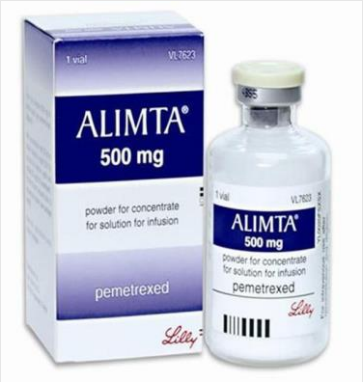
UK Supreme Court, 12 July 2017, Actavis v Eli Lilly



PATENT LAW

Scope of protection

The reformulated (guideline) questions for finding infringement are as follows:

i) Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, ie the inventive concept revealed by the patent?

ii) Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?

iii) Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?

In order to establish infringement in a case where there is no literal infringement, a patentee would have to establish that the answer to the first two questions was "yes" and that the answer to the third question was "no".

Appropriate use of prosecution history

- **Reference to the file would only be appropriate where (i) the point at issue is truly unclear if one confines oneself to the specification and claims of the patent, and the contents of the file unambiguously resolve the point, or (ii) it would be contrary to the public interest for the contents of the file to be ignored**.

87. In my judgment, it is appropriate for the UK courts to adopt a sceptical, but not absolutist, attitude to a suggestion that the contents of the prosecution file of a patent should be referred to when considering a question of interpretation or infringement, along substantially the same lines as the German and Dutch courts. It is tempting to exclude the file on the basis that anyone concerned about, or affected by, a patent should be entitled to rely on its contents without searching other records such as the prosecution file, as a matter of both principle and practicality. However, given that the contents of the file are publicly available (by virtue of article 128 EPC 2000) and (at least according to what we were told) are unlikely to be extensive, there will be occasions when justice may fairly be said to require reference to be made to the contents of the file. However, not least in the light of the wording of article 69 EPC 2000, which is discussed above, the circumstances in which a court can rely on the prosecution history to determine the extent of protection or scope of a patent must be limited.

88. […]. The first type of circumstance is, I hope, self-explanatory; the second would be exemplified by a case where the patentee had made it clear to the EPO that he was not seeking to contend that his patent, if granted, would extend its scope to the sort of variant which he now claims infringes.

Direct infringement by Actavis products

- **Looking at matters more broadly, the addressee of the Patent would, as I see it, understand that the reason why the claims were limited to the disodium salt was because that was the only pemetrexed salt on which the experiments described in the specification had been carried out. However, it does not follow that the patentee did not intend any other pemetrexed salts to infringe: the suggestion confuses the disclosure of the specification of a patent with the scope of protection afforded by its claims.**

Particularly given the facts set out in para 25 above, it seems to me very unlikely that the notional addressee would have concluded that the patentee could have intended to exclude any pemetrexed salts other than pemetrexed disodium, or indeed pemetrexed free acid, from the scope of protection.

75. Accordingly, I would conclude that, subject to considering the prosecution history, the Actavis products infringe claim 1 of the Patent.

- **Turning to the second issue, I do not consider that the contents of the prosecution file in this case justify departing from the provisional conclusion expressed in para 75 above. It seems to me clear that the reason why the examiner considered that the claims in the patent should be limited to pemetrexed disodium was because the teaching in the specification did not expressly extend to any other anti-folates.**

Indirect infringement

- **Accordingly, I would uphold the Court of Appeal's determination that Actavis are liable to Lilly for indirect infringement in the United Kingdom with respect to their products if Actavis know, or it is obvious in the circumstances, that ultimate users will dilute in saline - or at least Actavis would be liable for indirect infringement if they were not liable for direct infringement. The Court of Appeal said that this conclusion would apply equally to France, Italy, and Spain, and there is no challenge to that from Actavis.**

Source: **[2017] UKSC 48**

UK Supreme Court, 12 July 2017
(Lord Neuberger, Lord Mance, Lord Clarke, Lord Sumption, Lord Hodge)
JUDGMENT
Actavis UK Limited and others (Appellants) v Eli Lilly and Company (Respondent)
Eli Lilly and Company (Appellant) v Actavis UK Limited and others (Respondents)
Eli Lilly and Company (Appellant) v Actavis UK Limited and others (Respondents)
before
Lord Neuberger, President
Lord Mance
Lord Clarke
Lord Sumption
Lord Hodge
JUDGMENT GIVEN ON
12 July 2017
Heard on 4, 5 and 6 April 2017
Actavis and others, Daniel Alexander QC, Thomas Raphael QC, Isabel Jamal (Instructed by Bird & Bird LLP)
Eli Lilly and Company, Thomas Mitcheson QC, Andrew Waugh QC, Stuart Baran(Instructed by Hogan Lovells International LLP)

LORD NEUBERGER: (with whom Lord Mance, Lord Clarke, Lord Sumption and Lord Hodge agree)

1. The issue raised on this appeal and cross-appeal is whether three products manufactured by the Actavis group of companies ("Actavis") would infringe a patent whose proprietor is Eli Lilly & Company ("Lilly"), namely European Patent (UK) No 1 313 508 ("the Patent"), and its corresponding designations in France, Italy and Spain.

2. This judgment was circulated in draft to the parties' legal representatives in the normal way on 5 July 2017, on the basis that it would be handed down a week later. On the following day, just after midday, Actavis's solicitors emailed the Court expressing concern about the potential prejudice which their clients could suffer if they did not know of the outcome of this appeal until 12 July. Not least because publication of our decision could have an effect on the share prices of Actavis or Lilly or both of them, the Court proposed to the parties' respective solicitors that we should announce our decision at once, while maintaining the intention, in accordance with this Court's usual practice, to hand down the judgment a week after circulation of the draft. This was agreed by both solicitors, and accordingly on 7 July at 11.30 am, the following announcement appeared on the Court's website:

"The Supreme Court allows Eli Lilly's appeal and holds that Actavis's products directly infringe Eli Lilly's patent in the United Kingdom, France, Italy and Spain. The Court dismisses Actavis's cross-appeal on the basis that if its products did not directly infringe, they would indirectly infringe to the extent held by the Court of Appeal."

Accordingly, these are technically the reasons for those conclusions.

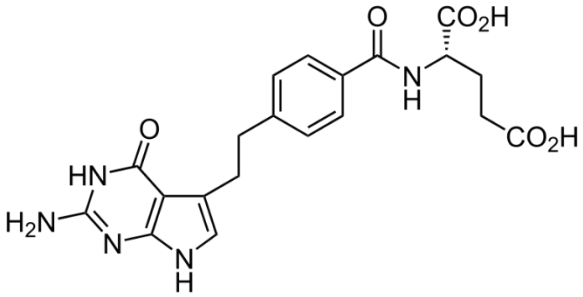
The factual and technical background

The factual background

3. Pemetrexed is a chemical which has been known for some time to have therapeutic effects on cancerous tumours. However, when used for that purpose on its own, pemetrexed can often have seriously damaging, sometimes even fatal, side-effects. Accordingly, its use as an anti-cancer drug was effectively precluded in practice. The essential disclosure of the Patent was that the damaging side-effects could largely be avoided if a compound called pemetrexed disodium was administered together with vitamin B12. This has enabled pemetrexed disodium to be used for treatment in the form of a medicament which includes the vitamin. Such a medicament has been successfully marketed, under the brand name Alimta, by Lilly since 2004.

4. The Patent primarily claims the use of pemetrexed disodium in the manufacture of a medicament for use in combination with vitamin B12 (and, optionally, folic acid) for the treatment of cancer.

5. Pemetrexed itself is a member of a class of chemicals known as antifolates, and its molecular structure is shown below, with C, N, O and H being respectively the chemical symbols for carbon, nitrogen, oxygen and hydrogen; and the unallocated points on the chains and the rings being carbon.



6. The presence of the two -CO2H units results in pemetrexed being an acid (hence it is also known as pemetrexed diacid), or as it is sometimes called, a free acid. When pemetrexed is dissolved in water, the hydrogens in those two units separate from the rest of the molecule as positively charged entities, protons, and the rest of the molecule becomes a negatively charged entity called an anion. The structure of pemetrexed disodium is similar except that, instead of the two -CO2H units, it has two -CO2Na units (Na being the symbol for sodium). Pemetrexed disodium dissolves in water, where the two sodiums separate from the rest of the molecule as positively charged entities called cations, and the rest of the molecule becomes an anion. Because it is the pemetrexed anion which is of interest, the sodium cation is often referred to as a counter-ion. A substance such as pemetrexed disodium, where the acidic hydrogens have been replaced, is known chemically as a salt.

7. Although one might have thought that the actual invention should have been characterised as a disclosure that pemetrexed could be administered safely if it was combined in a medicament with vitamin B12, the claimed invention in the Patent is, as mentioned in para 4 above, the manufacture of such a medicament.

This formulation was required by the then-prevailing law contained in article 52(4) of the European Patent Convention 1973 ("EPC 1973"), which prohibited from patentability any method of treatment of humans or animals. This led to inventions which otherwise might have been expected to be expressed as being new therapeutic treatments being cast as manufacturing claims. Such claims are known as Swiss form claims, and they were illuminatingly discussed by Kitchin J in Ranbaxy (UK) Ltd v Astrazeneca AB [2011] FSR 45, paras 42 to 60. As he explained, the prohibition was substantially modified in article 53 in the European Patent Convention 2000 ("EPC 2000"), but that modification had not come into force when Lilly applied for the Patent.

8. Actavis's proposed products involve pemetrexed compounds being used together with vitamin B12 for cancer treatment. However, rather than pemetrexed disodium, the active ingredient in those products ("the Actavis products") is (a) pemetrexed diacid, (b) pemetrexed ditromethamine, or (c) pemetrexed dipotassium. In other words, rather than including the disodium salt referred to in claim 1 of the Patent, the Actavis products include as the active ingredient (a) pemetrexed itself (ie the free acid), or pemetrexed with the hydrogens on the two -CO2H units replaced by (b) tromethamine, or (c) potassium. Actavis contend that, because they intend to use the Actavis products which do not include pemetrexed disodium, the claims of the Patent, which are expressed as involving the use of pemetrexed disodium, would not be infringed. By contrast, Lilly contends that there would be either direct or indirect infringement of the Patent if Actavis launch any of the Actavis products on the market in the UK or in France, Italy, or Spain. The allegation of direct infringement is based simply on the proposition that marketing or use of the Actavis products would infringe the Patent; indirect infringement is said to arise because pemetrexed disodium is claimed to be involved in the preparation of the Actavis products before they are administered.

