COURT OF MILAN

Specialised business division

Division A

The Court's Panel, represented by the following Judges:

Mr Claudio Marangoni President and Judge *rapporteur*

Ms Anna Bellesi Judge

Ms Alima Zana Judge

delivered the following

order

in the appeal proceedings under Art. 669-*terdecies* of the Italian Civil Procedure Code, entered in the General Docket No. 45209/2017, started by:

ELI LILLY & Co.

ELI LILLY ITALIA S.p.a.

Appellants

versus:

FRESENIUS ONCOLOGY PLC

FRESENIUS KABI ITALIA S.r.l.

Respondents

against the preliminary decision issued on 10.9.2017.

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1. Further to the petition brought by FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l., by order filed on 10.9.2017, hereby appealed by the Appellants, the

first instance Judge issued a declaration of non-infringement, stating – based on the outcome of the technical investigation phase carried out in those proceedings – that the marketing of the antitumor drug *Pemetrexed Fresenius Kabi* 100 mg and *Pemetrexed Fresenius Kabi* 500 mg powder for concentrate for solution did not infringe the Italian portion of patent EP 1313508 owned by ELI LILLY & Co., thus rejecting the counterclaim brought by ELI LILLY & Co. and by the intervening party ELI LILLY ITALIA s.p.a., which had filed a petition for preliminary injunction against any further act of manufacturing and marketing of the above drugs on the grounds that they would infringe the same patent.

In short, in the first instance preliminary proceedings the Judge held that the literal wording of claims 1 and 12 – respectively, a use claim and a product claim – showed that the patent claimed a specific chemical compound, *i.e.* the *disodium* salt of the antifolate *pemetrexed* (*pemetrexed disodium*), and that this was confirmed by the description of the patent (more specifically par. 22, whereby "*the antifolate or antifolate drug for use in this invention*" was exclusively "*pemetrexed disodium (ALIMTA) as manufactured by ELI LILLY*"), so that the alleged infringement by the petitioners' product had to be excluded, on the grounds that it includes another component, *i.e. pemetrexed diacid*.

In support of the above conclusion, the first instance Judge also relied on the *file history* of the examination phase of EP 1313508 and, in particular, on the progressive limitations introduced by the patent holder following the objections raised by the Examiner against the original wording of the patent application, which initially claimed the entire class of antifolates, was subsequently limited to the antifolate *pemetrexed* and then further limited, in its final version, to *pemetrexed disodium* alone.

According to the appealed order, this construction of the scope of protection of EP 1313508 also excludes its infringement by equivalents, on the grounds that this doctrine

cannot be relied upon when the patent was intentionally limited during the granting procedure or during an invalidity action pursuant to Art. 79 of the Italian Industrial Property Code. Indeed, the scope of protection of the patent allegedly cannot extend to features that were expressly excluded through the limitation.

Moreover, the circumstance that said limitations were made to overcome the Examiner's formal objections is allegedly irrelevant, given that, for the purposes of an objective construction of the patent's scope of protection, the behaviour of the patent holder must be taken into account regardless of the reasons underlying its decision to reword and limit the patent. Indeed, the patent holder cannot claim a broader scope of protection through the doctrine of equivalents, if this is in contradiction with the limitations he made.

In any case, the first instance Judge relied on the outcome of the technical investigation phase carried out in those proceedings, which had established that the subject-matter of the patent was not infringed, given that Fresenius' drug, although it has the same therapeutic action as Ely Lilly's *Alimta* – and thus is the generic version of such drug – does not amount to an obvious and technically equivalent replacement thereof. According to the appealed decision, the combination of *pemetrexed diacid* and *tromethamine* overcame an intrinsic technical prejudice of EP 1313508, whereby only the combination of *pemetrexed disodium* and vitamin B12 allows for the reduction of the adverse side effects of the antitumor treatment, while the skilled person should have made a number of changes (replacing a sodium salt with a free acid, identifying *tromethamine* as a suitable base to ensure a similar stability, reconstituting and diluting with a glucose solution instead of a saline) that implied too many variables to be considered obvious.

