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Leflunomide or the Risky Life of a Generic Manufacturer in Germany

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In its “Leflunomid” decision of 24 July 2012 (Case X ZR 126/09), the FCJ declared a patent claim to be invalid which covered a combination of leflunomide and teriflunomide, on the grounds that it had long been known in the prior art (for 100 years) that some leflunomide spontaneously and unavoidably converts teriflunomide over time (by a ring opening process). The combination was therefore obvious to the expert. The decision will be published in the Kluwer IP case databank.

The plaintiff in the case at issue was a generic company which had launched what it thought was a patent-free mono-product containing just leflunomide. However, due to the conversion of some leflunomide into teriflunomide, the generic company suddenly found itself faced with an infringement action brought by the patentee on the basis of the combination patent.

It turned out that this problem was not that easy to solve owing to legal aspects, with the FCJ essentially overturning both the first-instance decision of the Federal Patent Court and the infringement decision by the Regional Court Dusseldorf.

Facts of the Case

The patent in suit is related to a solid combination of two pharmaceutical ingredients known as leflunomide and teriflunomide, the latter being present in an amount of 0.3 to 50% of the former.

Claim 1 of the patent is directed at a solid preparation comprising a component 1 (leflunomide) having a content of 2 to 20 mg, a component 2 (teriflunomide) and/or a stereoisomeric form of this compound and/or a physiologically tolerated salt of this compound having a content of 0.3% to 50% of component 1, and a pharmaceutically acceptable excipient.

Both components of the above-mentioned claim were known prior to the priority date of the patent in question. The patent protection of component 1 (leflunomide) had already expired. In addition, it was known that component 2 (teriflunomide) in fact constituted the active principle responsible for the pharmaceutical action of leflunomide and that teriflunomide is metabolized from component 1 in vivo. Finally, it was known as well that leflunomide spontaneously and unavoidably forms some teriflunomide even while being stored.

A generic manufacturer intended to launch a generic medicament containing just leflunomide (no teriflunomide) for the treatment of rheumatoid arthritis. Before launching its product, it filed in time a nullity action against the above-identified combination patent in Germany before the

Federal Patent Court (FPC) alleging lack of novelty and inventive step of the claims in question based upon the prior art findings.

The FPC interpreted the patent as being directed at a solid combination of the two pharmaceutical components leflunomide and teriflunomide having the claimed proportions ab initio, or in other words: the FPC considered that in order to demonstrate a lack of novelty, the nullity plaintiff would have had to show that a combination product containing the two ingredients in the claimed amounts would have inevitably and reliably formed when preparing leflunomide.

The FPC considered that the uncontrolled spontaneous formation of some teriflunomide from leflunomide, even if it happens to result in a mixture that contains the two drugs in the claimed ratio, would not anticipate the patent, since it is not the result of a purposive activity, i.e. of deliberately adjusting a certain ratio. Rather, argued the FPC, it is just an arbitrary result that had not been described before and therefore was unknown to the skilled person. Thus, the generic manufacturer lost the pre-emptive nullity action (FPC, 4 August 2009, Case 3 Ni 52/07).

Following this logic, the generic manufacturer thought it would now be safe to launch the monopreparation (leflunomide only) since the possible (random) formation of some teriflunomide – which had already happened in prior art products – would not infringe the patent since if it produced the combination in the claimed amounts, this was not the result of a purposive activity. Indeed, it was not intended at all that teriflunomide should be present in the generic medicament.

The generic manufacturer filed an appeal against this decision to the Federal Court of Justice, but nevertheless started the marketing of its leflunomide product in October 2010.

However, the manufacturer could not avoid the spontaneous formation of some teriflunomide in his product after 6 months of storage, and indeed the amounts of teriflunomide that had formed were high enough to fall inside the claim of the combination patent.

As a consequence, the generic manufacturer found itself dragged into a patent infringement action before the Regional Court Dusseldorf. The Plaintiff requested, inter alia, an injunction by way of preliminary proceedings.