9. After a four-day trial, Arnold J decided that none of the Actavis products would directly or indirectly infringe the Patent in the UK or in France, Italy or Spain - [2015] Bus LR 154; [2015] RPC 6. The Court of Appeal allowed Lilly's appeal to the limited extent of holding that there would be indirect infringement in the four jurisdictions, but they agreed with the Judge that there would be no direct infringement - [2015] Bus LR 1068. Lilly appeals against the rejection of its case that there would be direct infringement, and Actavis cross-appeal against the rejection of their case that there would be no indirect infringement.

10. As Floyd LJ explained in the Court of Appeal, the appeal raises the issue of the correct approach under UK law (and the law of the three other states) to the interpretation of patent claims, and in particular the requirement of EPC 2000 to take account of "equivalents", and also the extent to which it is permissible to make use of the prosecution history of a patent when determining its scope. The issue on the cross-appeal is rather more fact-specific, namely whether the application of the law of contributory infringement justifies a finding of indirect infringement in this case.

11. It is appropriate to start by setting out the relevant provisions of the Patent and the knowledge of its assumed addressee, topics on which my account is largely taken from the clear judgment of Floyd LJ in the Court of Appeal. I will then turn to the issue of direct infringement, which involves considering the proper approach to that issue generally, and also the relevance of the prosecution history. I will then consider the position in the three other states and finally I will address the issue of indirect infringement.

The specification and claims in the Patent

12. The Patent is entitled "Combination containing an antifolate and methylmalonic acid lowering agent", and it has a claimed priority date of 30 June 2000.

13. The specification begins at para [0001] by stating that "[p]otentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates". It then explains at para [0002] that antifolates work by inhibiting anti-folate-requiring enzymes by competing with reduced folates for binding sites on those enzymes. The specification identifies several antifolate drugs as being in development, including Lilly's branded product Alimta.

14. The specification then explains at para [0003] that a limitation to the development of these drugs is that they may be associated with substantial toxicity, including mortality, for some patients. These toxicity effects had led to the abandonment of the development of some antifolates. In para [0004] the specification explains that previous work had been done on the use of folic acid as a treatment for toxicity in this area. It also records work on vitamin B12 as a predictor of cytotoxic events.

15. The specification then states in para [0005]: *"Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality and non-hematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent as vitamin B12, without adverse adversely affecting therapeutic efficacy. The present invention thus generally relates to a use in the manufacture of a medicament for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment with a methylmalonic acid lowering agent as vitamin B12."*

16. Para [0006] of the specification continues: *"Additionally, we have discovered that the combination of a methylmalonic acid lowering agent as vitamin B12 and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although, the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin B12 is known, the use of the combination for the treatment of toxicity associated with the*

administration of antifolate drugs was unknown heretofore."

17. These early, general statements are made in relation to antifolates as a class. However, at para [0010] the specification says, in what is known as a consistory clause, that the invention:

"specifically provides the use of the antifolate pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumour growth in mammals wherein said medicament is to be administered in combination with a methylmalonic acid lowering agent selected from vitamin B12 and pharmaceutical derivatives thereof."

18. Having referred specifically to pemetrexed disodium, the specification reverts to generality at para [0016], where it states:

"The current invention concerns the discovery that administration of a methylmalonic acid lowering agent such as vitamin B12 or a pharmaceutical derivative thereof, in combination with an antifolate drug such as pemetrexed disodium reduces the toxicity of the said antifolate drug."

19. Para [0022] contains a definition:

"The terms 'antifolate' and 'antifolate drug' generally refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways ... by competing with reduced folates for binding sites of these enzymes. The 'antifolate' or 'antifolate drug' for use in this invention is Pemetrexed Disodium (ALIMTA®), as manufactured by Eli Lilly & Co."

20. The invention is then illustrated by reference to a number of examples relating to animal and human tests, in which the only antifolate used is pemetrexed disodium. At para [0035] the specification states that animals were treated with "pemetrexed disodium (ALIMTA®) (100 mg/kg or 150 mg/kg) once daily … by intraperitoneal injection alone or along with folic acid". The specification also indicates at para [0044] that, in a typical clinical evaluation using cancer patients, the antifolate is to be administered in four doses over a two-week period by rapid intravenous injection.

21. Turning to the claims, it is only necessary for present purposes to refer to claims 1 and 12, which are in these terms:

"1. Use of pemetrexed disodium in the manufacture of a medicament for use in combination therapy for inhibiting tumour growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof [which it then specifies]."

"12. A product containing pemetrexed disodium, vitamin B12 or a pharmaceutical derivative thereof said pharmaceutical derivative [which it again specifies], and, optionally, a folic binding protein binding agent selected from [a specified group of chemicals including folic acid], as a combined preparation for the simultaneous, separate or sequential use in inhibiting tumour growth."

The notional addressee of the Patent

22. A patent is interpreted on the basis that it is addressed to a person or group of persons who is or are likely to have a practical interest in the claimed invention, ie through the eyes of a person or persons skilled in the art. There is now no challenge to the Judge's conclusion that the notional addressee of the Patent would be a group consisting of an oncologist and a chemist, a conclusion upheld by the Court of Appeal.

23. The Judge found that the common general knowledge of an oncologist as at the relevant time, 2001/2002, included the following:

i) Antifolates were used in cancer chemotherapy, but their use caused toxic side effects which it would be desirable to avoid or reduce.

ii) Pemetrexed was the subject of clinical trials for use in chemotherapy, and it targeted multiple enzymes and was administered intravenously.

iii) The only form of pemetrexed which had been shown to be effective and safe to any extent was pemetrexed disodium, which was manufactured by Lilly under the trade mark Alimta.

iv) The characteristics of both vitamin B12 and folic acid were well understood, and it was well known that there were many different safe and effective forms of both available.

24. The Judge also concluded that oncologists did not think about drugs such as pemetrexed in their ionic form, nor did they consider issues regarding the choice of counter-ion or the effect, if any, of counter-ions on the efficacy, safety or other properties of the drug. This was the province of the chemist and, because the properties of different salt forms and free acids were difficult to predict, a chemist would need to address any such issue by conducting experiments.

25. The Judge made the following findings as to the common general knowledge of a chemist as at 2001/2002:

i) Where a drug is or is based on an acid, different salts of the parent acid can be formed by reacting it with a complementary base or acid. The salt will often have different properties from the parent acid, and different salts will often have different properties from each other. So, salt screening is a routine but important exercise in determining the most suitable form of a drug.

ii) The facts set out in paras 5 and 6 above.

iii) Solid salts consist of the anions and cations regularly arranged in a fixed lattice structure. Because the cations and anions are present in fixed proportions and in fixed relative positions it is possible to speak meaningfully of the salt as being present in solid form.

iv) When a salt is dissolved in water, the ions dissociate, forming free cations and anions in solution. Although the salt ceases to exist, it is common to refer to "a salt solution" or "a salt in solution".

v) The salt form can have a significant impact on the effectiveness of a drug in that it can modify many aspects of the drug.

vi) When considering a drug for intravenous chemotherapy, the solubility of the salt form is crucial, as good solubility is an indicator of how likely it is that the drug will be absorbed in the gut.

vii) But if a salt is too soluble, it cannot be made in solid form.
viii) In general, there can be many dead-ends and false leads when attempting to prepare salts of a parent molecule for the first time.
ix) One cannot predict (a) whether one could make a particular salt form of a parent molecule, (b) what its properties would be once it was made or (c) whether it would affect the efficacy of the drug.

26. The Judge made specific findings about a chemist's state of knowledge about three types of salts and about free acids:

i) Sodium was generally the preferred counter-ion, and so would be first choice. Sodium salts generally were not toxic, and would be expected to be reasonably soluble, but they were not always easy to make.
ii) Potassium salts were also generally soluble, but there were exceptions. There were concerns about the potential toxicity of such salts, which was particularly significant if large quantities of the drug were involved.
iii) There were only a small handful of examples of tromethamine salts being used in 2001. It was known that tromethamine salts might well be too soluble, so one would not be able to make and harvest the solid form.
iv) In principle, the acidic parent molecule could be administered in the form of the free acid. But it was often necessary to change from the free acid to a salt form for various reasons including solubility.

Direct infringement

27. In a nutshell, the rival contentions are these. Lilly argues that the Actavis products infringe the Patent because they are medicaments to be used as a treatment for cancer consisting of pemetrexed diacid, or a pemetrexed salt, with vitamin B12, which represents the essence of the teaching and claim of the Patent. By contrast, Actavis argues that their products do not infringe because the claims of the Patent are limited to a specific pemetrexed salt, namely pemetrexed disodium, and the Actavis products contain either pemetrexed diacid or different pemetrexed salts.

The legislative context

28. The domestic provision governing direct patent infringement is section 60(1) of the Patents Act 1977. However, section 130(7) declares that certain provisions of that Act, including section 60, are "so framed as to have, as nearly as practicable, the same effects in the United Kingdom as the corresponding provisions of the European Patent Convention … have in the territories to which [that Convention applies]". Accordingly, it is common ground that it is appropriate to consider the present case by reference to the EPC 2000.

29. Article 69(1) EPC 2000 provides that "[t]he extent of the protection conferred by a European patent … shall be determined by the claims", although it is followed by another sentence, namely "[n]evertheless, the description and drawings shall be used to interpret the claims".