The first instance Judge also excluded any indirect infringement – claimed in connection with the circumstance that *Pemetrexed Fresenius Kabi* allegedly provides an essential element for the invention, *i.e.* the *pemetrexed* anions – as the invention is characterized by

the use of *pemetrexed disodium*, being an active ingredient other than *pemetrexed diacid*, whereas the glucose solution used for dilution is allegedly different from and not equivalent to a saline.

2. FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l. [this should read: *ELI LILLY & Co. and ELI LILLY ITALIA s.p.a.; Translators' note*] lodged an appeal against the above order.

First and foremost, they identified the technical problem solved by EP 1313508 in the prevention of the toxic side effects arising from the use of the antifolate *pemetrexed* without adversely affecting its therapeutic efficacy, a problem solved through the administration of a methylmalonic acid lowering agent such as vitamin B12 along with *pemetrexed*.

For the purposes of the invention – according to the Appellants – the starting form of the active ingredient *pemetrexed* is totally irrelevant, since *pemetrexed* can be manufactured in several pharmaceutically acceptable forms (*disodium*, *diacid* and *tromethamine*, *dipotassium*) all capable of enabling the release of the *pemetrexed* anions constituting the active moiety of the substance. The reduction in the toxic side effects of the *pemetrexed* anion is not associated with the active ingredient form at all – but rather with the treatment in combination with vitamin B12 – because, as a matter of fact, the counterions (salt cations in *pemetrexed disodium* and hydrogen protons in *pemetrexed diacid*) play no active role in connection with the technical problem addressed by the patent.

Stressing the relevance of the foreign decisions that addressed the same issues – and in particular the decision of the UK Supreme Court of 7 July 2017 – the Appellants argued that the conclusions drawn by the first instance Judge were wrong – wherein he held that the amendments made by the patent holder during the examination phase before the EPO excluded the application of the doctrine of equivalents – on the grounds that said

amendments did not follow from objections of lack of novelty or lack of inventive step raised by the Examiner.

According to the Appellants, a precise definition of the subject-matter of the invention is no reason to exclude the applicability of the doctrine of equivalents. The entire background of the patent description, the lack of any selection among different *pemetrexed* salts, the absence of any actual technical prejudice in respect of the use of other salts, as well as the wrongful assessment of the non-obviousness of the salt replacement, all suggest that the appealed decision should be overturned.

The Appellants also appealed against the alleged non-existence of an indirect infringement under Art. 66, paragraph 2-*bis* of the Italian Industrial Property Code.

The respondent ELI LILLY & Co. and the intervening party ELI LILLY ITALIA S.p.a. [this should read: *FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l.; Translator's note*] argued that the appealed order is well-grounded, supporting the arguments put forward therein and asking for it to be confirmed.

In the appeal proceedings, the Court ordered a new Technical Expert phase, appointing to this purpose a Panel made up of three Experts. The Experts were asked to identify the scope of protection of EP 1313508, also in light of the elements that may be gathered from the "*file history*" of the disputed patent, and to assess whether Fresenius' product infringed its claims directly, indirectly or by equivalents. This implied a thorough investigation of the relationship between antifolates and the respective salts used/claimed by the parties (*pemetrexed diacid* and *tromethamine*, on the one hand, and *pemetrexed disodium* on the other) having specific regard to the therapeutic effects of the combination covered by the patent and to the relevance of the replacement of *pemetrexed disodium* with *pemetrexed diacid* and *tromethamine* for the technical problem described in EP 1313508 and its solution. The Panel of Experts was also asked to ascertain whether said replacement

overcame any technical prejudice and whether it would have been obvious for the person skilled in the art or it would have required studies and trials implying unreasonable efforts compared to mere *routine* studies.

