Neutral Citation Number: [2013] EWCA Civ 925

Case No: A3/2012/2136

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT
The Hon Mr Justice Arnold
[2012]EWHC 1848 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 29/07/2013

Before :

LORD JUSTICE MOSES
LORD JUSTICE KITCHIN
and
LORD JUSTICE FLOYD

- -

Between :

GENERICS [UK] LIMITED t/a MYLAN	**Appellant**
- and -	
(1) YEDA RESEARCH AND DEVELOPMENT CO. LTD	
(2) TEVA PHARMACEUTICAL INDUSTRIES LTD	**Respondents**

Michael Tappin QC and **Piers Acland QC** (instructed by **Simmons & Simmons LLP**) for the **Appellant**
Andrew Waugh QC, Thomas Hinchliffe and **Jeremy Heald** (instructed by **Bird & Bird LLP**) for the **Respondents**

Hearing dates: 18-20 June 2013

Judgment

Lord Justice Floyd:

1. Generics (UK) Limited, who trade as Mylan ("Mylan"), sought revocation before Arnold J of European Patent (UK) No. 0 762 888 ("the patent") and a declaration of non-infringement. By his judgment dated 11 July 2012 and his subsequent order, Arnold J refused Mylan both forms of relief. Mylan appeals, with permission of the judge.

2. The first respondent Yeda Research and Development Company Limited and the second respondent Teva Pharmaceutical Industries Limited are respectively the registered proprietor of and exclusive licensee under the patent. The patent relates to a synthetic copolymer known as copolymer-1. Teva markets a product which it describes as copolymer-1 under the brand name Copaxone for the treatment of relapsing-remitting multiple sclerosis or MS.

3. Mylan attacked the validity of the patent at the trial for, amongst other things, obviousness over a number of identified prior publications, obviousness for lack of a technical contribution and insufficiency. They also contended that the product which they intended to launch in competition with Copaxone did not infringe the claims of the patent on its correct construction, and raised a related case of insufficiency if they were wrong on the issue of construction.

4. More specifically, on this appeal Mr Tappin QC and Mr Acland QC for Mylan have argued the following principal grounds:

    i) Certain claims of the patent are obvious over a publication known as Johnson 1994;

    ii) The patent is invalid for obviousness on the basis of a lack of a technical contribution because:

        a) The specification does not make it plausible that the technical problem which it describes is solved by products falling within the claims;

        b) Alternatively that problem is not in fact solved by products falling within the claims.

    iii) Mylan's product does not infringe because the copolymer does not conform to the claimed ratio of amino acids on a proper construction of the claims.

    iv) If the patent is not construed as Mylan contend then it is bad for ambiguity-type insufficiency.

5. The respondents, who were represented on the appeal by Mr Waugh QC, Mr Hinchliffe and Mr Heald, supported the judge's judgment and reasoning.

Background

6. Before embarking on the issues argued on this appeal, I should record some of the relevant history of the research into copolymer-1 and its testing. The judge explained this at [5] to [80] of his judgment. What follows borrows heavily on that part of his

judgment and extracts what is necessary for an understanding of the issues in this appeal.

7. In MS there is an inflammatory response which leads to the removal of the sheath around nerves. This sheath is comprised of the protein myelin. Without the insulation provided by the myelin sheath, the nerve cells are not able to function correctly. As MS progresses, it causes multiple lesions or scleroses to form on the brain and spinal cord, leading to cognitive, motor and sensory impairments. MS is usually characterised by episodes of neurological symptoms called "relapses" which often recover or "remit". This is referred to as "relapsing-remitting" MS. Over time, however, there is less recovery after relapses.

8. Copolymer-1 was developed in the late 1960s by Professor Ruth Arnon and co-workers at the Weizmann Institute of Science ("WIS") in Israel. Copolymer-1 is a synthetic polypeptide as opposed to a naturally-occurring polypeptide or protein. It is a random copolymer made from four amino acids: alanine, glutamic acid, lysine and tyrosine. Unlike naturally-occurring proteins, which are generally a single species, it is a mixture of different polypeptides of different lengths and different amino acid sequences.

9. Copolymer-1 was initially developed in order to induce a disease known as experimental allergic encephalitis ("EAE") in an animal model. EAE resembles MS and so is used to study that disease. For this reason copolymer-1 was designed to mimic myelin basic protein ("MBP"). However, copolymer-1 failed to induce EAE. The Weizmann Institute scientists then tested it to see if it suppressed EAE in guinea pigs, and found that it did. The results were first published in Teitelbaum et al, "Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide", Eur. J. Immunol., 1971, 1: 242-248 ("Teitelbaum 1971") and formed the basis for United States Patent No. 3,849,550 ("US 550"). Teitelbaum 1971 concludes by suggesting that copolymer-1 might "be of help as a potential suppressive agent for EAE and diseases of a similar nature". Teitelbaum 1971 described copolymer 1 as having a molecular weight in the region of 23 kiloDaltons (kDa). Teitelbaum 1971 was, but is no longer, relied on as a prior art citation by Mylan.

10. In 1987 Dr Murray Bornstein of the Einstein School of Medicine in New York and co-workers published the results of a pilot clinical trial of copolymer-1 in relapsing-remitting MS. They announced with a degree of caution that their results suggested that copolymer-1 might be beneficial in patients with relapsing-remitting MS. They recommended that evaluation continue in a full multi-centre clinical trial. Mylan's expert clinician, Dr Coles, described Bormstein 1987 as:

> "the landmark study published in the prestigious New England Journal of Medicine, which established that the efficacy of [copolymer-1] that had been noted in the earlier studies was real. … This demonstration of efficacy was important and exciting and paved the way for the confirmation of [copolymer-1's] efficacy in a larger, more definitive, clinical trial study."

11. The material tested in Bornstein 1987 was of a molecular weight of 14-23 kDa. The Bornstein paper was, but is no longer, relied on as a prior art citation by Mylan.

12. The further trial recommended by Bornstein went ahead. The chief investigator was a Dr Kenneth Johnson. Before the full results were known, a paper discussing the trial and giving a retrospective of the work on copolymer-1 was published by Dr Johnson ("Johnson 1994"). This is the sole item of prior art now relied on by Mylan. Dr Johnson introduces copolymer-1 as "*a compound developed at the Weizman Institute in Israel*". Johnson 1994 was published in Annals of Neurology, a publication of the American Neurological Association. Annals of Neurology is not a peer-reviewed journal. Dr Johnson records the fact that, when copolymer-1 was first used to treat EAE, the results provided the investigators with hope that it would be protective and not harmful to humans. He says that copolymer-1 has been the subject of a series of clinical trials over the previous 14 years, including three studies under Dr Murray Bornstein. He explains that:

> "Following these three provocative human studies, there was a long delay before further clinical study could be carried out with [copolymer-1]. In part this was due to difficulty in expanding drug production from a research laboratory to an industrial phase, which was undertaken by Teva Pharmaceutical Industries Ltd. the largest pharmaceutical company in Israel. It also proved difficult to develop a highly standardised preparation of [copolymer-1] that could be employed in further clinical trials."

13. It is not entirely clear what Johnson 1994 means by "a highly standardised preparation". It probably means a preparation whose composition is reliably reproducible. Johnson 1994 also contained one more piece of information of relevance for the purposes of the present appeal. It recorded that copolymer-1 had a molecular weight of approximately 7 kDa. This was a different and much lower figure than the figure of 23 kDa recorded in Teitelbaum 1971. There is no discussion or explanation in Johnson 1994 of the change, if such it was, in the molecular weight of copolymer-1.

14. The results of the trial being conducted under Dr Johnson were not published in a scientific paper until after the priority date, May 1995. However the results of the trial were announced by Dr Johnson, who was the lead investigator, at the annual meeting of the American Neurological Association ("ANA") in San Francisco on 10 October 1994. The announcement of the results was not pleaded as an item of prior art by Mylan, but they contended that the results, at least at some level, would have been part of the general knowledge of the skilled team. The judge agreed, saying:

> "… in May 1995 the clinician would have known that the results of the Phase III trial had been announced at the ANA meeting and that results were positive, in that copolymer-1 reduced relapse rate and the accumulation of disability compared to placebo among relapsing-remitting MS sufferers. I am not satisfied that he would have known any further detail than that."