30. As a matter of ordinary language, it is quite clear that the only type of pemetrexed compound to which the Patent's claims expressly extend is pemetrexed disodium. One only needs to read claim 1 and claim 12 to justify that: as a matter of ordinary language, "pemetrexed disodium" means that particular salt, and no other salt, let alone the free acid. If the first few words of each claim were not enough to make this good, the contrast between the specific reference to pemetrexed disodium and the wider reference to "vitamin B12 or a pharmaceutical derivative thereof" underlines the point. As Floyd LJ said, this conclusion is also supported by what is said in the specification - eg in paras [0010] and [0022] quoted above. It is fair to say that para [0016] could be said to point the other way, but it is far too weak a basis for even arguing that the Patent's claims extend, as a matter of language, to pemetrexed compounds other than pemetrexed sodium.

31. In these circumstances, The Protocol on the Interpretation of article 69 as amended in 2000 ("the Protocol") is crucial to Lilly's contention that the scope of protection afforded by the Patent extends to the Actavis products. The Protocol provides:

"Article 1
General principles
Article 69 should not be interpreted as meaning that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, 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. Nor should it be taken to mean that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patent proprietor has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patent proprietor with a reasonable degree of legal certainty for third parties.
Article 2
Equivalents
For the purpose of determining the extent of protection conferred by a European patent, due account shall be taken of any element which is equivalent to an element specified in the claims."

The original Protocol was agreed in 1973; the amendments made in 2000 effected very slight modifications to what is now article 1, and introduced article 2 for the first time.

32. The drafting of the Protocol bears all the hallmarks of the product of a compromise agreement. This is unsurprising. There is an inevitable conflict between the desirability of giving an inventor an appropriate degree of protection in a particular case and the need for clarity of principle as to the extent of such protection generally; and, of course, there is an unavoidable tension between the appropriateness of giving an inventor a monopoly and the public interest in maximising competition. In addition, the EPC 2000 and the Protocol apply in many different states which have different traditions and approaches in relation to the law of patents. In that connection, as the Supreme Court observed in Schütz (UK) Ltd v Werit (UK) Ltd (Nos 1

to 3) [2013] Bus LR 565; [2013] RPC 16, para 40, "complete consistency of approach" between different national courts of the EPC states "is not a feasible or realistic possibility at the moment", but nonetheless "it is sensible for national courts at least to learn from each other and to seek to move towards, rather than away from, each other's approaches".

33. More specifically, two points appear to be clear from the Protocol. The first, which can be deduced from article 1, is that the scope of protection afforded to a patentee is not to be limited by the literal meaning of the claims. However, it is not at all clear how far a court is permitted to move away from the literal meaning. I do not consider that the last part of the first sentence of article 1 only enables the description (ie the specification) and the drawings to be taken into account when interpreting the claims, in cases where the claims would otherwise be ambiguous. Any doubt about this must be put to rest by the second and third sentences, which make it clear to my mind that that would be too narrow a reading. However, it is very hard to be confident how far they were intended to permit a court to go beyond the actual language of a claim when interpreting a claim. Secondly, it is apparent from article 2 that there is at least potentially a difference between interpreting a claim and the extent of the protection afforded by a claim, and, when considering the extent of such protection, equivalents must be taken into account, but no guidance is given as to precisely what constitutes an equivalent or how equivalents are to be taken into account.

34. The question of how far one can go outside the wording of a claim to enable the patentee to enjoy protection against products or processes which are not within the ambit of the actual language, construed in accordance with ordinary principles of interpretation, has been considered in three significant UK cases and in a number of significant cases decided in the courts of other Convention states.

The domestic case law

35. The UK case of Catnic Components Ltd v Hill & Smith Ltd [1982] RPC 183 was decided under the previous, purely domestic, legislation, the Patents Act 1949. At pp 242 to 243, Lord Diplock deprecated the notion that there were two types of infringement, "textual infringement" and "infringement of the 'pith and marrow' of the invention", and said that there was "a single cause of action", which involved asking the question:

"whether persons with practical knowledge and experience of the kind of work in which the invention was intended to be used, would understand that strict compliance with a particular descriptive word or phrase appearing in a claim was intended by the patentee to be an essential requirement of the invention so that any variant would fall outside the monopoly claimed, even though it could have no material effect upon the way the invention worked."

He continued:

"The question, of course, does not arise where the variant would in fact have a material effect upon the way the invention worked. Nor does it arise unless at the date of publication of the specification it would be obvious to the informed reader that this was so. Where it is not obvious, in the light of then-existing knowledge, the reader is entitled to assume that the patentee thought at the time of the specification that he had good reason for limiting his monopoly so strictly and had intended to do so, even though subsequent work by him or others in the field of the invention might show the limitation to have been unnecessary. It is to be answered in the negative only when it would be apparent to any reader skilled in the art that a particular descriptive word or phrase used in a claim cannot have been intended by a patentee, who was also skilled in the art, to exclude minor variants which, to the knowledge of both him and the readers to whom the patent was addressed, could have no material effect upon the way in which the invention worked."

36. In that case, the patent was for a novel type of galvanised steel lintel, which the relevant claim described as including a rear support back plate "extending vertically" from a horizontal plate. The allegedly infringing article included a rear support member which was inclined between 6 degrees and 8 degrees from the vertical. Overruling the Court of Appeal's decision that this meant that there was no infringement, Lord Diplock said at p 244, that it would have been:

"obvious to a builder familiar with ordinary building operations that the description of a lintel in the form of a weight-bearing box girder of which the back plate was referred to as 'extending vertically' from one of the two horizontal plates to join the other, could not have been intended to exclude lintels in which the back plate although not positioned at precisely 90 degree to both horizontal plates was close enough to 90 degree to make no material difference to the way the lintel worked when used in building operations."

He then added this:

"No plausible reason has been advanced why any rational patentee should want to place so narrow a limitation on his invention. On the contrary, to do so would render his monopoly for practical purposes worthless, since any imitator could avoid it and take all the benefit of the invention by the simple expedient of positioning the back plate a degree or two from the exact vertical."

37. A few years later, Hoffmann J (as he then was) gave judgment in Improver Corpn v Remington Consumer Products Ltd [1990] FSR 181. The case concerned a patent for a depilator, known as the "Epilady", which worked by trapping hairs in a rotating "coiled helical spring", and the alleged infringement worked in very much the same way save that, instead of a spring, it used a slotted rubber rod. The case had already gone on an interlocutory issue to the Court of Appeal, where it was held that Lord Diplock's approach in Catnic [1982] RPC 183 was consistent with the 1977 Act, the EPC 1973 and the Protocol as it then was - see [1989] RPC 69.

38. At [1990] FSR 181, 189, Hoffmann J suggested the following approach, largely based on his reading of the reasoning in Catnic [1982] RPC 183, 242 to 243:

"If the issue was whether a feature embodied in an alleged infringement which fell outside the primary, literal or a contextual meaning of a descriptive word or phrase in the claim ('a variant') was nevertheless within its language as properly interpreted, the court should ask itself the following three questions:

(1) Does the variant have a material effect upon the way the invention works? If yes, the variant is outside the claim. If no -

(2) Would this (ie that the variant had no material effect) have been obvious at the date of publication of the patent to a reader skilled in the art? If no, the variant is outside the claim. If yes -

(3) Would the reader skilled in the art nevertheless have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention? If yes, the variant is outside the claim.

On the other hand, a negative answer to the last question would lead to the conclusion that the patentee was intending the word or phrase to have not a literal, but a figurative meaning (the figure being a form of synecdoche or metonymy) denoting a class of things which included the variant and the literal meaning, the latter being perhaps the most perfect, best-known or striking example of the class."

39. Hoffmann J then proceeded to apply those three questions to the facts of the case before him. He held that the first two questions were to be answered in the patentee's favour and then turned to the third question. On that question, he held that the patentee failed for the reasons he gave at p 197, namely that "[t]he rubber rod is not an approximation to a helical spring", that "the spring [cannot] be regarded as an 'inessential' or the change from metal spring to rubber rod as a minor variant", and that it could be appreciated that the patentee would wish to restrict his claim to helical springs as "[i]t would be obvious that the rubber had problems of hysteresis which might be very difficult to overcome".

40. Thereafter, for the next 15 years or so, this three-stage approach was almost routinely applied by judges in UK patent infringement cases, where the three "Improver questions" were subsequently renamed the three "Protocol questions" - see Wheatley v Drillsafe Ltd [2001] RPC 7, para 23.

41. Lord Hoffmann (as he had by then become) addressed the issue again in his speech in Kirin-Amgen Inc v Hoechst Marion Roussel Ltd [2005] RPC 9, where one of the issues was whether a protein manufactured by gene-activation infringed a patent relating to production of the same protein by recombinant DNA technology. At paras 27 to 35, Lord Hoffmann discussed "the English rules of construction". At paras 30 to 32 he effectively equated Lord Diplock's approach to patents in Catnic [1982] RPC 183, 243 with "purposive construction" of commercial contracts. At para 34, he said that "[t]he question is always what the person skilled in the art would have understood the patentee to be using the language of the claim to mean. And for this purpose, the language he has chosen is usually of critical importance".

42. Lord Hoffmann then turned to the doctrine of equivalents, which he explained in para 37 had been developed in the United States courts and "allow[ed] the patentee to extend his monopoly beyond his claims", so as to prevent "the unscrupulous copyist [from making] unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim, and hence outside the reach of law", quoting Jackson J in Graver Tank & Manufacturing Co Inc v Linde Air Products Co 339 US 605, 607 (1950). Lord Hoffmann expressed concern that "once the monopoly had been allowed to escape from the terms of the claims, it is not easy to know where its limits should be drawn", and concluded that, rather than adhering to literalism and adopting the doctrine, the solution was "to adopt a principle of construction which actually gave effect to what the person skilled in the art would have understood the patentee to be claiming", as Lord Diplock had done in Catnic [1982] RPC 183. He also said that article 69 EPC 2000 "firmly shuts the door on any doctrine which extends protection outside the claims" (see at paras 39 and 42 to 44).