2. As a preliminary matter, we shall deal with the latest requests filed by the Respondents. Indeed, FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l. asked this Court to address the invalidity of EP 1313508 in the present appeal proceedings, based on the circumstance that on 17 July 2018 the German Federal Patent Court (*Bundespatentgericht*) revoked the German portion of EP 1313508 due to the lack of inventive step, in an action filed by parties that are not involved in these proceedings. For the time being, only the operative part of the judgment is known, but the grounds of the decision have not been published yet.

The Appellants argued that this motion is inadmissible.

The Court holds that the motion cannot be admitted.

It should be highlighted that, in the petition filed before the first instance Judge, the Respondents expressly limited the subject-matter of their requests – and hence of the relevant assessments to be made – to the infringement of EP 1313508. Although the Respondents claimed that there were a number of invalidity grounds of the disputed patent – which were not further specified in the petition – they also alleged that these issues would be developed in the course of separate proceedings on the merits (see p. 11 of the petition lodged in the first instance proceedings: "*in order to obtain the requested measure as quickly as possible and, therefore, to launch the Product in Italy without fearing any legal action by the respondent, we reserve the right to raise any argument concerning the lack of the valid patentability requirements of EP'508, which – to say the least – lacks inventive step*").

It seems clear to the Court that the Respondents' motion conflicts with the clear and explicit exclusion of the validity issues of EP 1313508 from the preliminary proceedings – even as a mere defence. The fact that a full re-examination of the merits of the case is possible in the course of preliminary appeal proceedings (for the so-called devolutionary nature of the appeal) does not allow the introduction of aspects that were intentionally excluded from the debate by the petitioner and hence were never examined in the first instance preliminary proceedings.

Moreover, it should be noted that to this day the grounds of the alleged invalidity have not been specified, and it would seem that the Respondents are waiting for the grounds of the decision of the German Federal Court to be published. This *per se* prevents this Court from making any further observation and assessment on this topic, also taking into account the clear provision of Article 121, par. 1, of the Italian Industrial Property Code.

Within preliminary proceedings, the Court cannot assess autonomously the validity of a duly granted patent, if this was not disputed and if the opposing party has not filed specific arguments – as well as relevant documents – in this respect. Otherwise, the Court's investigation would be merely exploratory and end up essentially shifting the burden of proof resting on the parties.

On the contrary, assessing the scope of protection of a patent – the validity of which is not disputed – is as a necessary preliminary step for ascertaining the alleged infringement of the same. This assessment was thus carried out both in the first instance preliminary proceedings and in the appeal proceedings held before this Panel through specific questions submitted to the Court-appointed Experts.

3. An issue that was extensively addressed in these proceedings – although in the appealed order it was not the only element in support of the non-infringement of EP 1313508 by the antitumor drug *Pemetrexed Fresenius Kabi* – concerns the relevance that the Judge should

give to the *file history* (or *prosecution history*) of the proceedings held before the EPO Examiner, with specific regard to the patent holder's intention to limit the application as filed following the objections raised by the Examiner and, as a consequence, the relevance that may be attributed to the conduct of the patent applicant as to the possibility to rely on the doctrine of equivalents in Court, for the purpose of establishing the scope of protection of the patent pursuant to Article 52, paragraph 3-*bis* of the Italian Industrial Property Code.

In general, the Court believes that, in assessing the scope of protection of a patent, the Judge may only rely on the criteria provided by the law and, more specifically, by Article 52, par. 2, of the Italian Industrial Property Code. According to this provision, the scope of protection is established in the first place by the wording of the claims, while the description and drawings may be relied upon to interpret the claims. Paragraph 3 of the same article provides another criterion to be followed in the interpretation of a patent. It establishes that, for the purpose of interpretation, both a fair protection for the patent holder and a reasonable legal certainty for third parties must be ensured.

As the parties know, this latter provision is literally derived from the Protocol on the Interpretation of Article 69 EPC, which defines this way a balanced position to be attained in interpreting the patent, preventing – on the one hand – that the protection conferred by the European patent is established based on the strict and literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims, and – on the other – that the claims are read as a mere guideline, extending the protection to what, from a consideration of the description and drawings by a person skilled in the art, the patent proprietor has contemplated.