15. It is against this scientific background that the invention disclosed in the patent in suit is to be considered.

The patent

16. The patent states that it relates to "an improved composition of copolymer-1". The introductory paragraphs of the specification make clear that the invention consists of the compositions themselves, their use in the treatment of MS and a method for making copolymer-1. The specification identifies the invention by reference to the claims. It is enough to set out claim 1, which is to:

> "A copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight over 40 kilodaltons and wherein over 75% of said fraction is within a molecular weight range from 2 kilodaltons to 20 kilodaltons."

17. At [0002] and [0003] the specification makes reference to the fact that Dr Arnon and co-workers at the Weizmann Institute "*developed copolymer-1*", and that Teitelbaum 1971 and US 550 showed that "*copolymer-1 was shown to be beneficial for patients with exacerbating-remitting form of multiple sclerosis*". It then tells the reader what copolymer-1 is:

> "copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine and tyrosine in a molar ratio of approximately 6:2:5:1."

18. The specification then describes a number of examples. Only Examples 1 and 2 are important for present purposes. The judge described these examples in terms which attracted no criticism from either side, so I adopt his description gratefully:

> "Example 1 consists of two sections. The first describes a chromatographic method of preparing "low-toxicity" copolymer-1. The second describes molecular weight analysis. In the first section, two batches of copolymer-1 are said to have been prepared by known methods, for example as in US 550. One of these batches was subjected to chromatographic separation, and a fraction with an average molecular weight of 7-8 kDa (referred to as "Batch A") was isolated.
>
> The molecular weight analysis section states at [0019] that the molecular weight distribution of the two batches was determined "on a calibrated gel filtration column (Superose® 12)" using a UV detector. The specification continues:
>
> "[0020] Copolymer-1 batch A was found to have an average molecular weight of 7-8 kDa. 2.5% of this batch had a molecular weight above 32kDa but no copolymer-1 species present in this batch had a molecular weight of over 40kDa.
>
> [0021] The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 kDa. 2.5% of the batch had a molecular weight above 42

kDa and 5% of the total copolymer-1 species in this batch had a molecular weight over 40 kDa."

Example 2 is described as a "toxicity analysis". Two assays were performed: (A) *in vivo* in a mouse lethality test and (B) *in vitro* in an RBL degranulation test.

The *in vivo* test involved dissolving the sample in distilled water at a concentration of 2 mg/ml. Five mice were used in each experimental group. Each mouse was injected with 0.5 ml of solution into the lateral tail vein and was observed for mortality and relevant clinical signs over a 48 hour period. If all the animals were alive with no adverse signs after 48 hrs, the batch was designated "non-toxic". If one or more mice had died or had shown adverse signs, the batch was labelled "toxic".

In the *in vivo* test, results for three batches of copolymer-1 are reported. These had an average molecular weight of 7.3 and 8.4 kDa (less than 2.5% copolymer-1 species over 40 kDa) and 22 kDa (more than 5% copolymer-1 species over 40 kDa). Both the 7.3 and 8.4 kDa batches were found to be "non-toxic". With the 22 kDa batch, however, three out of five mice had died after 48 hrs, so the batch was designated "toxic".

The *in vitro* test is introduced at [0025]. This passage explains that histamine (or serotonin) release from basophil is an *in vitro* model for immediate hypersensitivity. The RBL-2H3 cell line is said to have been developed as a sensitive, uniform and reproducible system, citing Basumian *et al*, *Eur. J. Immunol.*, 11, 317 (1981). It is then said that degranulation can be induced by non-IgE mediated stimuli, including various peptides and synthetic polymers, citing Siraganian, *Trends in Pharm. Sci.*, October 1983, 432. The passage concludes:

"The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects."

The test method is explained at [0026]. RBL-2H3 cells are loaded with tritiated serotonin and incubated with 100 μg copolymer-1. Batches which induce degranulation release serotonin which is detected with a scintillation counter. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

Four batches of copolymer-1 with average molecular weight 6,250 – 14,500 were analysed for both the percentage of species with molecular weight over 40 kDa and the percentage of serotonin release. The results were as follows:

Average M.W. (Daltons)	% of species with M.W. over 40kDa	% Serotonin Release
6,250	< 2.5	12.4
7,300	< 2.5	21.0
13,000	> 5	66.9
14,500	> 5	67.8

The specification comments at [0028]:

> "As can be seen, when the % of high molecular weight species is low (< 2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa."

19. The *in vivo* test was known as a mouse lethality test. It is a test for toxicity. The *in vitro* test, the RBL degranulation test, is used to measure the release of the mediator serotonin which plays a role in allergy or hypersensitivity reactions. At a very broad level of generality the specification is asserting that the claimed lower molecular weight material is better from a toxicity and allergy standpoint than the known higher molecular weight copolymer-1.

The skilled team

20. The judge identified the skilled team at [81] to [84] in terms which Mylan does not challenge on this appeal. He summarised it in this way:

> "Broadly speaking, it is agreed that the skilled team would comprise the following:
>
> > (i) Someone with an interest in the treatment of MS. This person is likely to be a clinician by training, although a clinical qualification may not be essential. For convenience I will refer to this person as "the clinician".
> >
> > (ii) Someone with experience in assessing the adverse effects of drugs in both *in vivo* tests such as the mouse lethality assay and *in vitro* tests such as the RBL degranulation assay. This person is likely to be a toxicologist by training, although a toxicological qualification may not be essential. For convenience I will refer to this person as "the toxicologist".
> >
> > (iii) A synthetic chemist with expertise in synthesising polydisperse polymers.
> >
> > (iv) An analytical chemist with expertise in amino acid analysis.
> >
> > (v) An analytical chemist with expertise in SEC."

Obviousness over Johnson 1994

21. Mylan's case is that it was obvious in the light of Johnson 1994 and the headline results of the trial announced at the ANA meeting in October 1994 for the skilled clinician to recommend development of copolymer-1 with a molecular weight matching that disclosed by Johnson 1994. This case was founded on the evidence of their expert clinician, Dr Coles, whose evidence proceeded on the assumption that the difference between the molecular weight disclosed by Johnson 94 and that disclosed in the earlier work had been drawn to his attention. This was because, as he very frankly accepted, he would not as a clinician have noticed or been interested in the molecular weight of the copolymer. However, having had the difference drawn to his attention, he said that he would have recommended the development of the lower molecular weight in parallel with the higher molecular weight material. He would not have felt sufficiently informed about the lower molecular weight material to recommend the development of that material alone.

22. The judge's significant findings in relation to this argument were:

    i) If the clinician had taken an interest in the molecular weight information in Johnson 1994, he would have been confused by it and would have wondered whether there really had been a change in the molecular weight. Professor Schellekens had given evidence to that effect, and drawn attention to the fact that it was highly unusual for a change to be made to the active substance in the course of a series of clinical trials.

    ii) The skilled person would have regarded the headline results as a good basis for further action.

    iii) The best evidence for efficacy pending the publication of the full results of the trial was still Bormstein 1987.

    iv) The 7 kDa material was further away from MBP in molecular weight than the higher molecular weight material, which fact might adversely affect efficacy.

    v) To take two materials forward for further clinical study would have been costly.

23. The Judge concluded that Mylan's case was based on hindsight. Although he accepted that the skilled team would have been motivated to develop the product of the trial reported at the ANA, it did not follow that the skilled team would develop the 7 kDa material. The core of his reasoning was expressed thus:

> "… even on the basis that the difference in molecular weight had been pointed out to him and that he took an interest in this information, it was Dr Coles' evidence that he would not have felt sufficiently informed about the Phase III trial to recommend development of 7 kDa rather than 14-23 kDa copolymer-1. In those circumstances, I consider that the clinician would not have concluded that the headline results provided a good basis for developing 7 kDa copolymer-1. Rather, he would want to see the full report in order to see if

> this shed any light on the reasons for, and significance of, the difference in molecular weight between the material used in Bornstein 1987 and that used in the Phase III trial."

