reliable separation method was known for any analogous compound.

But if the prior art predicts the advantages of the separation of a racemate into its enantiomers, patentability may go the other way, as can be seen from the decision in *Aventis Pharma Deutschland GmbH v Lupin, Ltd* (8). Here, the Federal Circuit concluded that a claim to the 5(S) stereoisomer of ramipril (ALTACE) was obvious over the prior art racemate because it was known that a similar compound enalapril in the 3(S) stereoisomer form was 700 times more potent than the 2(S)(R) enantiomer. Thus, because the advantageous property of the 5(S) stereoisomer ramipril was not unexpected and its separation from the racemate was shown to be routine, the claim was considered obvious.

The importance of enantiomers was more recently highlighted in a challenge of patent term extension (PTE) on a patent claiming levofloxacin (9). The racemate had been claimed in an earlier patent and had been approved by the FDA previously. The S(-) enantiomer (levofloxacin) was described in a later patent as pharmaceutically superior to ofloxacin. The patent holders sought and were granted a PTE of more than 800 days (10). Lupin contested only the extension, arguing that the racemate was the first permitted commercial marketing or use of the product. Lupin argued that levofloxacin was the same 'drug product' as the previously marketed racemate, because an enantiomer is half its racemate and levofloxacin was the active ingredient of ofloxacin. However, the Patent and Trademark Office and the FDA have consistently recognised enantiomers as a different 'drug product' from its racemate. The PTO found levofloxacin to be separately patentable over the racemate, and the FDA determined it was a new product requiring full regulatory approval. Thus, the courts agreed that PTE to the enantiomer patent was properly granted.

Salts

Not every unexpected result, however, may be sufficient to clear the obviousness bar to patentability. In *Pfizer Inc v Apotex, Inc*, claims drawn to the besylate salt of amlodipine were held to be obvious in view of the prior art (11). As of the patent's priority date, besylate salts of various drugs were known but were relatively rare (0.25 per cent of FDA-approved salts). But because almost all salts except for hydrochloride are used rarely, the court was not persuaded that the besylate salt was non-obvious. The court also considered the genus of FDA-approved marketed anions useful for making pharmaceutically acceptable salts (around 50) was small, and that one of ordinary skill in the art would have considered benzene sulphonate. The court held that obviousness could not be avoided by showing some degree of unpredictability if there was a reasonable probability of success. In this case, reasonable expectation of success came from witness testimony and FDA correspondence. Although unexpected superior results is one objective indicia of non-obviousness, here the court concluded that it was insufficient to overcome the challenge on obviousness. Patentability, however, may still in some

instances be supported by an alternative salt form. For example, in *Sanofi-Synthelabo v Apotex, Inc*, the Federal Circuit concluded that a bisulphate salt of clopidogrel would not have been obvious where the prior art taught away from the use of sulphonic acid with an enantiomer as strong acids could encourage re-racemisation.

Prodrugs

A recent decision involving a PTE of a patent claiming the prodrug MAL hydrochloride highlights the potential importance of prodrugs (12). Here, the patentee sought an extension of a patent directed to MAL hydrochloride, the active ingredient in METVIXIA cream. The patentee argued that MAL hydrochloride had improved therapeutic properties over ALA, which was previously approved for the same use. MAL hydrochloride is the methyl ester of ALA, and the FDA considered it a 'new drug' for purposes of FDA approval.

In denying the PTE request, the Patent and Trademark Office interpreted 'active ingredient' in the statutory definition of 'drug product' as the 'active moiety' of that product, and not as the drug product that was approved by the FDA. In the Patent Office's view, ALA was simply formulated differently in the two different drugs. The district court and the Federal Circuit disagreed, finding that MAL hydrochloride and ALA are different 'products' with different 'active ingredients.' Moreover the court found that a compound can only qualify as the active ingredient of a drug if that compound itself is present in the drug.

Conclusion

The successful identification of a NCE and its patent protection are primary concerns of any pharmaceutical innovative company. However, the preceding review of the current case law makes clear that there must be a continuing concern regarding the potential patent protection of alternative forms of the NCE. In that regard, the innovator that does not consider alternative entities – polymorphs, hydrates, solvates, co-solvates, salts, enantiomers and prodrugs – proceeds at a great risk of not maximising the full value of its initial investment.

It is also important to recognise that these potential alternative entities, although discussed herein in a categorical fashion, do not necessarily exist in isolation, but may provide even more powerful protection when bundled together, for example, an enantiomeric salt. The case law, however, makes clear that the simple existence of an alternative entity does not necessarily warrant the issuance of patent protection for that entity. Clearly, the alternative entity must be new to obtain patent protection. It is also important for the applicant seeking patent protection for an alternative entity to illustrate and define the unexpected advantages of the alternative entity over the prior art. Improved efficacy, reduced side effects, improved stability and processability are all advantages that, if applicable, may be of significance.

The investment an innovator company makes to develop a NCE and bring a drug to market is enormous, and protecting this investment requires seeking patent protection for alternative chemical forms of the drug. The innovator company must be proactive in seeking such alternative forms or alternative formulations, because it is clear that the generic industry will almost certainly seek to carve out its own proprietary alternative forms to any successful innovative drug.

References

1. 35 U.S.C. §§ 154(a)(2), (c)(1).
2. *Abbott Labs v Sandoz Inc*, 566 F.3d 1282 (Fed Cir 2009) (en banc in part)
3. *Atlantic Thermoplastics Co Inc v Faytex Corp*, 970 F.2d 834 (Fed Cir 1992)
4. Although the Federal Circuit adopted the *Atlantic Thermoplastics* rule, it maintained that the determination of patentability of the product is based on the product itself. *Abbott* at 1292
5. *Ex parte Pfrengle*, Appeal 2010-004685 (BPAI, 2010)
6. *Ex parte Reddy*, Appeal 2009-001215 (BPAI, 2010)
7. *Sanofi-Synthelabo v Apotex, Inc*, 550 F.3d 1075 (Fed Cir 2008)
8. *Aventis PharmaDeutschland GmbH v Lupin Ltd*, 499 F.3d 1293 (Fed Cir 2007)
9. *Ortho-McNeil Pharm, Inc v Lupin Pharms, Inc*, 603 F.3d 1377 (Fed Cir, 2010)
10. For NCEs that have undergone a FDA regulatory period and received marketing approval as a drug, extension of patent term to recover some term lost while undergoing regulatory review may be obtained pursuant to 35 USC §156
11. *Pfizer, Inc v Apotex, Inc*, 480 F.3d 1348 (Fed Cir 2007)
12. *PhotoCure ASA v. Kappos*, 603 F.3d 1372 (Fed Cir, 2010)

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