Therefore, it cannot be doubted that the claims, together with the description and the drawings, are entrusted by the legislator with the task of giving an account of the will of

the patent holder and it is on these elements that the judge must carry out his assessments. In this context, the role of the *file history* – which is not formally included among the sources of knowledge available to the judge and therefore does not necessarily have to be known and examined by the third party and the person skilled in the art – can only be completely secondary and ancillary, and may at most provide merely circumstantial evidence as to the patent holder's willingness to exclude or not certain solutions from its scope of protection. However, any such exclusion should be primarily and effectively found in the patent text, *i.e.* the only document in which third parties can and must find the limits of the exclusive rights granted to the patent holder.

Therefore, it would be paradoxical to hold that the Judge – who is called upon to verify in full autonomy the compliance with the conditions established by law for the patentability of an invention for which an administrative title has been issued, reviewing its validity – is bound, in his judgment, to the events occurred during the examination procedure between the EPO Examiner and the patent applicant. The statements rendered and the actions taken by the applicant during the examination may thus be relied upon only to obtain a confirmation of the will already emerging from the patent text as granted and as an aid in construing the reasons underlying the drafting of the claims as granted. Within these limits, the *file history* may contribute to the determination of the patent' scope of protection and therefore also to any extension of the same to equivalents (see Court of Milan, 5.4.2011).

However, the interpretative aid that the examination of the *file history* of the patent can provide to the judge is substantially limited to the aspects of novelty and/or inventive step and that is to say, in particular, to the objections raised by the EPO Examiner to the original text based on prior art documents that relate to the subject-matter of the invention. Indeed, only in this respect the amendments made in the course of the examination may

affect, within the limits set out above, the Judge's assessment of the scope of the patent protection and, therefore, the possibility to extend it to equivalents. In this respect, it should not be forgotten that the path of amendments may be somehow flawed further to ungrounded or questionable objections of lack of novelty or inventive step, which might have improperly led the applicant to change the patent text.

Therefore, the items of the *file history* shall be examined carefully, for the purpose of gathering elements that strengthen and confirm a specific intention to limit the patent, the actual and primary findings of which must in any case be found in the patent text.

If the patent applicant submitted an amended version of the claims further to objections raised by the Examiner based on prior art documents allegedly disclosing part of the solution included in the application as filed, the Judge might acknowledge the reasons that led the applicant to limit the scope of protection established in the application, but shall however ascertain whether the solutions excluded through the limitation were actually obvious and could not be protected by the patent: in the affirmative, the behaviour of the applicant during the examination will confirm its limiting will, and he will not be allowed to recover the obvious solutions he had already excluded, whereas, in the negative, the assessment of the patent's scope of protection might include also equivalent solutions.

But the Court believes that these considerations cannot be extended beyond the objections made by the EPO Examiner in relation to the novelty and inventive step of the invention.

In the present case, the reconstruction of the examination phase of EP 1313508 carried out by the Panel of Experts confirmed that an objection was raised against the first limitation submitted by ELI LILLY & Co., according to which the compound *pemetrexed* – which had replaced the wider term "antifolates" used in the original wording of claim 1 – could be challenged under Article 123, paragraph 2, EPC since the object of the new claim 1 – referring to the use of *pemetrexed* – was not supported by the patent application as filed.

According to the EPO Examiner, *pemetrexed* was to be considered a distinct compound (CAS Registry number 137281-23-3) from "*pemetrexed disodium*" (CAS Registry number 150399-23-8) as mentioned in the original description and covered by claim 10, so that the amendment proposed would have extended the subject-matter beyond the content of the application as filed.

In fact, this remark did not imply any objection of lack of novelty or lack of inventive step – but, if anything, of novelty compared to the original wording of the claim – and simply pointed out that the wording of the original claims did not allow to protect *per se* the compound *pemetrexed*, taking into account that the only mention of the compound found in the text referred to the specific pharmaceutical form of *pemetrexed disodium*, corresponding to the drug Alimta which had been the subject of ELI LILLY & Co.'s clinical trials.