24. As Mr Tappin frankly recognised, an appellant faces a significant hurdle in showing that a judge's conclusion on the issue of obviousness should be disturbed on appeal where he has not gone wrong in principle. As Lord Hoffmann pointed out in *Biogen v Medeva* [1996] UKHL 18:

> "Where the application of a legal standard such as negligence or obviousness involves no question of principle but is simply a matter of degree, an appellate court should be very cautious in differing from the judge's evaluation."

25. On the other hand, Mr Waugh acknowledged that if the skilled person could have been certain that the material used in the trials was a 7 kDa version of copolymer-1, then it would not be possible to support the judge's finding that the invention was not obvious in the light of Johnson 1994. The combination of the headline results and certain knowledge of what the material tested was would have led the skilled team to conduct further testing on that form of copolymer-1.

26. Mr Tappin submitted, firstly, that the judge focused unduly on the expert clinician and Dr Coles' lack of interest. Secondly, he submitted that there was no evidence on which the judge could base his finding that there was real doubt about the identity of that material. Thirdly, he submitted that the judge's reasoning that the skilled person would wait to see the results of the trial contained a logical fallacy given his finding that the headline results provided a good basis for further action.

27. I do not think it right to say that the judge focused unduly on the clinician. Even though the judge concluded that the clinician would not be interested initially in molecular weight, he went on to consider what the skilled team would do once appraised of the difference in molecular weight. Once the judge had found that the headline results provided a good basis for further action, the question for the skilled team which had read Johnson 1994 with interest would be the identity of the material used to produce those results. This led the judge to consider whether the team could be sure what that material was. This did not involve giving undue weight to the views of the clinician.

28. I think there was ample material for the judge to conclude that Johnson 1994 would have left the skilled team in a state of uncertainty as to what was being used in the Phase III trial.

29. Firstly, there was the evidence of the Johnson paper itself, which appeared to treat the material which was the subject of the current clinical trial as the same as the material which had been the subject of the earlier trials. The statement in Johnson that the material had been "standardised" is not the same as a statement that the material had been changed in a significant way. As to that, there was evidence that it was highly unusual for a material to be changed in any substantial way in the course of a series of trials. Secondly, and against that background, the judge was entitled to accept the evidence of Professor Schellekens to the effect that he would have been confused by the disclosure. Professor Schellekens also pointed out that, unlike the prestigious

New England Journal of Medicine in which Bornstein appeared, the Johnson paper appeared in a journal which is not peer-reviewed and accordingly could more credibly contain an error in reporting the molecular weight without further comment.

30. It is true that it was not specifically put to Dr Coles that the reference to 7kDa in Johnson could have been a mistake. However, given his frank acceptance that he would not have been interested in the molecular weight, it is questionable what value this would have had. Mr Tappin also relied on the unchallenged evidence of Professor Hunter, Mylan's expert synthetic chemist, that he would have drawn the difference in molecular weight to the attention of the team. This led to a dispute about whether the judge was right to question (as he did at [296]) whether there was any good reason why the chemist would have taken this step. I do not think any of this matters. Once the skilled team is motivated to take forward the material used in the trials, the question of what that material consists of arises automatically. The Johnson paper would be referred to the synthetic chemist. The team as a whole would have to decide which of the two materials it would make or whether it would make both of them.

31. Mr Tappin also relied on the fact that it was not suggested to Professor Hunter that Johnson's figure could be a mistake. That is a fair point, but it does not take Mr Tappin very far. The judge was entitled to consider whether the clinician on the team would think it to be a mistake. It is the clinician's background knowledge of the earlier trials on the higher molecular weight material, his knowledge of the rarity of changes in active ingredient and his knowledge of the relative authority of the publications, which provides the context for the conclusion about whether there is or might be a mistake. Even if one assumes in Mr Tappin's favour that the synthetic chemist would not think it was a mistake, the thinking of the team as a whole would be affected by the clinician's uncertainty.

32. Given the lack of clarity as to whether the material in the trials was 7 or 14-23 kDa, the next question was whether the skilled team would have considered it worthwhile to include the 7 kDa material in further testing. Relying on Dr Coles, Mr Tappin submitted that both materials would have been taken forward. The judge thought the skilled team would not have done so. Again, I consider there was material before the judge on which he could properly reach that conclusion. Firstly, there was Dr Coles' own evidence. He did not feel he knew enough about the 7 kDa material to recommend its substitution for the 14-23 kDa material. Whilst it is of course true that it may be obvious to pursue two parallel lines of enquiry, it would be surprising if the skilled team were to consider it worthwhile to do so when the uncertainty surrounding which of the two candidates was in fact being tested was shortly to be dispelled.

33. Secondly, there was, as Dr Coles pointed out, a downside to departing from the 14-23 kDa material which had been the subject of the earlier trials. That was the material for which the best safety and efficacy data existed. Embarking on the development of the 7 kDa material without knowing where it would stand on safety and efficacy would risk developing a product which would throw away what had been established thus far.

34. Finally, copolymer-1 had been developed to mimic MBP. The change from 14-23 kDa to 7 kDa would move it further away from MBP, and therefore might have an effect on efficacy.

35. It follows that I do not think there was any logical fallacy in the judge's approach. There was ample evidence on which to base a finding that, despite the reference to it in Johnson 1994, the 7 kDa material was not an obvious candidate for further testing in May 1995. I would reject this ground of appeal.

Lack of technical contribution: legal issues

36. Mylan also advance a case of obviousness by challenging the technical contribution propounded by the patent. This gives rise to an issue of law. The judge held that if a patent specification made a technical effect "plausible", it was not open to Mylan to mount a challenge to the existence of that effect by the use of later evidence. In order to understand why he did so it is necessary to review some authority, in the European Patent Office ("EPO") and here.

37. Neither the European Patent Convention ("EPC") nor the Patents Act 1977 includes amongst the available grounds of invalidity of a granted patent an objection that the patent does not make a technical contribution to the art. However the "problem and solution" approach adopted by the EPO under the EPC to the ground of lack of inventive step necessarily involves isolating from the patent (in comparison with the prior art) some technical contribution or effect. The EPO adopt this approach in order to formulate a technical problem which is solved by the patent - achieving that technical effect - as a precursor to asking whether the patent solves that problem in an obvious or non-obvious way.

38. The problem and solution approach is summarised in the EPO's own publication "Case Law of the Boards of Appeal of the European Patent Office" 6th Edition 2010, in the following terms:

> "To assess inventive step, the boards normally apply the "problem and solution approach". This consists essentially of:
>
> (a) identifying the "closest prior art",
>
> (b) assessing the technical results (or effects) achieved by the claimed invention when compared with the "closest state of the art" established,
>
> (c) defining the technical problem to be solved as the object of the invention to achieve these results, and
>
> (d) examining whether or not a skilled person, having regard to the closest state of the art, would have suggested the claimed technical features in order to obtain the results achieved by the claimed invention."

39. As with any consideration of obviousness, the technical results or effects must be shared by everything falling within the claim under attack. This follows from the fundamental principle of patent law, which underpins many of the grounds of objection to validity, that the extent of the monopoly conferred by a patent must be justified by the technical contribution to the art. If some of the products covered by a claim demonstrate a particular property, but others do not, then the technical problem

cannot be formulated by reference to that property. Either the products which do not exhibit the property must be excised from the claim by amendment, or the problem must be formulated by reference to some other, perhaps more mundane, technical contribution common to the whole claim.