43. Having considered the issue in the three preceding paragraphs of his speech, at para 48 Lord Hoffmann stated that the approach adopted by Lord Diplock was "precisely in accordance with the Protocol", as it was "intended to give the patentee the full extent, but no more than the full extent, of the monopoly which a reasonable person skilled in the art, reading the claims in context, would think he was intending to claim". He concluded his discussion by quoting with approval the passages quoted above from Catnic [1983] RPC 183, 243 and Improver [1990] FSR 181, 189, and saying in para 52 that the principle of purposive construction as Lord Diplock and he had explained it, gave "effect to the requirements of the Protocol" and was "the bedrock of patent construction, universally applicable", whereas the Protocol or Improver questions were simply "guidelines for applying that principle to equivalents … , more useful in some cases than in others".

The approach in the courts of other EPC states

44. In Germany, the Bundesgerichtshof has stated that a variant will infringe if (i) "it solves the problem underlying the invention with modified but objectively equivalent means", (ii) this would be recognised by the person skilled in the relevant art, and (iii) that person "focus[sing] on the essential meaning of the technical teaching protected in the patent" would regard the variant "as being equivalent to the solution" offered by the invention - see Case No X ZR 168/00, 2002 GRUR 519 (Schneidmesser I), para 30. (It is worth noting that in paras 36 to 38 of its judgment in that case, the Bundesgerichtshof expressly considered the approach which had been adopted in Catnic [1982] RPC 183 and

Improver [1990] FSR 181.) Judge Meier-Beck of the Bundesgerichtshof, writing extra-judicially (The Scope of Patent Protection - The Test for Determining Equivalence (2005) 36 IIC 339, 342 to 343) has suggested that the second step involves asking whether "the person skilled in the art, using his specialist knowledge, [would be] able to find the modified means at the priority date as having the same effect", which he then says has the "meaning that no inventive step is needed". That seems to be supported by what was said by the Bundesgerichtshof in Case No X ZR 156/97, 1999 GRUR 977, (Räumschild), paras II.2(c)(aa) and III.1.

45. Further guidance as to the German approach to equivalents was very recently given by the Munich Oberlandesgericht, upholding the decision of the Landgericht, in Case No 6 U 3039/16 (Eli Lilly & Co v ratiopharm GmbH), when considering whether pemetrexed ditromethamine infringed the German equivalent of the Patent in this case. At para II.B.3(a), the Oberlandesgericht said that in order for "an embodiment that deviates from the literal meaning of the claim" to be within the scope of protection, "generally three requirements must be met". The first was that "the embodiment must solve the problem underlying the invention with means that are indeed modified, but are objectively equivalent". The second requirement was that "the expertise of the person skilled in the art must enable him to discover the modified embodiment with its divergent means to be equivalent". Thirdly, "the thought processes that the person skilled in the art has to perform in order to do so must be oriented on the meaning of the teaching protected in the claim". In para II.B.3(b)(aa), the Oberlandesgericht suggested that "the decisive factor" was "what individual effects the features according to the patent … provide in order to attain the object underlying the claims and whether these effects are achieved through other means by the [allegedly infringing] embodiment". The court added that the doctrine of equivalence would apply to an embodiment "if it not only essentially achieves the entire effect of the invention, but specifically also achieves the effect that the feature, which has not been literally implemented, is supposed to achieve".

46. French law, according to the expert witnesses in this case, applies the doctrine of equivalents where the variant is "different in form but perform[s] the same function" as the invention, but only where "the function [claimed in the patent] is a new one". This seems to be supported by Azéma and Galloux, Droit de la propriété industrielle, 7th ed (2012), which distinguishes at p 442 between two categories of patents. The first category is those which "in general terms claim the means that provide for a particular function" (moyens généraux), or as Arnold J put it in para 160 of his judgment, claims which cover "general means". The second category is patents "which indicate the particular means which infer such function" (moyens particuliers), or claims which are "narrowly worded to cover specific means" as Arnold J expressed it. The doctrine is only normally applicable to the first category of claims. Arnold J added in para 160 that the categorisation of a patent for this purpose may depend in part on what was known at the priority date - see the decisions of the Cour de Cassation in Appeal S 09-15668 Institut Pasteur v Chiron Healthcare, 23 November 2010 and of the Paris Tribunal de Grande Instance in Case 09/01863 Mundipharma Laboratories GmbH v Sandoz SAS, 2 July 2010.

47. As Arnold J also explained in para 159 of his judgment, "there is no need for the claim to be unclear or for it to be widely worded" for the doctrine of equivalents to be invoked in the French court. Thus, in the decision of the Cour de Cassation in Appeal No 06-17915 B2M Industries v Acome, 20 November 2007, "the function of the particular integer that was said to be infringed pursuant to an equivalent was held to be novel, and therefore because the means that was said to be equivalent to that integer performed the same function and produced the result sought by the invention the means was equivalent to that integer", to quote from para 161 of Arnold J's judgment.

48. In the Italian courts, the expert witnesses in this case agreed that a variant would be held to infringe if (i) it reproduced the "inventive core" of the patent and (ii) it was an obvious variation, although (iii) the fact that the variant included some modifications which were not obvious and/or the fact that the variant does not include some of the elements of the patent claim does not necessarily prevent the variant infringing - see per Arnold J at para 171 of his judgment. This analysis is supported by the Corte di Cassazione decisions in Case No 257, Forel SpA v Lisec (13 January 2004), Case No 30234, Barilla GER Fratelli SpA v Pastifico Fazion SpA (30 December 2012) and Case No 622, Entsorga Italia Srl v Ecodeco Srl (11 January 2013).

49. At any rate at local appellate level, Spanish courts appear to have effectively adopted the approach embodied in the three questions suggested by Hoffmann J in Improver [1990] FSR 181 - see for instance Laboratorios Cinfa SA v Eli Lilly & Co Ltd ("Olanzapine") Court of Appeal of Barcelona judgment no 8/2008, 17 January 2008.

50. Following circulation of this judgment in draft, Actavis referred us to a decision of the Spanish Tribunal Supremo Lundbeck v Cinfa, no 223/2015, 29 April 2015. In the closely reasoned section ELEVEN of its judgment, the Tribunal Supremo (i) recorded the fact that none of the parties challenged the approach of the Court below which applied the three Improver questions (para 5), (ii) stated that the real issue in the case centred on the second question (para 6), (iii) cast some doubt on the applicability of the Improver questions in Spanish law (para 10), (iv) disapproved the notion that the test for obviousness in patentability is necessarily applicable to the second Improver question (paras 10 and 14), (v) disapproved the notion that, for the second Improver question to be answered yes, "the skilled person must be absolutely certain that the variant … would work successfully in resolving the technical problem faced by the patented invention" (paras 11 and 12), (vi) preferred instead, a test of "easy to see or comprehend" and "a degree of predictability" (paras 11 and 18), which involves "a high probability", rather than a "reasonable

expectation" that the variant would work (paras 15 and 18), and (vii) concluded on this basis that the Court of Appeal was right to rule that the allegedly infringing products in that case did not infringe (paras 18 and 19).

51. As for the Netherlands, helpful guidance may be found in a lecture given in 2016 by Judge Kalden, the head of the IP division in the Court of Appeal in The Hague - Article 69 EPC - the Scylla and Charybdis of the European Patent Convention - Which route did the Dutch courts take? (2016 Symposium German Bundespatentgericht). She said that, although there have been subtle changes of emphasis in its decisions, the Supreme Court tends to focus on "the inventive concept in order to prevent a too literal interpretation of the claims, which could do injustice to fair protection for the patentee (or lead to an unnecessary broad interpretation)". She also explained that the doctrine of equivalents applies if (i) the variant is "foreseeable at the priority date", (ii) "the inventive concept is sufficiently broad to … cover [the] variant", (iii) "the variant makes use of - and thus benefits from - the inventive concept", and (iv) "reasonable legal certainty [is not thereby] unduly compromised". She added that, despite the first condition:

"Variants that are not foreseeable at the priority date may well, due to later developments, become an obvious variant at a later date. This may happen in case of a pioneer invention, where at the priority date the full breadth of the possible applications could or has not been fully recognised and therefore was not sufficiently taken into account when drafting a claim. Another possibility is that a new technique becomes available after the patent was granted, which makes available an obvious variant. It would be harsh and contrary to fair protection for the patentee to deny him the right to attack those, again provided such variant falls within the inventive concept and reasonable legal certainty is taken into account. So infringement by equivalence is not limited to foreseeable variants only."

52. It may be of some significance that the product which Hoffmann J concluded in Improver [1990] FSR 181 was non-infringing was held by the German, Italian and Dutch courts to infringe. Of course, the fact that courts of two states reach different conclusions on the same issue does not of itself mean that there is a difference in the law of those states, let alone that one court is wrong and the other right: the evidence may be different, and there may be issues of judgment on which reasonable judges could differ. However, consideration of the judgments in those three other courts does suggest a difference of approach. Thus, in Germany, the Düsseldorf Oberlandesgericht based its conclusion on the propositions that "a person skilled in the art will not interpret the coil spring as a spring, but as an elastic body with gaps ... as it is obvious that the helical spring is not used as a spring per se", and that its only essential function, which was shared by the allegedly infringing product's slitted rubber rod, was that it could "enter between adjacent areas of the body (walls), and that the walls must approach it up to clamping it" - see Epilady Germany II (1993) 24 IIC 838. In Italy, the Milan District Court held that there was infringement because the slitted rubber rod had structural characteristics which enabled it to perform the same function in the same way as the coiled spring referred to in the patent in suit - see Epilady Italy (1992) Giur Ann Dir Ind, Case No 2823. In the Netherlands, the Gerechtshof upheld the first instance decision that the allegedly infringing "device embodies an application of the patented invention, on the grounds that the hair-engaging component [ie the slitted rubber rod] of the device is a mechanical equivalent of the helical spring specified in the patent claims", and the rod was "not state of the art in the field of depilatory devices" - Epilady Netherlands III (1993) 24 IIC 832, paras 9 and 11.