It must be acknowledged that in such event – unlike limitations arising from prior art objections – a limitation introduced further to an objection of added matter cannot materially affect the application of the doctrine of equivalents, since such objection only concerns formal issues regarding the literal wording of the amended claims, as compared to the patent application as filed. Instead, the finding of an infringement by equivalents is based on elements that are neither described nor claimed in the patent, and must thus be set against a background that has nothing to do with the question of whether the limitation falls within the scope of the application as originally filed.

The assessment of added matter, indeed, exclusively concerns the literal wording of the claims, whereby equivalent solutions added by limiting the claims cannot be allowed if they are absent from the original description or claims of the patent. It is not up to the Examiner, as part of his preliminary analysis, to assess whether a patent's scope of

protection extends to the possible equivalents, as this lies within the jurisdiction of the Court in respect of the patent as granted.

In the case in point, it can thus be safely ruled out that the amendment made by the applicant and introduced in the text as granted may *per se* be considered to restrict the interpretation of the patent's scope of protection in such a manner as to exclude compounds that are equivalent to *pemetrexed disodium*.

Furthermore, an analysis of the file history may provide evidence to the contrary, *i.e.* that there was no intention to restrict the scope of protection to the pharmaceutical form of *pemetrexed disodium* alone (see ELI LILLY & Co.'s reply to the EPO Examiner dated 8.3.2006 – Appellants' Exhibit 40 – in which the Appellants clarified that the changes had been made in order to refer to the "*preferred*" embodiment, *i.e.* the use of *pemetrexed disodium* as the antifolate drug manufactured by the company).

4. Besides, it is this Court's opinion that the wording of the claims and description of EP 1313508 does not provide significant elements to the person skilled in the art to conclude that the owner intended to exclude equivalents of *pemetrexed disodium* from the patent's scope of protection.

It was shown that EP 1313508 claims the use of *pemetrexed disodium* in the manufacture of a medicament for use in a combination therapy for inhibiting tumor growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof (see claim 1). However – as confirmed by the Panel of Experts – such reference cannot be automatically associated with a negative meaning, such as to infer that every other salt of *pemetrexed* could not be used to achieve the technical effect of the invention.

There is absolutely no hint of any such exclusion, especially considering that the invention does not regard the selection of a *pemetrexed* salt but is rather aimed at reducing the toxic effects of the active moiety of said active ingredient, *i.e.* the anion.

As confirmed by the Panel of Experts, at the filing date of EP 1313508 the person skilled in the art was aware that the active moiety of the ingredient *pemetrexed* – *i.e.* the one capable of penetrating inside the cells and exerting both its inhibiting but also its toxic effects – is the anion, a part of the molecule that can be obtained from a wide range of pharmaceutical forms other than *pemetrexed*.

The person skilled in the art was also aware that the counterion played absolutely no role for the purposes of the invention, since the non-dissociated acid form of *pemetrexed* is not capable of penetrating into the cells: only the anion is capable of doing so, exploiting the bond with anion carriers. Hence, as part of the therapy, *pemetrexed* must be administered in a dissociated form, with the anion in a free form.

Therefore, the person skilled in the art would not attach any particular significance to the fact that the antifolate *pemetrexed* was in the *disodium* salt form: the person skilled in the art would treat this as a clearly non-essential element of the invention, since the invention is aimed to solve a clinical issue of toxicity by associating vitamin B12 to the active (and toxic) moiety of *pemetrexed disodium*, *i.e.* the anion.

In short, what the person skilled in the art would immediately grasp from the claims of EP 1313508 is that sodium was exclusively used as one of the possible counterions that must be present in the solid form of the drug for its distribution.

Hence, the Court-appointed Expert in the first instance preliminary proceedings appears to have placed excessive importance on the reference to "*pemetrexed disodium*" in par. 22 of the description of EP 1313508, while – according to the Panel of Experts – such reference should have been interpreted based on the functional definition of "*antifolate*" or

"*antifolate drug*" provided in the same paragraph in respect of the capacity to inhibit at least one key folate-requiring enzyme, a capacity that solely and exclusively belongs to the active moiety of the antifolate, *i.e.* the anion, regardless of the starting form.