40. These principles emerge from the decision of a Board of Appeal of the EPO in *AgrEvo* T 939/92; [1996] EPOR 171. In that case the claim was to a very large class of chemical compounds said to possess herbicidal activity. In the proceedings leading to the appeal, the Board of Appeal questioned the applicant as to whether it was credible that *all* the claimed compounds had a herbicidal effect. The Board also informed the applicant of their view that, absent a herbicidal effect, they might well have regarded the claimed compounds, and thus the invention, as mere products of conventional synthetic methods. One argument deployed by the applicant was that the prior art, which disclosed similar compounds having herbicidal activity, would not have suggested the claimed compounds, because even small changes in chemical structure could have a significant effect on activity. The applicant argued that, even if the claims included compounds with no technically useful properties, the objection of lack of inventive step did not provide a basis for invalidating the claims (see Summary of Facts and Submissions at V). The Board's reasoning in relation to this argument is illuminating:

> "2.4 …During the oral proceedings the Appellant argued that the only question arising under Article 56 EPC in the present case was whether or not, in the light of the above state of the art, a skilled person would have prepared, or tried to prepare, the claimed compounds of formula I (see point IV above), wherein R3 was optionally substituted phenyl. Article 56 did not expressly require, so he submitted, that the subject matter of a patent application had to solve a technical problem, and that, accordingly, the issue of inventive step had to be decided without regard to the solution of any technical problem.
>
> 2.4.1 Whilst the Board agrees with the Appellant that the above question is the one which has to be answered under Article 56 EPC, it does not agree with his inference that the existence of a technical problem and its solution, including the problem of proposing alternatives to known activities (e.g. chemical processes) or physical entities (e.g. chemical compounds), is irrelevant to answering this question and so deciding the issue.
>
> 2.4.2. The reason for this is, that it has for long been a generally accepted legal principle that the extent of the patent monopoly should correspond to and be justified by the technical contribution to the art (see T 409/91, OJ EPO , No. 3.3. and 3.4 of the reasons, and T 435/91, OJ EPO 1995, 188, reasons No. 2.2.1 and 2.2.2). Now, whereas in both the above decisions this general legal principle was applied in relation to the extent of the patent protection that was justified by reference to the requirements of Articles 83 and 84 EPC, the same legal principle also governs the decision that is required to be made under Article 56 EPC, for everything falling within a valid

> claim has to be inventive. If this is not the case, the claim must be amended so as to exclude obvious subject-matter in order to justify the monopoly. Moreover, in the Board's judgment, it follows from this same legal principle that the answer to the question what a skilled person would have done in the light of the state of the art depends in large measure on the technical result he had set out to achieve. In other words, the notional "person skilled in the art" is not to be assumed to seek to perform a particular act without some concrete technical reason: he must, rather, be assumed to act not out of idle curiosity but with some specific technical purpose in mind.
>
> 2.4.3 For this reason, the Boards of Appeal consistently decide the issue of obviousness on the basis of an objective assessment of the technical results achieved by the claimed subject-matter, compared with the results obtained according to the state of the art. It is then assumed that the inventor did in fact seek to achieve these results and, therefore, these results are taken to be the basis for defining the technical problem (or, in other words, the objective) of the claimed invention (which problem may, as already stated above, be to provide a further - or alternative - process or physical entity, here a group of chemical compounds). "

41. The Board went on to reason that if all the compounds did not possess the technically useful property, then the technical problem would be "*the mimimalist one … namely the mere provision of further (or alternative) chemical compounds as such, regardless of their useful properties.*" The applicant's response to this was that, in such a situation the skilled person would face the possibility of making thousands of chemical compounds, and his particular selection could be regarded as inventive, even if arbitrary. The Board refuted the suggestion that one could claim as inventive an arbitrary selection of compounds to make from amongst these theoretical possibilities:

> "2.5.3 This argument must, however, fail, since in the Board's judgment the answer to the question as to what a person skilled in the art would have done depends on the result he wished to obtain, as explained in point 2.4.2 above. If this result is only to be seen in obtaining further chemical compounds, then all known chemical compounds are equally suitable as the starting point for structural modification, and no inventive skill needs to be exercised in selecting, for instance, the compound of formula XIV of D3 for this purpose. …
>
> It follows from these considerations that a mere arbitrary choice from this host of possible solutions of such a "technical problem" cannot involve an inventive step (see also e.g. T 220/84 of 18 March 1986, No. 7 of the reasons). In other words, the Board holds that, in view of the underlying general legal principle set out in point 2.4.2 above, the selection of such compounds, in order to be patentable, must not be arbitrary but must be justified by a hitherto unknown technical effect which

> is caused by those structural features which distinguish the claimed compounds from the numerous other compounds.
>
> 2.5.4 It follows directly from these considerations that a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the selected compounds."

42. The Board found the patent to be obvious on this basis, the onus lying on the applicant to establish (in those pre-grant proceedings) that the claimed compounds had the properties claimed for them.

43. In *Johns Hopkins University School of Medicine/ Growth Differentiation Factor* T 1329/04 [2006] EPOR 8, the Board of Appeal dealt with the question of the extent to which the technical effect relied upon needed to be supported by evidence disclosed in the specification or could be proved by later evidence. The rule established by that case was that an effect could be relied on if the specification disclosed enough to make the relevant effect "plausible". At [12] of their reasons the Board said:

> "12. The appellant filed post-published evidence … establishing that GDF-9 was indeed a growth differentiation factor. This cannot be regarded as supportive of an evidence which would have been given in the application as filed since there was not any. The said post-published documents are indeed the first disclosures going beyond speculation. For this reason, the post-published evidence may not be considered at all. Indeed, to do otherwise would imply that the recognition of a claimed subject-matter as a solution to a particular problem could vary as time went by. Here, for example, had the issue been examined before the publication date of the earliest relevant post-published document, GDF-9 would not have been seen as a plausible solution to the problem of finding a new member of the TGF-Beta superfamily and inventive step would have had to be denied whereas, when examined thereafter, GDF-9 would have to be acknowledged as one such member. This approach would be in contradiction with the principle that inventive step, as all other criteria for patentability, must be ascertained as from the effective date of the patent. The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve. "

44. *AgrEvo* has been considered in a number of cases in this jurisdiction. In *Conor Medsystems Ltd v Angiotech Pharmaceuticals Inc* [2008] UKHL 49; [2008] RPC 28 the patent claim was for a coronary stent coated with the drug taxol and suitable for

preventing restenosis of the artery into which it was placed. The trial judge, Pumfrey J, and the Court of Appeal had held the patent obvious. They had approached the question of inventive step on the basis of a somewhat diluted version of what was claimed on the grounds that they did not consider that the patent specification demonstrated that the claimed stent would work, merely that it was predicted to be worth trying. Accordingly Pumfrey J and the Court of Appeal had tested inventive step on the basis that a taxol coated stent might work to prevent restenosis, not that it did. Lord Hoffmann rejected this approach: see [28]. Lord Hoffmann went on to refer to the *AgrEvo* line of authority. At [36] he said that that case, and *Johns Hopkins,* were far from the facts of *Conor*. In *Conor*:

> "The specification did claim that a taxol coated stent would prevent restenosis and Conor did not suggest that this claim was not plausible. That would have been inconsistent with the evidence of its experts that taxol was just the thing to try. It is therefore not surprising that implausibility was neither pleaded nor argued. The same was true of the proceedings in the Netherlands (see paragraph 4.17 of the judgment)."

45. Thus there was no attempt in *Conor* to show that a taxol coated stent would not in fact represent a technical contribution to the art. Conor had been trying to establish that the technical effect had not been demonstrated sufficiently in the specification of the patent. They had not (and could not have) gone as far as to say that the idea was not plausible, or that it did not work in fact. It is in this context that Lord Hoffmann says at [37] :

> "The Court of Appeal upheld the judgment of Pumfrey J on the ground that the patent contained no "disclosure" saying that taxol was specially suitable for preventing restenosis. Again, I agree that the description, though offering a theory (its anti-angiogenic properties) as to why taxol would prevent restenosis, did not offer any evidence that this would turn out to be true. If it had not turned out to be true, the patent would have been insufficient. But there is in my opinion no reason as a matter of principle why, if a specification passes the threshold test of disclosing enough to make the invention plausible, the question of obviousness should be subject to a different test according to the amount of evidence which the patentee presents to justify a conclusion that his patent will work."

46. I do not read anything in Lord Hoffmann's speech as casting any doubt on the approach to obviousness established by *AgrEvo*. It is true that Lord Hoffmann says that if the predictions in the patent had turned out not to be true, the patent would have been insufficient, but he does not say that the invention could not have been attacked on the *AgrEvo* basis as well because it made no, or alternatively some much more modest, technical contribution to the art. The focus in *Conor* was on what needs to be shown by the specification.

47. In *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly and Co Ltd* [2010] RPC 9 the Court of Appeal was concerned with the rules which apply where a patent is sought for a compound or class of compounds which are a selection from a broader class disclosed

by a prior document. Jacob LJ summarised the approach of the EPO to that question at [50] as being:

> "Has the patentee made a novel non-obvious technical advance and provided sufficient justification for it to be credible? This is the basis of all the reasoning - see e.g. [2.4.2] of *AgrEvo*. A selection which makes a real technical advance in the art is patentable."