The proper approach to infringement claims

53. Any patent system must strike a balance between the two competing factors referred to at the end of article 1 of the Protocol, namely "a fair protection for the patent proprietor [and] a reasonable degree of legal certainty for third parties". The balance cannot be struck on an ad hoc case-by-case basis without any guiding principles, as that would mean that there was no legal certainty. On the other hand, striking the balance by adopting a normal approach to interpretation would risk depriving patentees of a proper measure of protection; as explained in paras 37 to 39 and 52 above, that is clear from the approach of all the courts which considered the "Epilady" patent, where it could not seriously have been suggested that, as a matter of language, a slotted rubber rod falls within the expression "helical metal spring", even if one was construing those words in the context of the claim in the patent in suit. But, if one departs from ordinary language, it is necessary to have some guidance or to draw some lines, as Lord Hoffmann implied in Kirin-Amgen [2005] RPC 9, para 37. That is why he promulgated his three questions in Improver [1990] FSR 181, 189. By means of an extended version of the ordinary concept of "construction" or "interpretation", Hoffmann J explained how our domestic law, as laid down in Catnic [1982] RPC 183, implements article 2 of the Protocol and thus, as I see it, how it gives effect to the doctrine of equivalents. That approach was (perhaps unsurprisingly) then adopted in Kirin-Amgen [2005] RPC 9.

54. In my view, notwithstanding what Lord Diplock said in Catnic [1982] RPC 183, 242, a problem of infringement is best approached by addressing two issues, each of which is to be considered through the eyes of the notional addressee of the patent in suit, ie the person skilled in the relevant art. Those issues are: (i) does the variant infringe any of the claims as a matter of normal interpretation; and, if not, (ii) does the variant nonetheless infringe because it varies from the invention in a way or ways which is or are immaterial? If the answer to either issue is "yes", there is an infringement; otherwise, there is not. Such an approach complies with article 2 of the Protocol, as issue (ii) squarely raises the principle of equivalents, but limits its ambit to those variants which contain immaterial variations from the invention. It is also apparent that the two issues comply with article 1 of the Protocol in that they involve

balancing the competing interests of the patentee and of clarity, just as much as they seek to balance the encouragement of inventions and their disclosure with the need for a competitive market. In my view, issue (i) self-evidently raises a question of interpretation, whereas issue (ii) raises a question which would normally have to be answered by reference to the facts and expert evidence.

55. In Kirin-Amgen [2005] RPC 9, Lord Hoffmann, following his approach in Improver [1990] FSR 181 (which itself had followed Lord Diplock's analysis in Catnic [1982] RPC 183) effectively conflated the two issues, and indicated that the conflated issue involved a question of interpretation. I have considerable difficulties with the notion that there is a single conflated, or compound, issue, and, even if that notion is correct, that that issue raises a question of interpretation. Indeed, in my view, to characterise the issue as a single question of interpretation is wrong in principle, and unsurprisingly, therefore, can lead to error. While normal principles of interpretation could, I think, accommodate the notion that "vertically" extended to an item which was not at precisely 90° to another item, I do not see how such principles could possibly lead to the conclusion that a slotted rubber rod was within the expression "helical metal spring". As Hoffmann J said in Improver [1990] FSR 181, 197, "the angle of the support member [in the allegedly infringing product in Catnic [1982] RPC 183] can be regarded as an approximation to the vertical", but "[t]he rubber rod is not an approximation to a helical spring". The problem with treating the issue as one of normal interpretation is thus that that point alone may be thought to have been sufficient to put an end to the patentee's infringement argument on facts such as those in Improver [1990] FSR 181, and there would seem to have been little purpose in going through the three questions in that case.

56. I had wondered whether the question whether issue (ii) truly involves a question of interpretation raised what was merely an arid issue of categorisation. However, I have concluded that that nettle needs to be grasped, because, so long as the issue is treated as one of interpretation, it will lead to a risk of wrong results in patent infringement cases and it will also lead to a risk of confusing the law relating to the interpretation of documents. In my opinion, issue (ii) involves not merely identifying what the words of a claim would mean in their context to the notional addressee, but also considering the extent if any to which the scope of protection afforded by the claim should extend beyond that meaning. As Sir Hugh Laddie wrote in his instructive article Kirin-Amgen - The End of Equivalents in England? (2009) 40 IIC 3, para 68, "[t]he Protocol is not concerned with the rules of construction of claims" but with "determining the scope of protection".

57. I might add that the notion of a product or process which infringes despite an immaterial variation from the invention as claimed is by no means new to domestic patent law. That point is convincingly demonstrated by Sir Hugh in his article at paras 33 to 39. Thus, in Walton v Potter & Horsfall (1843) 1 WPC 585, Tindal CJ told the jury that they had to decide whether the defendant's product was "perfectly distinct" from the patented product, or whether it varied "only in certain circumstances, which are not material to the principle and substance of the invention". And Lord Cairns LC in Clark v Adie (1877) 2 App Cas 315, 320, referred to the alleged infringer having "really taken and adopted the substance of the instrument patented", and having "taken in substance the pith and marrow of the invention". The patents in these cases included relatively primitive forms of claim, but that does not undermine the fact that our domestic law has long recognised that an immaterial variation does not get an infringer off the hook. Particularly in the light of what he said in Catnic [1983] RPC 183, 242, it is worth mentioning that Lord Diplock himself in Beecham Group Ltd v Bristol Laboratories Ltd [1978] RPC 153, 200 rejected a submission that "[t]he increasing particularity with which claims are drafted … has made the doctrine [of pith and marrow] obsolete", and said that the doctrine "still remains a part of patent law".

58. Turning to the two issues identified in para 54 above, issue (i), as already mentioned, involves solving a problem of interpretation, which is familiar to all lawyers concerned with construing documents. While the answer in a particular case is by no means always easy to work out, the applicable principles are tolerably clear, and were recently affirmed by Lord Hodge in Wood v Capita Insurance Services Ltd [2017] 2 WLR 1095, paras 8 to 15. In the present case, there is no doubt that, according to normal principles of interpreting documents, the Actavis products do not infringe the Patent, as in no sensible way can pemetrexed free acid, pemetrexed ditromethamine, or pemetrexed dipotassium mean, ie be said to fall within the expression, "pemetrexed disodium" in claim 1 of the Patent, any more than a slotted rubber rod can be said to be within the expression "a helical metal spring" in the claim in the Improver patent. According to normal principles of interpreting documents, then, this would be the end of the matter.

59. However, the second issue poses more difficulties of principle: what is it that makes a variation "immaterial"? In that connection, I consider that Hoffmann J's three questions in Improver [1990] FSR 181 provide helpful assistance, a view supported by the fact explained in paras 44 to 52 above that similar but not identical tests have been adopted in other EPC jurisdictions. However, each of the three questions requires some exegesis, and, particularly the second question, some reformulation.

60. The first Improver question, which asks whether the variant has a material effect on the way in which the invention works, seems generally satisfactory. It is a question which was framed in the context of a mechanical patent, and is not wholly aptly expressed for every type of case. However, in practice, the question as framed by Hoffmann J, with its emphasis on how "the invention" works, should correctly involve the court focussing on the "the problem underlying the invention",

"the inventive core", or "the inventive concept" as it has been variously termed in other jurisdictions. In effect, the question is whether the variant achieves the same result in substantially the same way as the invention. If the answer to that question is no, then it would plainly be inappropriate to conclude that it could infringe. If, by contrast, the answer is yes, then it provides a sound initial basis for concluding that the variant may infringe, but the answer should not be the end of the matter.

61. The second Improver question is more problematic. In my view, it imposes too high a burden on the patentee to ask whether it would have been obvious to the notional addressee that the variant would have no material effect on the way in which the invention works, given that it requires the addressee to figure out for himself whether the variant would work. The facts of the present case serve to make that proposition good. As Floyd LJ explained in para 65 of his judgment below, because a chemist "would not be able to predict the effect of [a] substitution [for the sodium counter-ion] without testing at least the solubility of the [active ingredient in the Actavis products]", it followed that "predicting in advance whether any particular counter-ion would work was not possible", and therefore that the second Improver test could not be answered yes. However, as mentioned in para 25(i) above, salt screening is a routine exercise in determining suitability, and as Floyd LJ said, "the chemist would be reasonably confident that he would come up with a substitute for the sodium counter-ion". In those circumstances, given that the inventive concept of the patent is the manufacture of a medicament which enables the pemetrexed anion to be administered with vitamin B12, it appears to me that application of the second Improver question fails to accord "a fair protection for the patent proprietor" as required by article 1 of the Protocol.

62. In my opinion, the second question is better expressed as asking whether, on being told what the variant does, the notional addressee would consider it obvious that it achieved substantially the same result in substantially the same way as the invention. In other words, it seems to me that the second Improver question should be asked on the assumption that the notional addressee knows that the variant works to the extent that it actually does work. That, I think, would be a fair basis on which to proceed in terms of balancing the factors identified in article 1 of the Protocol, and it is, I think, consistent with the approach of the German, Italian and Dutch courts. It is also consistent with the fact that the notional addressee is told (in the patent itself) what the invention does.

63. This reformulated second question should also apply to variants which rely on, or are based on, developments which have occurred since the priority date, even though the notional addressee is treated as considering the second question as at the priority date. Such an approach is supported by the desirability of both consistency of approach and pragmatic justice. It seems right in principle to have the same question, including the same assumption (ie that the variant works) for all cases. As to pragmatism, the point is touched on by Judge Kalden in the passage quoted at the end of para 51 above: while the notional addressee may answer the reformulated second question affirmatively even where the variant was unforeseeable at the priority date, he is less likely to do so than in relation to a variant which was unforeseeable as at that date.

64. The second test applied by the German courts, as I understand it, at least sometimes appears to require the variation not to be inventive, but I am not sure that that is an appropriate requirement, although it is unnecessary to decide that point on this appeal. If the variation represents an inventive step, while it may render it less likely that the patentee will succeed on the second reformulated question, I find it hard to see why that alone should prevent the resultant variant from infringing the original invention. It may entitle the infringer to a new patent, in the same way as the invention of a novel use for a patented invention can itself be patented, but like such a novel use I see no reason why the variant should not infringe the original patent. Having said that, it should be added that the German version of the second test will, I suspect, usually produce the same result as the reformulated second question.