The anion is released only upon reconstitution/dilution of the solid *pemetrexed* – irrespective of its specific pharmaceutical form – along with its counterions (of whatever nature, sodium, hydrogen, etc.), which are totally uninvolved in the biological mechanism: the anion is a chemical compound existing as an independent entity within the reconstituted/diluted solution administered to patients as part of the claimed combination therapy.

The Panel of Experts thus concluded that, from the definition of the term "*antifolate*" based on its antineoplastic function, as provided in par. 22 of the description, the skilled person cannot but understand that such term must be deemed to refer to the anion and not to the specific salt form used, and therefore the fact that the initial paragraphs of the description of EP 1313508 mention the general category of "*antifolates*", and the fact that the claims relate to "*pemetrexed disodium*" does not prevent the application of the doctrine of equivalents to other pharmaceutical forms of *pemetrexed*.

On the other hand, no statements excluding the use of different pharmaceutical forms of *pemetrexed* and no claim that only *pemetrexed disodium* had been specifically selected to achieve the desired anti-toxic effect – an effect that, as already mentioned, does not depend on the pharmaceutical form of *pemetrexed* used – are anywhere to be found in the description.

The reference to the active ingredient (*pemetrexed*), its salt (*disodium*) and the trade name (*Alimta*) of the drug would thus derive from the fact that this was the form of the active ingredient used by ELI LILLY & Co. during the trials that led to the invention at stake.

5. We also wish to refer to the critical observations provided by the Panel of Experts in respect of the objection raised under art. 123, par. 2 EPC by the EPO Examiner against the first limitation proposal submitted by ELI LILLY & Co., which had substantially replaced the term *antifolate* with *pemetrexed*.

In such respect, the Panel of Experts highlighted that, against the technical background of the invention subject-matter of EP 1313508, "*pemetrexed*" and "*pemetrexed disodium*" could not be considered two different active ingredients, because in both cases the *pemetrexed* anion was the active moiety capable of penetrating inside the cells and exerting its inhibiting and, at the same time toxic, effect; likewise, the different CAS numbers quoted by the Examiner do not play a substantial role in identifying the actual solution to the clinical problem underlying EP 1313508, regardless of the literal wording the claims, since – as can be inferred from the reference to the website www.cas.org – a CAS number has no chemical significance and the different pharmaceutical forms of the same active ingredient have different CAS numbers.

According to the Panel of Experts, the fact that "*pemetrexed*" and "*pemetrexed disodium*" have different CAS numbers does not mean that they are different antifolates or substances with different chemical or pharmaceutical properties, but only that these substances have two different molecular structures, such that – as can be also inferred from the website www.chemicalbook – the terms "*pemetrexed*", "*pemetrexed disodium*", "*pemetrexed diacid*", "*pemetrexed disodium (Alimta)*", "*Alimta*" and the chemical name "N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid disodium salt" are commonly indicated as synonymous to one another.

6. The Panel of Experts thus conducted the so-called *Triple Test* to assess whether – once literal infringement has been excluded – infringement by equivalents exists between *Pemetrexed Fresenius* and the *pemetrexed disodium* of EP 1313508.

The Panel established that both have the same therapeutic function, highlighting how the SmPC (Summary of Product Characteristics, attached to the MA) of the Respondents' product specifies that "*Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication*" and that Pemetrexed Fresenius is indicated for use in the treatment of specific types of cancer, since the premedication therapy in combination with vitamin B12 and folic acid reduces the toxicity of the treatment and the severity of skin reactions caused by such treatment.

The following can also be read in the CHMP (Committee for Medicinal Products for Human Use) Report concerning Pemetrexed Fresenius: "*The aim of the pharmaceutical development was to develop a finished product generic to the reference medicinal product, Alimta (Eli Lilly Nederland B.V). The active substance in Pemetrexed Fresenius Kabi is pemetrexed diacid instead of pemetrexed disodium (Alimta). Since the active moiety in the solution for infusion remains the same irrespective of the salt form used for manufacture it has no impact*".