48. Later he explained the basis of the rule against "arbitrary" selection as being found in the guiding principle "is there a real technical advance?"

49. I would summarise the position thus far in the following way:

i) Article 56 of the EPC is in part based on the underlying principle that the scope of the patent monopoly must be justified by the patentee's contribution to the art;

ii) If the alleged contribution is a technical effect which is not common to substantially everything covered by a claim, it cannot be used to formulate the question for the purposes of judging obviousness;

iii) In such circumstances the claim must either be restricted to the subject matter which makes good the technical contribution, or a different technical solution common to the whole claim must be found;

iv) A selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious because it does not make a real technical advance;

v) A technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step;

vi) Later evidence may be adduced to support a technical effect made plausible by the specification;

vii) Provided the technical effect is made plausible, no further proof of the existence of the effect is to be demanded *of the specification* before judging obviousness by reference to the technical effect propounded.

50. None of the authorities thus far addresses the question of what happens in relation to the objection of inventive step when it turns out that a technical property or effect made plausible by the specification turns out not to exist in fact. Mr Waugh argued successfully before the judge that later evidence cannot be adduced to *contradict* the existence of the plausible effect. He did so by reference to the *Johns Hopkins* rule, that later evidence could not be adduced to *support* an effect not made plausible by the specification (although it can be adduced to lend further support to a plausible effect). If so, says Mr Waugh, it cannot be adduced to contradict a plausible effect either. Mr Acland submitted that later evidence is admissible to contradict the effect made plausible in the specification.

51. The judge recorded at [343] that there was no dispute that if the patent, when read with the skilled person's common general knowledge, did not disclose enough to make it plausible that the invention solved the technical problem, then that was the end of the matter, and it was not permissible for the patentee to rely upon evidence which post-dated the patent to demonstrate the technical effect. He identified the dispute as being over a second proposition advanced by Mylan, namely whether, if the patent did make the invention plausible, it remained open to the other party to cast doubt on this by post-dated evidence. At [350], having reviewed some EPO cases and a decision of his own in *Sandvik Intellectual Property AB v Kennametal* [2011] EWHC 3311 (Pat), he concluded as follows:

> "In my judgment, however, these decisions represent the limits to which post-dated evidence may properly be put. In short, post-dated evidence may be relied on to confirm that the disclosure in the patent either does or does not make it plausible that the invention solves the technical problem. Post-dated evidence may not be relied upon either to establish a technical effect which is not made plausible by the specification in order to rebut an allegation of obviousness or to contradict a technical effect which is made plausible by the specification in order to found an allegation of obviousness. In my view it would be bizarre if, as counsel for Mylan submitted, a patent which at the time it was applied for disclosed what everyone thought was a good invention could be revoked 20 years later because subsequent advances in science had revealed that in fact the invention did not solve the technical problem. "

52. I would start from the proposition that, in general, evidence may be deployed if it is relevant to a matter properly in issue between the parties. Evidence that the claimed invention does not in fact result in a particular technical advance will be admissible if, under Article 56 EPC, one of the issues which may properly and relevantly arise is whether the patentee has made the technical advance on which he relies. I think there are a number of reasons why, under Article 56, it is relevant to ask whether the alleged technical contribution has in fact been made.

53. Firstly, the problem and solution approach suggests, by its very name, that it is an approach which shows that the patentee has in fact provided a solution to a problem.

54. Secondly, and more importantly, the underlying principle which the problem and solution approach to Article 56 seeks to encapsulate and promote is that the patentee's monopoly must be justified by his contribution to the art. It would be a surprising result if the effect of applying this approach was that a monopoly could be justified by reference to an alleged contribution which could be demonstrated not to exist in fact.

55. Thirdly, if all that the patentee has contributed is a plausible but untrue prediction, this is the very antithesis of a contribution. What he would have contributed is a suggestion that something might plausibly work. But as Lord Hoffmann said in *Conor* at [28]:

> "It is hard to see how the notion that something is worth trying or might have an effect can be described as an invention in respect of which anyone would be entitled to a monopoly"

56. Fourthly, as shown by *AgrEvo*, if the patentee is inviting the court or tribunal considering its patent to assess inventive step by reference to a claimed technical contribution or effect, the issue for the court will be whether it was obvious to adopt the technical features of the invention in order to achieve that contribution or effect. In general, the greater the quantum of the technical contribution, the more difficult it will be for the party attacking the patent to show that the invention was obvious. It seems to me to be wrong in principle not to allow a challenge on the facts to the existence of the technical effect relied on by the patnetee.

57. Fifthly, Jacob LJ in *Dr Reddy's*, albeit in the context of the selection of compounds from a prior disclosed class, posed the test in terms of "a real technical advance". In the same case he cited with apparent approval the reasoning in 2.4.2 of *AgrEvo*, drawing on the "*generally accepted legal principle that the extent of the patent monopoly should correspond to and be justified by the technical contribution to the art*."

58. Sixthly, there is support for this view in the judgment of Kitchin LJ in *Regeneron and another* v *Genentech Inc* [2013] EWCA Civ 93. In that case he observed at [96] that the requirement of sufficiency of description is another aspect of the well established principle that the scope of the monopoly must correspond to the technical contribution to the art. That requirement may be satisfied if it is possible to make a reasonable prediction that the invention will work - it is not necessary for the patentee to prove that everything falling within the claim will work: see [100]. However at [101] he went on to say this:

> "On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose." (emphasis supplied)

59. The judge at [348] of his judgment in the present case supported his conclusion that evidence was not admissible to contradict a technical effect made plausible by the specification by reference to "*the fundamental principle … that whether a claimed invention is obvious or not should be judged as at the priority or application date.*" He went on to say at [350]:

> "it would be bizarre if, as counsel for Mylan submitted, a patent which at the time it was applied for disclosed what everyone thought was a good invention could be revoked 20 years later because subsequent advances in science had revealed that in fact the invention did not solve the technical problem."

60. I do not dispute for one moment the fundamental principle which the judge identified. The evidence which is relied on to show that the invention was an obvious step for the skilled person to take must, plainly, be evidence which would have been available to the skilled person at the time. But in order to determine whether an invention is obvious at the priority date one needs to decide an anterior, and purely factual question: what is the invention?

61. There is, of course, no general principle that *all* the evidence which is admitted on the issue of obviousness must be evidence which was available at the priority date. Thus, it is well settled that the reaction of those skilled in the art to the invention (something which occurs after the priority date) can be secondary evidence of inventiveness. So, in *Schlumberger Holdings Limited v Electromagnetic Geoservices A/S* [2010] EWCA (Civ) 819 Jacob LJ said at [81]:

> "Another important matter to consider is the reaction of experts at the time of the invention, both before and after."

62. Equally it is common to admit evidence of subsequent commercial success, although it is necessary to make sure it is commercial success of the invention: see *Schlumberger* at [79] to [80] referring to Laddie J's lucid explanation of the principles in *Haberman v Jackel* [1999] FSR 683. Similarly, the fact that a defendant has later copied, or applied to patent the invention himself, may be factors of weight in appropriate cases: see as to patenting e.g. *Unilever v Chefaro* [1994] FSR 567. One of the matters often taken into account in assessing obviousness has always been whether the invention brings with it important practical benefits. Fletcher Moulton LJ made clear the importance of the practical consequences of the invention (which might only be demonstrated later) in *British Westinghouse Electric & Manufacturing Co. v Braulik* (1910) 27 RPC at 230:

> "I confess I view with suspicion arguments to the effect that a new combination, <u>bringing with it new and important consequences in the shape of practical machines</u>, is not an invention, because, when it has once been established, it is easy to show how it might have been arrived at by starting from something known, and taking a series of apparently easy steps." (emphasis supplied)

63. The problem and solution approach to obviousness requires the court or tribunal to judge inventiveness by reference to what it is that the invention brings with it: its technical effect or advance. Like any other fact relevant to an issue, however, it must be open to being refuted. In doing so one is not judging the obviousness of the claimed invention by reference to later evidence: one is simply defining by evidence what it is that the invention is or brings with it.

