**NL – Lilly's Pemetrexed patent is valid**

On 16 January 2019, the District Court of The Hague ruled that the Dutch part of Eli Lilly and Company's patent EP 1 313 508 is valid. The judgment was handed down in an invalidation action brought by Sandoz International GmbH.

EP 508 relates to the use of pemetrexed in combination therapy with vitamin B12 and optionally folic acid. The claims are mainly formulated in Swiss-type form.

This is an important decision, as in 2017 Lilly had obtained preliminary injunctions based on EP '508 against the sale of three generic pemetrexed products, i.e. those of Sandoz, Fresenius Kabi and Teva. These decisions (in Dutch) can be found here (for Lilly/Sandoz), here (for Lilly/Teva) and here (for Lilly/Fresenius). EPLaw has furthermore published a blog about the injunction against Teva and Fresenius. This can be found here.

Sandoz had brought an accelerated case on the merits against Lilly, seeking the revocation of the Dutch part of EP 508. Sandoz' invalidity arguments were based on the grounds of lack of novelty and lack of inventive step. The prior art for the assessment of the validity of EP 508, consisted of (among others) the following publications: Worzalla, Jackman, Hammond and Rinaldi.

**Novelty**
Sandoz argued that Worzalla was novelty destroying for EP 508. Worzalla discloses the results of a study in which mice were treated with pemetrexed. The study concerns the effects of folic acid on the toxicity of pemetrexed in mice that had been implanted with cancer tumor cells. There were two groups of mice: i) a group that was kept on a diet with low folic acid levels, and ii) a group that was kept on a *'standard diet'*, which included folic acid. Sandoz argued that this *'standard diet'* also included vitamin B12 in a higher amount than usual. Sandoz said that for this reason the mice must have intentionaly been given both folic acid and vitamin B12, although the study itself does not make any reference to B12 and only discusses the effects of a diet with or without folic acid on the efficacy of pemetrexed.

The Court ruled that Sandoz had not proven that any administration of vitamin B12 in the Worzalla-study – if any at all – was done for therapeutic purposes. This fact alone renders EP 508 novel over Worzalla. The Court concludes that it is therefore irrelevant to look at the actual composition of the food given to the mice (and whether or not this food contained vitamin B12, which Lilly had denied).

**Inventive step**
In its inventive step attack Sandoz focussed on claim 2, protecting the combination therapy of pemetrexed, vitamin B12 and folic acid (claim 1 covers the combination of pemetrexed and vitamin B12 only). It was common ground between the parties that if claim 2 was invalid for lack of inventive step, the same would apply to claim 1.

Sandoz' primary argument focussed on Jackman as closest prior art. Sandoz argued that Jackman would be a handbook, disclosing the combination of pemetrexed and folic acid. According to Sandoz, the skilled person would know at the priority date that it would be beneficial to combine a pemetrexed therapy with the administration of folic acid. The combination, according to Sandoz, would be a given for the skilled person. Taking that as a starting point, Sandoz argued the skilled person would be motivated to also administer vitamin B12. It would be common general knowledge that vitamin B12 is necessary to make the folic acid functionally available. Without vitamin B12 the

folate acid would remain in the human body in an inactive form, because of the so-called methyl-trap. The Court disagreed.

The Court ruled that whilst Jackman does disclose the combined use of pemetrexed with folic acid, it does not consider Jackman as a realistic starting point for the skilled person. This is because Jackman is a mere compilation of articles and not a handbook. Moreover, Jackman does not include any articles written after 1997, while the skilled person has an incentive to look to such later publications published before the 2001 priority date. The Court concludes that the starting point for the inventive step assessment is the prior art disclosing research into the combination of pemetrexed and folic acid.

This prior art consists of, amongst others, Worzalla (mentioned above) and abstracts of Rinaldi and Hammond. With regard to Worzalla, the Court ruled that it teaches the skilled person that the combination of pemetrexed and folic acid leads to a reduced toxicity of pemetrexed, but also that this leads to a reduced efficacy of pemetrexed. A higher dose of pemetrexed would thus be necessary to obtain the same level of efficacy. The Court ruled that it would be questionable for the skilled person, whether these lessons from Worzalla also apply on humans.

The Court continues with Hammond and Rinaldi. These publications are clinical treatment studies wherein human cancer patients were treated with pemetrexed. In Rinaldi, no folic acid was administered whereas in Hammond it was. According to the Court, Hammond confirms the idea that the addition of folic acid reduces the toxicity of pemetrexed. However, Hammond does not confirm that the addition of folic acid to a pemetrexed therapy would have a positive effect on the efficacy of the therapy (anti-tumour response). Hammond only discloses one partial response (out of thirty-three patients). In Rinaldi, a study without the administration of folic acid, there was a major antitumor response in ten out of thirty-seven patients. The Court ruled that this would be a sign for the skilled person that folic acid affects the efficacy of pemetrexed. Furthermore, the Court ruled that it may also be a concern for the skilled person that higher doses of pemetrexed would have adverse effects on kidney function of humans, as disclosed in Hammond.

In conclusion, the Court does not accept Sandoz' assertion that the combination therapy of folic acid with pemetrexed is a given in the prior art, let alone that the application of such therapy should be considered as common general knowledge. The Court therefore does not deal with Sandoz' arguments relating to vitamin B12, as the combination therapy of folic acid with pemetrexed is not even a given for the skilled person.

The Court also dealt briefly with the arguments of Sandoz which take Worzalla and Calvert as the starting point. The Court held in essence that these attacks fail for similar reasons.

**Reference to the BPG**

At the end of the decision, the Dutch Court explicitly refers to the German decision by the Bundespatentgericht (BPG). The Dutch Court says that it is aware of the fact that it comes to a different outcome than the BPG. The Dutch Court suggests that this might be because the Bundespatentgericht based its decision on (partly) different (combined) prior art than the art in the Dutch proceedings, and because the debate at the BPG also seems to have been different on other points.

A copy of the decision of the District Court of The Hague (in Dutch) can be found here. A translation of this decision can be found here.