The administration of Pemetrexed Fresenius according to the methods described in the SmPC – after reconstitution in 5% glucose solution and subsequent dilution of a powder containing also mannitol, hydrochloric acid and trometamol – necessarily leads to forming the anionic species having trometamol (or tromethamine) as a counterion instead of sodium.

Since the active moiety is the same both in Fresenius' *pemetrexed diacid* and in ELI LILLY & Co.'s *pemetrexed disodium,* and since such active moiety is used in combination with vitamin B12 and folic acid, the Panel of Experts concluded that the mechanism of action of *Pemetrexed Fresenius* is the same as *pemetrexed disodium* according to the medical use defined in EP 1313508. As acknowledged in the CHMP

Report for *Pemetrexed Fresenius*, the salt form used has no relevance, since the *diacid* and the *disodium* salt act in the same manner.

The Panel of Experts thus concluded that Pemetrexed Fresenius infringes the scope of protection of patent EP 1313508 by direct equivalence.

The Panel also established that such product is *pemetrexed diacid* formulated with excipients comprising mannitol, hydrochloric acid and trometamol. The reconstitution in 5% glucose infusion and subsequent dilution of such formulation necessarily leads to forming the anionic species having *trometamol* – instead of sodium – as a counterion.

The fact that the features of claim 1 of EP 1313508 and of the dependent claims have been reproduced is proven by Fresenius' direct teaching to use the drug in a combination therapy with vitamin B12 (claim 1) and folic acid (claim 3). As the combination therapy is defined as mandatory in the SmPC, therefore – regardless of the fact that vitamin B12 and folic acid are not sold along with the Fresenius product – this amounts to an infringement.

7. As to the replacement of *pemetrexed disodium* with *pemetrexed diacid*, the Panel of Experts deemed such replacement to be obvious based on several arguments.

While salt screening is undoubtedly a routine activity, the fact that it required extensive trials is, on the one hand, irrelevant, because the stability profile referred to by Fresenius is mandatory to obtain the marketing authorisation for a medicinal product, and cannot *per se* provide any indication as to the fact that the development of the drug raised complex issues or difficulties. On the other hand, *pemetrexed diacid* as a compound was already known on the date of filing of EP 1313508, while *tromethamine* plays the same role as pH regulator of the pH regulator used by ELI LILLY & Co. in its product *Alimta* (sodium hydroxide), a replacement that falls within the standard activity of the person skilled in the art.

Having excluded the issues relating to the compound's stability – which is *per se* unrelated to the technical problem underlying EP 1313508 and, in any event, was not proven to have been improved by the Fresenius product – the Panel of Experts also ruled out that the replacement of *pemetrexed disodium* overcame a technical prejudice.

While according to well-established principles, a technical prejudice must emerge as an opinion shared by a large majority of experts, in the case at issue such prejudice could not be inferred neither from the fact that *tromethamine* is considerably less used than sodium in acid active ingredients to be administered parenterally – given that its use should be excluded altogether in case of a theoretical prejudice – nor from the very wording of EP 1313508, which does not mention any hindrance whatsoever in the use of other forms of *pemetrexed*, the use of which in forms other than the disodium salt had already been described in the patent literature (WO2010/030598).

Hence, the Respondent's activities aimed at replacing *pemetrexed disodium* with *pemetrexed diacid* and *tromethamine* involve no inventive step, and must rather be considered to be obvious and within the reach of a person skilled in the art.

8. This Court deems that the assessments made and the conclusions reached by the Panel of Experts can be relied on, given the exhaustive arguments presented, the extensive discussion of the issues at stake and the in-depth assessment of further issues that, in the first instance proceedings, had been dealt with only partially and based on judgement criteria that were not always acceptable.