64. The rule in *John Hopkins* that a technical effect relied upon must be made plausible by the specification, and cannot be established for the first time by subsequent evidence, was not in issue before the judge and is not in issue in this appeal, and I need say no more about it. It is sufficient to say that it does not provide a basis for the different rule arrived at by the judge as to whether subsequent evidence may be used to negate an effect made plausible by the specification. I respectfully disagree with the judge when he concluded that it was not open to Mylan to challenge an effect

made plausible by the specification. For my part, I cannot see any principled objection to the admission of evidence as to the true nature of the advance made by the invention in connection with an objection of lack of inventive step.

65. The mere fact that the primary technical contribution relied upon by the patentee is negated by evidence does not of course lead inexorably to the conclusion that the patent is obvious. The patentee may advance an alternative less ambitious technical contribution of the kind discussed in *AgrEvo*. The party attacking the patent will still have to persuade the court that that invention was obvious, and do so by reference to what the skilled team would have known and done at the priority date. In the present case, however, Mr Waugh was content to put his case on the basis of the inventive contribution propounded in the patent. He did not, for example, argue in the alternative that the invention simply provided further compounds of the same activity as copolymer-1.

The technical contribution propounded by the patent

66. The judge held at [359] that the technical contribution claimed in the patent lay in "the proposition that copolymer-1 as claimed caused (not might cause) less irritation at the injection site and/or a reduced incidence of systemic side effects." The case was conducted on that basis.

Was the technical contribution made plausible by the specification?

67. The judge carefully analysed the disclosure of the examples in the specification. Based on the specific disclosure of the mouse lethality test in Example 2A, he found at [363] that it was made plausible that copolymer-1 with an average molecular weight of 7.3 or 8.4 kDa and less than 2.5% over 40 kDa is less toxic in mice than copolymer-1 with an average molecular weight of 22 kDa and more than 5% over 40 kDa. Based on the specific disclosure of the RBL degranulation assay in Example 2B, he found at [370] that it was made plausible that copolymer-1 with an average molecular weight of 6.25 and 7.3 kDa and less than 2.5% over 40 kDa causes less degranulation in vitro than copolymer-1 with an average molecular weight of 13 or 14.5 kDa and more than 5% over 40 kDa.

68. Before the judge Mylan pointed out, and the judge accepted, that these results do not strictly support the claims, in that claim 1 requires that more than 75% of the fraction is within a molecular weight range 2-20 kDa, whereas Example 2B is silent in that respect. Moreover claim 1 suggests that the critical threshold of species having a molecular weight of more than 40 kDa is 5%, whereas Example 2B does not disclose the actual percentage of such species.

69. The judge held at [372] that the lack of strict support for the limits of the claim did not matter. The general trend disclosed by the results made it plausible that as a general proposition the claimed copolymer-1 was superior to copolymer-1 falling outside the claim. There was a degree of arbitrariness as to where one drew the line, but that was not fatal. He also accepted that the skilled person would not be able to predict whether or to what extent the three-fold increase in degranulation between the 7.3 kDa and 13 kDa batches in the example was occasioned by the difference in average molecular weight or the difference in % species over 40 kDa. Furthermore, the skilled person would have had no means of knowing or predicting the level of

degranulation if the percentage of species over 40 kDa were to be in the range 2.5-5 %.

70. Mylan's submission was that the judge fell into error in holding that the discrepancy between the specific disclosure and the specific limits of the claim did not matter. The difficulties of prediction which the judge found meant that it was not made plausible that all the material falling within the claim would be superior to material falling outside it. I was not persuaded that the judge fell into error in this respect. The judge was entitled to reach the conclusion that it was made plausible that there was a connection between lower molecular weight and reduced toxicity and reaction. By specifying that 75% of the fraction is within the range 2-20 kDa and that no more than 5% is over 40 kDa, the patentee is making a claim to material of lower molecular weight than was known to have been used. The fact that the skilled person would not have been able to predict the level of degranulation at any particular point in the claim does not detract from the plausibility of the general proposition.

Technical contribution in fact?

71. The analysis of whether the invention in fact made a technical contribution involved a review of published clinical trials data. The early trials to which I have already referred (e.g. Bornstein 1987) used material with a molecular weight in the range 14-23 kDa, whilst later trials (such as Johnson and subsequent trials) used 7 kDa material. None of these trials involved a direct head to head comparative trial of the two materials. Such a comparative trial would have been the most scientifically valid approach to establishing whether the difference in molecular weight was responsible for a difference in toxicity or allergic reaction.

72. The judge heard evidence from expert statisticians who had examined the results of the trials on various different bases in order to attempt to see whether any statistically significant difference could be observed between the results for the 7 and the results for the 14-23 kDa material. The statisticians concluded that the material available was inconclusive. There was no evidence of a difference. That is, as Mylan accepts, not the same thing as positive evidence that the two materials have equivalent tendency to cause side effects. No evidence of a difference is not the same thing as evidence of no difference.

73. Mylan's case that there was in fact no difference between the two materials depended on whether it was legitimate for their expert clinician, Dr Coles, to express a view on the basis of the clinical trials independently of any statistical support. He had concluded in paragraph 7.35 of his first report that:

> "These clinical trial analyses include up to 957 patients on Cop-1 compared to up to 642 patients on placebo. I believe this is enough to assess whether there is, in fact, a clinically meaningful difference between the local and systemic adverse effect profiles of the Earlier Cop-1 and the Later Cop-1. By "clinically meaningful difference", I mean a difference which will influence clinical decision-making. I conclude that there is no such clinically meaningful difference between the adverse effects profiles of the Earlier Cop-1 and the Later Cop-1 and that a reduction in molecular weight of Cop-1 from that used in

> the Bornstein 1987 and 1991 studies does not lead to a reduction in the adverse effects as the Patent claims."

74. In cross-examination Dr Coles confirmed that his view was not merely that there was no evidence of a difference but that there was evidence of no difference.

75. The judge declined to accept Dr Coles' evidence and concluded, therefore, that Mylan (to use the double negative) had not proved that difference in molecular weight made no difference. Mr Acland submitted that the judge had no basis on which to reject Dr Coles' evidence. Dr Coles was, he submitted, expressing his views based on his experience of using clinical trials data to direct his clinical prescribing. He was accordingly qualified to express an expert opinion independently of the statisticians.

76. I think that the judge was entitled to reject Dr Coles' evidence. Dr Coles relies on the number of patients on copolymer-1 as compared with the number on placebo. That, of course, tells one nothing about the reliability of any comparison between the two types of copolymer-1. We were told that 76 out of the 947 patients received the high molecular weight material, namely those on the two very early trials. Whether or not that is correct, what it shows is that Dr Coles was engaged on what was essentially a statistical exercise. There was nothing in his clinical expertise which would allow him to override the judgment of the statisticians that the data was inconclusive. I would reject this ground of appeal.

Construction/insufficiency

77. The principles which apply to the construction of patent claims have been explained by the House of Lords in *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 9. There is a valuable summary of the application of those principles in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8 at [5]. The principles were not in dispute on this appeal and there is no need to repeat them here.

78. It is sometimes difficult to determine where the precise boundary of a claim lies. In such cases what matters is whether the skilled person knows what the test is he has to apply to determine infringement. The judge expressed this well in the following passage at [193]:

> "… it is necessary to distinguish between claims that are difficult to construe or that have a "fuzzy boundary" (in the words of Lord Hoffmann in *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2004] UKHL 46, [2005] RPC 9 at [126]) on the one hand from claims that are truly ambiguous on the other. It is regrettably common for claims to be difficult to construe, but the court will nevertheless strive to give such claims a sensible meaning having regard to the inventor's purpose. It is also common for claims to have a fuzzy boundary, because an integer of the claim involves some question of degree or an imprecise functional limitation. It is well established that is not itself objectionable. If a claim is truly ambiguous, so that it is unclear what is the correct test to determine whether or not a

> product or process infringes, however, then the claim is insufficient..."

79. The claims of the patent refer simply to "copolymer-1". The parties have both treated the patent at [0003] as a definition of what copolymer-1 means in the claims, i.e. "… *a mixture of polypeptides composed of alanine, glutamic acid, lysine and tyrosine in a molar ratio of approximately 6:2:5:1*."