65. The third Improver question as expressed by Hoffmann J is whether the notional addressee would have understood from the language of the claim that the patentee intended that strict compliance with the primary meaning was an essential requirement of the invention. That is in my view an acceptable test, provided that it is properly applied. In that connection, I would make four points. First, although "the language of the claim" is important, consideration of the third question certainly does not exclude the specification of the patent and all the knowledge and expertise which the notional addressee is assumed to have. Secondly, the fact that the language of the claim does not on any sensible reading cover the variant is certainly not enough to justify holding that the patentee does not satisfy the third question. Hence, the fact that the rubber rod in Improver [1990] FSR 181 could not possibly be said to be "an approximation to a helical spring" (to quote from p 197) was not the end of the infringement issue even in Hoffmann J's view: indeed, as I have already pointed out, it was because the rubber rod could not possibly be said to be a helical spring that the allegedly infringing product was a variant and the patentee needed to invoke the three Improver questions. Thirdly, when considering the third question, it is appropriate to ask whether the component at issue is an "essential" part of the invention, but that is not the same thing as asking if it is an "essential" part of the overall product or process of which the inventive concept is part. So, in Improver [1990] FSR 181, 197, Hoffmann J may have been (and I mean "may have been") wrong to reject the notion that "the spring could be regarded as an 'inessential'": while it was undoubtedly essential to the functioning of the "Epilady", the correct question was whether the spring would have been regarded by the addressee as essential to the inventive concept, or inventive core, of the patent

in suit. Fourthly, when one is considering a variant which would have been obvious at the date of infringement rather than at the priority date, it is, as explained in para 63 above, necessary to imbue the notional addressee with rather more information than he might have had at the priority date.

66. In these circumstances, given the weight that has been given by courts in this jurisdiction (and indeed in some other jurisdictions) to the three "Improver questions", I think it must be right for this court to express in our own words our reformulated version of those questions. In doing so, it is right to emphasise, as Lord Hoffmann did in Kirin-Amgen [2005] RPC 9, para 52, that these questions are guidelines, not strict rules (as indeed the Oberlandesgericht indicated in Case No 6 U 3039/16, when saying that it was "generally" true that "three requirements must be met"). While the language of some or all of the questions may sometimes have to be adapted to apply more aptly to the specific facts of a particular case, the three reformulated questions are as follows:

i) Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, ie the inventive concept revealed by the patent?

ii) Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?

iii) Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?

In order to establish infringement in a case where there is no literal infringement, a patentee would have to establish that the answer to the first two questions was "yes" and that the answer to the third question was "no".

Provisional conclusion on direct infringement in the UK

67. Given that the Actavis products do not infringe on the basis of a normal interpretation of claim 1 of the Patent, it is necessary to consider whether they represent an immaterial variation on that claim. I propose to address that issue initially disregarding the prosecution history, and having reached a provisional conclusion, I will then address that history and its effect on the provisional conclusion.

68. In my view, application in the present case of the three questions just identified results in the conclusion that the Actavis products infringe. So far as the first question is concerned, there can be no doubt but that those products work in the same way as the invention: they all ultimately involve a medicament containing the pemetrexed anion and vitamin B12. Thus, they achieve substantially the same result in substantially the same way as the invention. Indeed, as in the Court of Appeal, Actavis realistically accept that the first question is to be answered yes.

69. As to the second question, it seems to me clear that the notional addressee of the Patent would appreciate (and would have appreciated as at the priority date) that each of the Actavis products would work in precisely the same way as pemetrexed disodium when included in a medicament with vitamin B12. When it comes to different versions of pemetrexed medicaments, it is clear that the use of a free acid, and of ditromethamine and dipotassium salts was in each case well established as at the priority date - see para 26(ii) to (iv) above. Furthermore, the notional addressee of the Patent would regard investigating whether pemetrexed free acid, pemetrexed ditromethamine or pemetrexed dipotassium worked as a purely routine exercise - see para 25(i) above. The reason why I differ from the Court of Appeal and Arnold J on this second question is that, in accordance with the second question as formulated in Improver [1990] FSR 181, 189, they considered that the notional addressee should not be treated as knowing that the Actavis products did in fact work at all, whereas, as explained above, that seems to me to involve too strict a test.

70. Turning to the third question, the Court of Appeal considered that the notional addressee "would understand that the patent was clearly limited to the disodium salt, and did not extend to the diacid, or the dipotassium or ditromethamine salts". They based this conclusion on the fact that the specification of the Patent contains a number of passages (eg in Para [0022] of the specification, quoted in para 19 above) which refer to "anti-folates" and the like and other passages which refer to pemetrexed disodium, which is "a highly specific chemical compound", and the fact that the claim is limited to pemetrexed disodium would therefore lead the notional addressee to conclude that the claim is indeed intended to be so limited (see paras 71 and 72 of Floyd LJ's judgment).

71. In my opinion, the Court of Appeal adopted an approach which places too much weight on the words of the claim and not enough weight on article 2 of the Protocol (and it is only right to add that, in doing so, they were, like Arnold J at first instance, following Lord Hoffmann's guidance in Kirin-Amgen [2005] RPC 9). Thus, when considering the third test, Floyd LJ made the point at para 72(ii) of his judgment that "there is no obvious leeway as a matter of language for giving it a broad as opposed to a narrow construction". That seems to me to demonstrate the risk of treating the issue raised by the third question as being one of normal interpretation. (Another way of looking at the point is, in the language of Sir Hugh Laddie, that it involves wrongly conflating the issue of interpretation with the issue of scope of protection.) As already explained, if it was a decisive point it would make a nonsense of asking the three questions: if one cannot depart from the language of the claim when considering those questions, what is the point of the questions in the first place?

72. More specifically, I do not agree with the Court of Appeal's view that, because the specification referred to "anti-folates" and "anti-folate drugs", the fact that the claims were limited to pemetrexed disodium

means that the drafter of the Patent would have been understood to intend that the other pemetrexed compounds would not infringe. As Mr Mitcheson QC contended in his well argued case, the point is neutral because there is no reference to pemetrexed salts as a class in the specification, and the contrast therefore does not help on the question whether pemetrexed salts other than pemetrexed disodium were intended to be excluded.

73. Further, contrary to the Court of Appeal's reasoning, I would have thought that if the specification had not referred to anti-folates but had only referred to pemetrexed disodium, that would have been a more powerful indication that the patentee was intending to limit himself to pemetrexed disodium. The very fact that the specification teaches that there are other anti-folate drugs which have a similar effect to pemetrexed disodium (coupled with the fact that it was generally known that cations other than sodium could be successfully used with anti-folates) highlights a point similar to that made by Lord Diplock in Catnic [1982] RPC 183, 244, namely "No plausible reason has been advanced why any rational patentee should want to place so narrow a limitation on his invention" as to limit the scope of protection afforded by the Patent to pemetrexed disodium - a telling but not always conclusive point. Additionally, there is no teaching in the specification which relates to the relevance or importance of the sodium cation.

74. Looking at matters more broadly, the addressee of the Patent would, as I see it, understand that the reason why the claims were limited to the disodium salt was because that was the only pemetrexed salt on which the experiments described in the specification had been carried out. However, it does not follow that the patentee did not intend any other pemetrexed salts to infringe: the suggestion confuses the disclosure of the specification of a patent with the scope of protection afforded by its claims. Particularly given the facts set out in para 25 above, it seems to me very unlikely that the notional addressee would have concluded that the patentee could have intended to exclude any pemetrexed salts other than pemetrexed disodium, or indeed pemetrexed free acid, from the scope of protection.

75. Accordingly, I would conclude that, subject to considering the prosecution history, the Actavis products infringe claim 1 of the Patent.

The effect of the prosecution history

76. The application for the patent was filed at the EPO in June 2001, and it contained claims directed to a method of treatment, claims in Swiss form, and purpose-related product claims. In January 2003, Dr Burnside, Lilly's patent attorney, filed a revised set of claims which omitted the method of treatment claims. Claims 1 and 2 were as follows:

"1. Use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate.

2. Use of a methylmalonic acid lowering agent in the preparation of a medicament useful in lowering the mammalian toxicity associated with an antifolate, and the medicament is administered in combination with an antifolate and a FBP binding agent."

Claim 10 was a dependent claim "wherein the antifolate is ALIMTA".

77. As Floyd LJ said, these claims are in the reverse order from the claims ultimately granted (as they start with the use of the methylmalonic lowering agent rather than pemetrexed disodium), but nothing hangs on that. The essential point is that these claims were entirely general as to the identity of the antifolate. In March 2004, the EPO examiner wrote raising various objections including some under articles 83 and 84 EPC 2000 (disclosure and clarity). The clarity and lack of disclosure objections were that the claims related to too many possible combinations of compounds by using general expressions such as "antifolate", "methylmalonic acid lowering agent" and "FBP binding agent". Moreover, the examiner was concerned that the claims covered all compounds having these characteristics or properties, whereas the application provided support and disclosure for only a very limited number of such compounds.

78. Dr Burnside replied in a letter of December 2004, under cover of which he filed new claims 1 and 2, this time starting with the use of the antifolate, now limited to "pemetrexed" in these terms:

"1. Use of pemetrexed in the manufacture of a medicament for use in combination therapy for inhibiting tumour growth in mammals wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof.

2. Use according to claim 1 wherein said medicament is to be administered in combination with vitamin B12 or a pharmaceutical derivative thereof and a folic binding protein binding agent [which was then defined]."

In support of these new claims, Dr Burnside said that, "in order to expedite the application proceeding to grant", Lilly had elected to amend the claims so as to reflect more closely the specific examples provided. However, he added, the amendments were made without prejudice to Lilly's right to obtain protection for other patentable subject matter in one or more divisional applications.