The generic manufacturer claimed non-infringement of the monoproduct in comparison to the claims directed at a combination product. Moreover, the manufacturer argued that it would only make use of an already patent-free technical process of the state of the art, pointed to the narrow claim interpretation of the FPC and alleged the invalidity of the patent based upon the arguments summarized above.

However, the generic manufacturer was again not successful.

Interestingly, the infringement court in Dusseldorf understood the claims in question entirely differently than the FPC in Munich had, and thus developed its own claim interpretation: The solid composition would only require the objective presence of both components within the claimed range. The infringement court considered it irrelevant whether these amounts were obtained by an intentional preparation of a combination product or just by the spontaneous conversion of some leflunomide into teriflunomide over time (broad interpretation) and consequently considered the marketing of the old and already patent-free mono-product leflunomide as infringing the claims in question (Regional Court Dusseldorf of 14 April 2011, Cases 4b O 29/11 and 30/11).

If one were to take this broad interpretation as the correct one, one should think that such a broad interpretation of the scope of the claims should now equally render the patent open to validity attacks. But the Dusseldorf Court (which has a long tradition of being patentee-friendly) arrived at the conclusion that even these broadly construed claims were novel and inventive. The Court even went one step further, and granted a preliminary injunction against the generic manufacturer.

It argued that a skilled person did not know which ratios of leflunomide and teriflunomide would result in the synergistic effect claimed and demonstrated in the patent. Moreover, it was unknown before the priority date how much teriflunomide would actually form and a skilled person did not know in which range of amounts the desired pharmacological effect according to the invention would actually materialize.

The Federal Court of Justice (FCJ) as the appeal instance in the invalidation trial applied a broad interpretation of the claim (as did the Dusseldorf Court in the infringement action), arguing that the claim “protects the combination as such, irrespective of the time point at which it forms and also how it forms”.

However, the Federal Court of Justice followed the inherent logic of this interpretation, which resulted in the invalidity of the patent.

The FCJ acknowledged that it was known before the priority date of the patent in suit that leflunomide would inevitably and permanently undergo a process of chemical conversion by ring-opening during storage to form teriflunomide. During this conversion process, the proportion at which leflunomide converts to teriflunomide reaches a magnitude that falls within the range claimed in the patent. So much was also confirmed by the court-appointed expert, who testified during the oral proceedings before the Federal Court of Justice that such ring-openings of compounds of this type have been described for more than 100 years in the technical literature.

Although the Court was not able to find that the patent lacked novelty, probably as a consequence of the recently established narrow approach to novelty following the “Olanzapin” decision of 16 December 2008, X ZR 89/07, and the “Escitalopram” decision of 10 September 2009, X ZR 130/07, and partly owing to the fact that there was no mono-preparation of leflunomide on the market prior to the priority date of the patent in suit, it firmly held that the patent lacks inventive step. The key statement of the ruling is:

“A pharmaceutical composition that includes a combination of two active ingredients (here: leflunomide and teriflunomide) is rendered obvious by the prior art when a person skilled in the art, who before the date of priority could have produced a mono-product (here: with the active ingredient leflunomide) using instructions rendered obvious by the prior art, would have obtained a product thereby which would convert by a chemical reaction during the conventional storage period into the combination of said two active ingredients.”

The FCJ expressly emphasized in the decision that if it had come to a different conclusion, namely that even the use of a leflunomide mono-product according to the teaching of the prior art would result in an infringement of said claim, this “would unjustifiably restrict the freedom of competitors to make use of the state of the art”.

As a consequence, all claims were held to be invalid and the patent was revoked for lack of inventive step.

This case once more highlights the peculiarities of the bifurcated German patent system. For a more detailed review, please see Kröger/Bausch, “Leflunomide – Or: The Risky Life of a Generic Manufacturer in Germany”, in Patents & Licensing, April 2013, p. 34 et seq.
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