A review of the replies provided by the Panel of Experts to the critical observations of the Respondents shows that they were examined exhaustively. It should also be noted that said observations substantially repeated the arguments already presented to and considered by the Panel of Experts in their preliminary report, and therefore no further comments need to be provided in respect of such observations.

9. Hence, there is a *prima facie* case (*fumus boni iuris*) in the claims lodged by ELI LILLY & Co. and by the intervening party ELI LILLY ITALIA S.p.a.. Moreover, there is also a real risk of an impending damage (*periculum in mora*), which justifies the granting of the requested preliminary measures.

The Appellants have highlighted that, after the end of the first instance preliminary proceedings, the price negotiation and reimbursement procedure started by Fresenius with AIFA was completed, and the disputed drug was expressly included within the so-called "Reimbursement Class H". This allows hospitals to request and obtain from AIFA a reimbursement of the price of the medicinal product purchased from the generic drug manufacturers, which essentially equates the generic drug to the original drug covered by the patent, also in terms of reimbursement policy.

Hence, the requested preliminary measures must be granted as a matter of urgency, so as to safeguard the patent and the manufacturer's exclusive right to place the product on the market. Indeed, if the disputed medicinal product started or continued to be marketed, this might adversely affect the global market position of the Appellants, who would run the risk of losing their shares on the market both as a direct consequence of the sale of the infringing product and due to the possible early entry on the market of other manufacturers of the generic drug.

10. Reversing the appealed order, thus, the action seeking a declaration of non-infringement lodged by FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l. must be dismissed, and conversely the preliminary measures requested by ELI LILLY & Co. and by the intervening party ELI LILLY ITALIA s.p.a. must be granted, issuing an injunction that prohibits the former companies from manufacturing, marketing and promoting the medicinal product *Pemetrexed Fresenius*, or howsoever named, ordering that such medicinal product be withdrawn from the market (as far as its

distribution network is concerned) and setting a penalty in the amount specified in the operative part of this decision.

The Court does not deem it necessary to order the publication of this decision, given its preliminary nature, nor to issue an exhibition order, since the grant of such measure before the potential proceedings on the merits is not justified on grounds of urgency.

As to the costs of both preliminary proceedings – which may be awarded now because this decision is potentially stable between the parties, even without the relevant proceedings on the merits – the Court orders FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l. to refund the costs for the proceedings as set out in the operative part here below, plus the costs incurred for both Technical Expert phases, as awarded during the proceedings.

FOR THE ABOVE REASONS

The Court, having regard to art. 669-*terdecies* of the Italian Civil Procedure Code:

1) upholding the appeal lodged by ELI LILLY & Co. and by the intervening party ELI LILLY ITALIA S.p.a. against the order of 10.9.2017:

- rejects all motions for interim relief lodged by FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l.;

- having established that the medicinal products *Pemetrexed Fresenius Kabi* 100 mg and *Pemetrexed Fresenius Kabi* 500 mg powder for concentrate for solution infringe the Italian portion of patent EP 1313508 by equivalents, enjoins FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l. from manufacturing, offering for sale, using, promoting, importing and exporting, in any form whatsoever, the medicinal products *Pemetrexed Fresenius Kabi* 100 mg and *Pemetrexed Fresenius Kabi* 500 mg powder for concentrate for solution (or howsoever named);

2) orders FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l. to withdraw said medicinal products from the market (distribution network) within seven days from the communication hereof, and sets a penalty of € 30,000.00 for each day of delay starting from such deadline;

3) rejects the additional interim measures sought by ELI LILLY & Co. and by the intervening party ELI LILLY ITALIA s.p.a.;

4) orders FRESENIUS ONCOLOGY PLC and FRESENIUS KABI ITALIA S.r.l., jointly, to refund to the Appellants the costs incurred for both preliminary proceedings, awarded in € 40,000.00 as legal fees, plus general costs and the additional expenses as provided by the law, as well as the costs for both Technical Expert phases in the amount awarded during the proceedings.

Decided in Milan, during the hearing in Chambers held on 20 September 2018.

The President of the Division, as Judge *rapporteur*

Claudio Marangoni