79. Notwithstanding these amendments, in May 2005 the EPO examiner formally objected to the admissibility of the new claims. He contended that the amendments introduced subject matter beyond the content of the originally filed documents, contrary to article 123(2) EPC 2000. Thus, he said, the inclusion in claim 1 of "use of pemetrexed ..." and similar provisions in other claims did not find any basis in the application documents as filed. According to the examiner, "pemetrexed" was a distinct compound from pemetrexed disodium. (This is supported by the Chemical Abstracts Service Registry, where the "pemetrexed" is recorded as being the free diacid.) The patent does contain one mention of the term "pemetrexed" at para [0004] of the specification, followed by a Lilly reference number which shows it to

be pemetrexed disodium. It was therefore, at best, uncertain as to what the term "pemetrexed" on its own was intended to refer.

80. Dr Burnside replied in March 2006 by a letter under cover of which he filed new claims, which this time were limited to pemetrexed disodium, and are now embodied in the claims of the Patent as set out in para 21 above. Dr Burnside said:

"The Claims have been amended to refer to the preferred embodiment, the use of pemetrexed disodium (ALIMTA®) as manufactured by Eli Lilly and Company, as the antifolate drug. The Claims have also been amended to incorporate the list of vitamin B12 derivatives set out on p 7 lines 6-7 of the application as filed."

The EPO examiner accepted the claims in this form, and the application proceeded to grant.

81. Actavis contends that the prosecution history, as summarised in paras 76 to 80 above, makes it clear that the claims of the Patent should be interpreted as being limited to pemetrexed disodium not only as a matter of language, but in the sense that the use of any other pemetrexed compound, including other pemetrexed salts and the free acid, could not infringe. This contention gives rise to two issues. The first is one of relatively general application, namely whether and if so when it is permissible to have recourse to the prosecution history of a patent when considering whether a variant infringes that patent. The second issue is whether the prosecution history of the Patent in this case alters the provisional conclusion reached in para 75 above.

82. So far as the first issue is concerned, Lord Hoffmann said in Kirin-Amgen [2005] RPC 9, para 35:

"The courts of the United Kingdom, the Netherlands and Germany certainly discourage, if they do not actually prohibit, use of the patent office file in aid of construction. There are good reasons: the meaning of the patent should not change according to whether or not the person skilled in the art has access to the file and in any case life is too short for the limited assistance which it can provide. It is however frequently impossible to know without access, not merely to the file but to the private thoughts of the patentee and his advisors as well, what the reason was for some apparently inexplicable limitation in the extent of the monopoly claimed."

83. In the absence of good reason to the contrary, it would be wrong to depart from what was said by the House of Lords. It is said by Actavis that there is good reason to depart from what Lord Hoffmann said on the ground that he was wrong in his description of the German and Dutch approaches to this issue, and that anyway he failed to have regard to the jurisprudence of other European courts.

84. In my view, Lord Hoffmann was right about the approach of the German and Dutch courts to this issue. Thus, the Bundesgerichtshof, in a decision involving the German equivalent of the instant Patent, Case No X ZR 29/15 (Eli Lilly v Actavis Group PTC), paras 39-40, stated that "it is permissible … to use statements made by the applicant [and the examiner] during the grant procedure as an indication of how the person skilled in the art understands the subject matter of the patent" but "such indications cannot be readily used as the sole basis for construction". And in Ciba-Geigy AG v Oté Optics BV (1995) 28 IIC 748, the Dutch Supreme Court said that "a court will only be justified in using clarifying information from the public part of the granting file, when it holds that even after the average person skilled in the art has considered the description and the drawings, it is still open to question how the contents of the claims must be interpreted".

85. It is argued by Actavis that this limited approach to the circumstances in which reference can be made to the prosecution file may be more restrictive than the approach adopted in France, Italy, and Spain, as analysed by Arnold J. Thus, he said in para 162 of his judgment, that the Cour d'Appel observed in Case No 08/00882, Hewlett Packard GmbH v Agilent Technologies Deutschland GmbH (27 January 2010) that "the patentee who amended its clauses to give them a limited scope may not, without putting the safety of third parties at risk, claim that the amendments were not necessary, nor that the limited claims have the same scope as the broader claims". However, the court in that case had already decided on the natural meaning of the patent, and the contents of the file were merely being invoked to confirm the decision. The position in Italy, according to Arnold J in para 174 of his judgment, is that "there is no doctrine of prosecution history estoppel" and "there is no clear rule as to the relevance, if any, of the prosecution history as an aid to the interpretation of claims". In Spain there is a doctrine of actos propios, which as Arnold J explained in para 184, is "the doctrine of one's own acts", but it only justifies relying on the prosecution file in relation to statements which are "unequivocal, clear, precise, conclusive, undoubted and [do] not reflect any kind of ambiguity".

86. While the French courts appear to be more ready to refer to the prosecution file on issues of interpretation or scope than the German or Dutch courts, it is unclear how much, if any, difference there is in outcome. The position in relation to the Italian courts is more unclear, and it may well be that the effect of the approach of the Spanish courts is the same in outcome as that of the German and Dutch courts. In those circumstances, particularly as it may be inevitable that there is a degree of difference in the approach of different national courts on such an issue, there is nothing in the French, Italian, or Spanish jurisprudence which causes me to depart from the conclusion expressed by Lord Hoffmann.

87. In my judgment, it is appropriate for the UK courts to adopt a sceptical, but not absolutist, attitude to a suggestion that the contents of the prosecution file of a patent should be referred to when considering a question of interpretation or infringement, along substantially the same lines as the German and Dutch courts. It is tempting to exclude the file on the basis that anyone concerned about, or affected by, a patent should be entitled to rely on its contents without searching other records such as the prosecution file, as a matter of both

principle and practicality. However, given that the contents of the file are publicly available (by virtue of article 128 EPC 2000) and (at least according to what we were told) are unlikely to be extensive, there will be occasions when justice may fairly be said to require reference to be made to the contents of the file. However, not least in the light of the wording of article 69 EPC 2000, which is discussed above, the circumstances in which a court can rely on the prosecution history to determine the extent of protection or scope of a patent must be limited.

88. While it would be arrogant to exclude the existence of any other circumstances, my current view is that reference to the file would only be appropriate where (i) the point at issue is truly unclear if one confines oneself to the specification and claims of the patent, and the contents of the file unambiguously resolve the point, or (ii) it would be contrary to the public interest for the contents of the file to be ignored. The first type of circumstance is, I hope, self-explanatory; the second would be exemplified by a case where the patentee had made it clear to the EPO that he was not seeking to contend that his patent, if granted, would extend its scope to the sort of variant which he now claims infringes.

89. Turning to the second issue, I do not consider that the contents of the prosecution file in this case justify departing from the provisional conclusion expressed in para 75 above. It seems to me clear that the reason why the examiner considered that the claims in the patent should be limited to pemetrexed disodium was because the teaching in the specification did not expressly extend to any other anti-folates. It is unnecessary to decide the issue, but, at least as at present advised, I am inclined to think that the examiner was wrong in taking that view. Indeed, in the course of his well-presented argument for Actavis, Mr Alexander QC seemed to accept that Lilly could have expressed its claims more widely than it did (albeit that this was not a point which was carefully explored). However, even if the examiner was right or at least justified in taking the stance that he did, I do not consider that that consideration can have any bearing on the question whether any pemetrexed salts other than pemetrexed disodium should be within the scope of the patent pursuant to the doctrine of equivalents. The whole point of the doctrine is that it entitles a patentee to contend that the scope of protection afforded by the patent extends beyond the ambit of its claims as construed according to normal principles of interpretation.

90. This point was well made by the Dutch Court of Appeals in Boston Scientific Ireland Ltd v Cordis Europa NV 01/639 (unreported) 3 July 2003, when they held that the contents of the prosecution file were of no assistance, as they related to a concern which the examiner had expressed about added matter which went to disclosure, whereas that had no relevance to the point at issue which was the scope of the claim - which properly included equivalents.

91. I draw comfort from the fact that neither party was able to refer to a case where a French or Spanish Court had relied upon the patentee's response to a disclosure or added matter objection by the examining officer as being relevant to the scope of claim. It is true that the Madrid Appeal Court in Inmobiliaria Masife SL v Vale y Tino SA (decision 268/2013) (unreported) 27 September 2013 held that a patentee was bound by an exclusion which he had agreed during prosecution but that was "to overcome an objection of the examiner based on the prior art", a very different point. I draw even greater comfort from the fact that the Bundesgerichtshof reached the same conclusion on this very issue in relation to the German equivalent of the Patent in this case in Case No X ZR 29/15 (Eli Lilly v Actavis Group PTC), para 72.

Direct infringement in France, Italy and Spain

92. Having concluded that the Actavis products directly infringe the Patent as a matter of UK law, it is necessary to consider whether the same result obtains under French, Italian and Spanish law. In my judgment, direct infringement is established in those jurisdictions as well.

93. Turning first to French law, it appears to me that the answer to the question of direct infringement ultimately turns on whether the Patent in this case falls into the moyens généraux category or the moyens particuliers category, because, as discussed in para 46 above, the doctrine of equivalents is apparently only applicable to patent claims in the former category. With some diffidence, I have reached a different conclusion from Arnold J on this issue and have concluded that the Patent in this case falls into the former category. It is of course true that an appellate court should be very slow indeed to differ from the trial judge on a question of fact. However, the notion that the resolution of a dispute as to foreign law involves a factual finding rather than a legal conclusion is somewhat artificial, and in any event, the Judge did not hear any oral evidence from the expert foreign law witnesses. We are therefore in as good a position as he was to analyse the effect of the evidence as to foreign law.

94. The Judge considered that the Patent in this case represents a moyen particulier, because pemetrexed disodium was the relevant means and the Patent did not reveal it having a novel function: it merely revealed a new and better way in which its function could be achieved. To my mind the better analysis is that the Patent discloses that pemetrexed disodium could be used for a function for which it could not previously have been satisfactorily or safely used in practice; specifically, that pemetrexed disodium could be used with vitamin B12 to achieve an end which could not have been achieved by either chemical on its own, pemetrexed disodium because of its harmful side-effects and vitamin B12 because it would not have worked. The essential point, as I see it, is that the Patent revealed for the first time the existence of a combined means which functioned in a certain way, namely to alleviate certain cancers without serious side-effects. It would be different if the overall function of the combination of the two chemicals had not been new.