80. The issue of construction is what the skilled person would understand the patentee to mean by "*a molar ratio of approximately 6:2:5:1*". A molar ratio of 6:2:5:1 translates into molar percentages or fractions of 42.9% alanine, 14.3% glutamic acid, 35.7% lysine and 7.1% tyrosine.

81. Mylan contended before the judge and again before us that the word "approximately" covers compositions in which the molar fraction of any single amino acid does not differ from those percentages by more than ±10% of their value. Mylan's secondary contention is that, if this is not correct, the patent fails to provide any criterion by which to determine what is covered by the word "approximately", and thus is ambiguous.

82. The problem with Mylan's construction is that it sought to place rigid numerical limitations on a claim when the patentee had chosen not to do so.

83. The respondents' contention, as recorded by the judge, was in essence that the word "approximately" reflects the fact that copolymer-1 is a random copolymer whose composition is not precisely defined. Thus the skilled reader would understand that, in this respect, the claims have a fuzzy boundary. The skilled reader would also understand that the claims embrace compositions in which the molar ratios of the amino acids (as distinct from the molecular weight distributions) correspond to those of the prior art copolymer-1 compositions referred to in the patent.

84. The problem with the respondents' construction as so summarised was that it was not really an attempt to give a meaning to the claim at all. To say that the claim is one with a fuzzy boundary which at least includes certain prior art copolymer-1 compositions does not help the skilled person to know what the claim means, or to decide, even allowing for fuzzy boundaries, where he can safely say it ends. No doubt for this reason Mr Waugh put forward a more helpful summary on this appeal, as a test for determining infringement:

> "is the ratio of amino acids in the sample in question approximately 6:2:5:1, taking into account the variation that will arise in both amino acid analysis and the synthesis of copolymer-1"?

85. The judge recorded, importantly, that it was common ground that the skilled team would appreciate that two reasons why the inventors had referred to the molar ratio as being "approximately 6:2:5:1" were to allow for the variability in amino acid analysis and to allow for the variability in syntheses of materials such as copolymer-1. He held that the burden of interpretation would primarily fall on the analytical chemist with expertise in amino acid analysis and the synthetic chemist. Professor Kent

addressed this issue for Mylan, while Professor Sampson addressed it for the Respondents.

86. The judge concluded at [219]:

> "The skilled team would consider that the word "approximately" was intended to cater for variations in both amino acid analysis and the synthesis of copolymer-1. They would proceed on the basis that the inventors might well be intending to allow for a level of error in analysis of greater than ±5%. As for the variability in synthesis, they would not think it was appropriate to take twice the variance in the analysis as marking the limit of compositions that could properly be regarded as constituting copolymer-1. They would take into account the effect of changes in molar ratio in terms of numbers of amino acids as shown by Prof Sampson's illustrations, and as a result would be inclined to accept a greater deviation in the proportion of tyrosine than in the case of the other amino acids. Accordingly, the skilled team would conclude that the claim was one that had a fuzzy boundary. It is therefore not possible to say precisely where that boundary lies. What can be said is that in my judgment the skilled team would not regard a relative difference in tyrosine of 29.6%, as in the case of batch GMA2, as taking the batch outside the claim. Furthermore, I do not consider that the claim is ambiguous."

87. There were a number of separate strands of reasoning which led the judge to this conclusion. The judge dealt with them as five sub-issues under the headings: variabilility of amino acid analysis, variability in synthesis, the documents referred to in the patent, immunogenicity of tyrosine and the manner in which differences are assessed.

88. The judge concluded at [198] that the skilled person would expect from his common general knowledge that amino acid analysis should have a reproducibility of ± 5% or better, but that in practice many laboratories did not achieve such a low level. He concluded that by using the word "approximately" the inventors "might well be intending to allow for a greater degree of experimental error than ± 5%. This finding is no longer challenged by Mylan.

89. As to the variability associated with the synthesis, Mylan's expert had said this in his report:

> "Based on the Patent alone, I understand 'approximately' to allow for the variability associated with the amino acid analysis technique and for the variability associated with the synthesis of the copolymer-1. I have explained above that if experimentally determined values for the composition of two samples differed by more than twice the variance [of the reproducibility of the amino acid analysis technique], then it is highly unlikely that the two samples have the same compositions. Therefore, I would understand 'approximately

> 6:2:5:1' to exclude any composition in which the molar fraction of any single amino acid differed by more than ± 10% from the calculated value of its molar fraction …"

90. However the judge concluded at [200] that the skilled team would not have had any knowledge of the degree of variation in the molar ratio of the four amino acids to be expected in manufacture. The synthetic chemist would be aware from the nature of the random copolymer that repeat syntheses would not result in the same composition.

91. The judge then considered what the skilled person would get from the prior art documents, US 550, Teitelbaum 1971 and Bornstein 1987. Teitelbaum 1971 disclosed two batches of copolymer-1 of differing molar ratios, the first of which was the same ratio as Bornstein 1987. He set out a table of these batches, expressed in terms of molar fraction rather than ratio to enable comparison:

	Exactly 6:2:5:1	US550 6:2:4.5:1	Teitelbaum Batch I/ Bornstein 6.0:1.9:4.7:1.0	Teitelbaum Batch II 6.7:2.1:4.2:1.0
Alanine	42.9%	44.4%	44.1%	47.9%
Glutamic acid	14.3%	14.8%	14.0%	15.0%
Lysine	35.7%	33.3%	34.6%	30.0%
Tyrosine	7.1%	7.4%	7.4%	7.1%

92. The parties deployed elaborate arguments as to why the skilled person would or would not derive from the patent, and its reference to these prior documents, a conclusion as to the permitted variability in the molar ratio for copolymer-1. The judge favoured the respondents' submissions that the skilled person would conclude that all the compositions disclosed by these documents fell within the definition "approximately 6:2:5:1". The significance of this is that the figure for lysine in Batch II of Teitelbaum 1971 differs by 16% from the figure for "Exactly 6:2:5:1". This exceeded Professor Kent's threshold of ± 10%, and therefore showed that the patentee was expressly contemplating a greater degree of variation than Professor Kent's threshold.

93. Mr Tappin submitted that in reaching this conclusion the judge lost sight of the purpose of the invention and the fact that small changes in chemical composition can effect significant changes in efficacy. Unlike Batch I of Teitelbaum 1971 which had been taken forward in Bornstein 1987, Batch II was simply reported as equally efficacious. The skilled person would accordingly not have regarded Batch II with its ratio of 6.7:2.1:4.2:1.0 (i.e, about 7:2:4:1) as approximately the same as 6:2:5:1. He relied on evidence given by Professor Kent that he would primarily be guided by Bornstein 1987, as the results reported there were for the use of copolymer-1 for treating MS in humans. He had also said that if the amino acid ratio was altered one might not get the same activity, or it might cause different side effects in humans. Dr Coles had also said that he believed the skilled person would be reluctant to change the molar ratio of copolymer-1 for fear it might adversely affect its safety or efficacy.

94. These opinions of Professor Kent and Dr Coles were not the subject of specific challenge at trial. Mr Waugh did ask Professor Kent whether he was aware of any material difference in biological activity, efficacy or side effects between a composition where the tyrosine was present at .078 as opposed to .08, to which Professor Kent replied that he had no expertise in those areas. I do not think that either witness was thereby disqualified from expressing the very general opinion that the skilled team would be concerned to avoid changes to the molar ratio of copolymer-1 for fear of losing activity, safety or efficacy.

95. However, and despite this, the information to be derived from the prior art documents does show that the expression "approximately 6:2:5:1" when construed having regard to the variability in amino acid analysis and copolymer-1 synthesis should not be limited to Professor Kent's ± 10%. It showed that the patentee regarded a batch with a molar fraction varying by 16% from 6:2:5:1 was within his "approximately" term. It also showed that the two batches made by the same method in the same laboratory could yield molar ratios in which the molar fraction of the lysine component varied by 16% from another batch. It therefore pinpointed something which fell within the claims, and was some evidence of the degree of variability.