95. Support for this conclusion appears in the book referred to in para 46 above, Droit de la propriété industrielle, whose two authors were the expert witnesses on French law in this case. At para 719, p 443, they wrote "when the claim is over a combination of means for which global function is novel, any combination of means with a different structure but achieving the same global function is a priori equivalent and thus infringing". That passage was effectively applied by the Cour de Cassation in Appeal P08-14741, Diffusion Equipements Loisirs v Helge, 15 September 2009.

96. As to Italian law, Arnold J said at paras 178 and 179 of his judgment that he had concluded that the Actavis products did not infringe the Italian designation of the Patent on two grounds. The first (which he only accepted with "some hesitation") was "because on its face the patent clearly demonstrated a conscious intention of the patentee to limit the claims to pemetrexed disodium". The second ground was "because if there was any doubt about that, it was amply confirmed by the prosecution history". It is clear that (as one would expect) the Italian courts accept the doctrine of equivalents, and accordingly for the reasons given in paras 70 to 74 above, I would reject the first ground; and, for the reasons given in paras 91 to 93 above, I would reject the second ground also.

97. So far as Spanish law is concerned, it is common ground that the Spanish courts have followed the United Kingdom approach, which leads to the difficult question whether one should assume that they would follow this decision in modifying the Improver questions and in particular the second question. I incline to the view that judicial comity would tend to suggest that the Spanish courts would follow this court in modifying the Improver questions, not least because this appears to render the UK courts and therefore the Spanish courts more consistent with the German and Dutch courts, and no more inconsistent with the French and Italian courts.

98. In a written note dated 10 July 2017, Actavis applied for what would amount to a reconsideration of the conclusion expressed in para 97 above, on the ground that the reasoning of the Spanish Tribunal Supremo in the Lundbeck decision, discussed in para 50 above, should lead to the opposite conclusion, namely that marketing Actavis's products in Spain would not infringe the Patent.

99. In my view, it is too late for Actavis to raise such an argument. Lilly had sought to rely on the Lundbeck decision in its written case in this appeal, and Actavis had objected on the ground that the decision had been given after the Court of Appeal decision in these proceedings. It seems to me that in these circumstances it would be wrong to permit Actavis to raise the Lundbeck decision to support their case, especially as they are seeking to do so after knowing the result of this appeal and the reasons for that result. I am unimpressed by Actavis's argument that their application is nonetheless justified because the reasoning in para 97 above was not raised on this appeal. Actavis's written case stated that "Spanish law has been directly modelled on Catnic and Improver", and in paras 182 and 187 of his judgment on this case Arnold J effectively treated the Improver questions as part of Spanish law. It appears to me that the conclusion that, if the UK Supreme Court modifies the Improver questions, the Spanish courts would adopt any such modification, was therefore within the scope of the argument raised in this Court.

100. Furthermore, I consider that it would be wrong for Actavis to be permitted to raise a new ground in support of their contention that their products would not infringe in Spain, after publication of our decision, which was done with their consent and at their instigation following receipt of our draft judgment which concluded that their products would infringe in Spain. It is not as if Actavis had come across new information since they had agreed to that publication. It is true that, as explained in para 2 above, Actavis's solicitors wrote to the Court very shortly after they received the draft judgment, but thereafter they had nearly a full 24 hours within which they could have withdrawn their agreement to publication of our decision. In any event, there is obvious force in the simple point that, having agreed to publication of the decision in advance of the handing down of the judgment, they have to take the consequences. I do not suggest that, in every case where the decision is published with the consent of the parties after they have seen the draft judgment, it would be impossible for either party to invite the court to change the decision, or any aspect of it. However, it seems to me that, in the absence of a good reason, the interests of finality and certainty should prevail, and I do not consider that Actavis have come up with a good enough reason in this case.

101. It is right to add that I am by no means convinced that, even if we had permitted Actavis to re-argue their case in relation to Spain, on the basis of the Lundbeck decision, I would have reached a different conclusion from that expressed in para 97 above. Quite what constitutes "a degree of predictability" or "a high probability" when it comes to assessing whether the notional addressee would expect the variant to work must be fact-sensitive. Further, if, as seems likely but not, I accept, certain, the German, Dutch, French and Italian courts would all hold that Actavis's products infringed, there would have been much to be said for the view, which I have already expressed, that the Spanish courts would follow suit.

102. Accordingly, I would hold that the French, Italian and Spanish designations of the Patent are also directly infringed by the Actavis products.

Indirect infringement

103. In these circumstances, Actavis's cross-appeal, which seeks to challenge the Court of Appeal's conclusion that its products indirectly infringed does not, I think, arise in the sense that it has no practical effect on the parties (other, perhaps, than on the issue of costs). However, as the point was fully argued, gave rise to a disagreement between the Court of Appeal and the trial

judge, and can be dealt with shortly, it is appropriate to consider it.

104. Indirect infringement is provided for in section 60(2) of the 1977 Act, and it states that a person infringes a patent if, without the patentee's consent, he supplies or offers to supply in the United Kingdom to someone not authorised by the patentee with "any of the means, relating to an essential element of the invention, for putting the invention into effect when he knows, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect".

105. The reason why Lilly contends that, even if they did not directly infringe, the Actavis products would indirectly infringe is because, when they are supplied to a doctor or a pharmacist, they are, as Actavis would know, dissolved in a saline solution in order to enable them to be administered to patients. Saline is a solution of common salt, ie sodium chloride, in water, and when common salt is dissolved in water, it separates into sodium cations and chloride anions. Accordingly, when one of Actavis's products, say that containing pemetrexed dipotassium, is dissolved in saline, the solution contains pemetrexed anions and potassium cations plus sodium cations and chloride anions. In those circumstances, argues Lilly, even if pemetrexed dipotassium would not of itself infringe if it was administered with vitamin B12, at least provided that the ratio of sodium ions to pemetrexed ions was at least 2:1, there will be infringement when it is administered in saline solution, because the solution which is administered will contain pemetrexed disodium.

106. The Court of Appeal, disagreeing with the Judge, acceded to Lilly's argument on this point.

107. Actavis argue that a solution consisting of, or including, pemetrexed ions and sodium ions is not within the expression "pemetrexed disodium" in the Patent, because it is limited to the solid, or crystalline, chemical. I agree with Floyd LJ in rejecting that argument. There is no reason to think that the patentee intended to limit the expression in that way; quite the contrary. It is clear that solubility was an important issue, and indeed that was one of the two main reasons on which Actavis rested their contention that their products did not infringe, as discussed in paras 24 to 25, 59, and 66 above. Further, and even more in point, as Floyd LJ said, in the passages quoted in para 19 above the specification made it clear that references to pemetrexed disodium extended to that chemical in solution.

108. Actavis also argue that there is an inconsistency between the Court of Appeal holding, when considering direct infringement, that the notional addressee could not be assumed to know that pemetrexed dipotassium would dissolve, and holding, when considering indirect infringement, that pemetrexed dipotassium did in fact dissolve. Even if I had not concluded that the notional addressee should be treated as knowing that pemetrexed dipotassium could dissolve, I would have rejected that argument which seems to me to involve a non-sequitur. By the time that they were ready to market their products, Actavis knew perfectly well that they were all soluble.

109. Actavis further argue that a solution of pemetrexed dipotassium dissolved in saline does not in any event contain "pemetrexed disodium" within the meaning of that term in the Patent; it is simply pemetrexed dipotassium dissolved in saline. In my view that is a bad point. If dissolving pemetrexed disodium in an aqueous solution of potassium chloride can be said to result in a solution containing pemetrexed disodium (as Actavis's argument impliedly accepts), then it must follow as a matter of elementary chemical logic that dissolving pemetrexed dipotassium in saline also result in a solution which contains pemetrexed disodium: the two solutions are chemically identical, as each would consist of potassium and sodium cations and chloride and pemetrexed anions in water.

110. Actavis additionally argue that it is irrational to hold that there could be indirect infringement because it would all depend on the solvent in which the Actavis product is dissolved, and, even if that solvent was saline, it would depend on the proportion of sodium ions and pemetrexed ions in the solution which would vary by reference to the weight of the patient. The fact that infringement may depend on the nature of solvent and the relative amounts of ions in the solution does not seem to me to be irrational. It is simply a result of the extent of the scope of protection afforded by the patent given that (as determined by the Court of Appeal) its claims are limited to pemetrexed disodium, which, when dissolved in water produces two sodium cations to every one pemetrexed anion.

111. Finally, Actavis argue that, rather than being used in the manufacture of a medicament as described in claim 1 of the Patent, pemetrexed disodium is part of the medicament. Like the Court of Appeal, I do not agree. The pemetrexed disodium comes into the manufacturing process rather later than it would if the original medicament included pemetrexed disodium rather than pemetrexed dipotassium, but that cannot alter the fact that, before it is administered to the patient, the medicament includes pemetrexed disodium and vitamin B12.

112. Accordingly, I would uphold the Court of Appeal's determination that Actavis are liable to Lilly for indirect infringement in the United Kingdom with respect to their products if Actavis know, or it is obvious in the circumstances, that ultimate users will dilute in saline - or at least Actavis would be liable for indirect infringement if they were not liable for direct infringement. The Court of Appeal said that this conclusion would apply equally to France, Italy, and Spain, and there is no challenge to that from Actavis.

Conclusion

113. For these reasons, I would (i) allow Lilly's appeal in direct infringement and hold that the Actavis products infringe the Patent in the United Kingdom, and also in France, Italy and Spain, (ii) dismiss Actavis's cross-appeal on the basis that if its products did not directly infringe, they would indirectly infringe to the extent held by the Court of Appeal.