96. The judge then dealt with a passage in the 550 patent which mentioned the immunogenicity of tyrosine. It was suggested by Mylan that this would indicate to the skilled person that variations in tyrosine greater than ± 10% would be regarded as giving rise to problems. The judge rejected this as placing too much weight on the passage. On this appeal Mr Tappin deployed this as an example of the skilled person's general knowledge that changes in composition could give rise to unwanted loss of efficacy or side effects.

97. The judge then had to resolve a dispute as to the correct approach to the assessment of differences in molar ratio. The judge identified two questions which arose for decision. The first was whether the skilled reader would consider the difference in the proportion of each amino acid as a percentage of that proportion (i.e. the difference relative to that amino acid) or the difference as a percentage of the whole composition (i.e. the difference relative to the whole). Professor Kent supported the former approach, whereas Professor Sampson supported the latter approach. The second question was whether, if the latter approach is taken, the skilled reader would proceed to make a comparison based on the total absolute difference, as Professor Sampson advocated.

98. Professor Sampson's absolute difference approach involved adding up the absolute differences in percentage molar fraction between exactly 6:2:5:1 and the sample in question (ignoring the direction of difference). On this basis she was able to show that the absolute difference for Teitelbaum Batch II was 12%, which was greater than that for any of Mylan's proposed products. This approach masked a large relative difference in the percentage of tyrosine, because the absolute amount of additional tyrosine was small in relation to the composition as a whole.

99. The judge accepted Professor Kent's approach, but disputed some of his "premises". He rejected Professor Sampson's approach as "having very little logic to it at all". Professor Kent's first premise was that "approximately" caters for variability in both amino acid analysis and synthesis. The judge accepted that proposition, and indeed it was common ground and it forms part of the respondents' case on this appeal. The

other two premises were that the variability in amino acid analysis is ±5% for each amino acid and that that figure should be doubled to allow for variability in synthesis. He rejected both these quantitative limits. Thus he explained that:

> "the skilled reader would proceed on the basis that the inventors might well be intending to allow for more than a 5% error in amino acid analysis. If the skilled reader allowed for a 10% error in analysis, Prof Kent's own logic would lead to a 20% limit; and if he allowed for a 15% error, that would lead to a 30% limit.", and
>
> "the skilled reader would appreciate from the Patent and his common general knowledge that copolymer-1 did not consist of a single species, but rather a random mixture of different species, and would note from Teitelbaum 1971 that two batches synthesised in an identical manner had appreciably different molar ratios."

100. This still left the claim fairly open ended, in the absence of any concrete evidence as to the total level of variability to be expected. So the judge turned to Professor Sampson's illustrations. Particularly important was her illustration which took the case of an illustrative copolymer-1 chain of 70 amino acids. Dividing that chain in the ratio of exactly 6:2:5:1 resulted in 30 alanines, 10 glutamic acids, 25 lysines and 5 tyrosines. If one did the same for the Mylan's product, identified as batch GMA 2, the corresponding numbers were 30, 10, 24 and 6. In other words one lysine had been swapped with a tyrosine. In doing so the molar fraction of tyrosine had been altered by 29.6%.

101. Mr Tappin submitted that the judge's approach was flawed. Professor Sampson's illustrations were illustrations of her absolute difference approach which the judge had rejected. Because tyrosine was present at a relatively low molar proportion of the composition as a whole, a small absolute change in the amount of tyrosine resulted in a very large relative change of its molar fraction. The judge had previously rejected the absolute difference approach precisely because it took no account of the relative abundance of the different amino acids. By relying on the illustrations, he was bringing the absolute difference approach back into play. Furthermore, there was no evidence that the skilled person, asking himself how much variability is permitted, would think in these terms at all.

102. The judge's approach accepted the swapping of a single amino acid as being the sort of change which the skilled person would regard as being within the term "approximately". Copolymer-1 is however a mixture of random copolymers of differing chain lengths. It is therefore conceptually wrong to think of it in the same way as a single species of defined structure and chain length for which the change of a single amino acid might represent the smallest change possible. If manufacturing tolerances result in more tyrosine ending up in the copolymer, it does not follow that the chains will all be extended by the same amount, or, more importantly, by an integer number of amino acid molecules. The amount of tyrosine which ends up in the copolymer chains is infinitely variable. Taking the example of a single tyrosine being added to the average chain is not, at first sight, a logical way of assessing the degree of variation likely to result from manufacturing variability.

103. Professor Kent had made the point when cross-examined by reference to Professor Sampson's illustrations that they were oversimplifications of complex mixtures. He also explained that the illustrations did not enable one to see non-integral changes in the number of amino acids which in a real mixture you could and did have. He also pointed out that the relevant average difference was closer to 1.5 tyrosines, but that this had not been shown on the illustration.

104. I think that there is in fact very little difficulty over the question of construction. The parties are agreed that the skilled team would understand the patentee to be using the term "approximately 6:2:5:1" to allow for variations in amino acid analysis and variability in copolymer-1 synthesis. I think that the only other evidence which was material to the question of what the skilled person would have understood that term to mean was that given by Dr Coles and Professor Kent, namely that the skilled person would be concerned that variations might affect the known efficacy and safety of co-polymer-1. Accordingly the question to be asked on infringement was whether the percentage difference from 6:2:5:1 expressed as a molar fraction in any given sample is within the variability which can arise from amino acid analysis and copolymer-1 synthesis. The skilled person would not consider a difference which exceeded such variability as being within the scope of the claim.

105. That, in my judgment, is where the question of construction ended and the question of infringement should have begun. It did not matter that the skilled person would not have known from their common general knowledge how to quantify the maximum degree of variability. That was a question for evidence. I differ with respect from the judge when he derived from Professor Sampson's illustrations the proposition that the skilled team would tolerate a greater variation in tyrosine, and that such variation could be as much as 29.6%. The evidence did not support the conclusion that the skilled team would think that the patentee was using the term "approximately 6:2:5:1" to convey this meaning.

Infringement

106. The Mylan product differs from one in which the molar ratios are 6:2:5:1 principally in the respect that the molar fraction of tyrosine is 29.6% greater in the Mylan product. It will be recalled that Mylan sought a declaration of non-infringement. As I have explained above, the judge made a finding that the difference was not sufficient to take the Mylan product outside the claim. Accordingly he made a positive finding that the product did infringe, and on that basis made an order dismissing the part of Mylan's action which sought a declaration of non-infringement.

107. In the light of the discussion above of the issue of construction, I would not have felt justified in reaching the conclusion which the judge did on the basis of Professor Sampson's illustrations, which I do not regard as having a role to play either in construing the claim or arriving at a conclusion on infringement.

108. Nevertheless, the burden of establishing non-infringement fell on Mylan. It was necessary for Mylan to establish that, in the case of their proposed product, the percentage differences from the molar fractions of a 6:2:5:1 copolymer-1 exceeded those which one could expect from the variability due to amino acid analysis and copolymer-1 synthesis.

109. In my judgment Mylan did not adduce sufficient evidence to justify a finding that they did not infringe. Teitelbaum 1971 itself was some evidence of the degree of variability that could occur in copolymer synthesis, with a variation of 16% in the molar fraction of one of the amino acids. Moreover, the evidence did not establish that errors due to amino acid analysis would always be 5% or less.

110. There was, in my judgment, no evidence to show that a 29.6% variation in the molar fraction of one amino acid is greater than that which could occur from amino acid analysis and copolymer-synthesis. That was the relevant question on infringement, and the evidence did not provide the answer to it.

111. It follows that, although I reach the conclusion which I do by a different route, I consider that the judge was right to refuse the declaration of non-infringement. It also follows that his appeal against his order refusing the declarations must be dismissed.

Ambiguity-type insufficiency

112. The judge rejected the allegation of ambiguity-type insufficiency. I would do so as well. I have been able to come to a conclusion as to what the claim means. The fact that the evidence does not allow one to come to a conclusion on non-infringement is not the fault of the claim. Mylan's difficulties do not arise because the claim is ambiguous, but because they failed to establish that the differences between their product and one which has an amino acid molar ratio of 6:2:5:1 could not be attributed to errors of amino acid analysis or copolymer synthesis.

Conclusion

113. For the reasons given above, the judge was right to dismiss the revocation action and to refuse the declaration of non-infringement.

Lord Justice Kitchin

114. I agree.

Lord Justice Moses

115. I also agree.