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Case No: HC11C00459

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 11 July 2012

Before :

THE HON MR JUSTICE ARNOLD

- -

Between :

GENERICS [UK] LIMITED trading as MYLAN	**Claimant**
- and -	
(1) YEDA RESEARCH AND DEVELOPMENT CO. LTD **(2) TEVA PHARMACEUTICAL INDUSTRIES LIMITED**	**Defendants**

- -
- -

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

Hearing dates: 14-18, 21-25, 29-31 May 2012

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE HON MR JUSTICE ARNOLD

MR JUSTICE ARNOLD :

Contents

Introduction

1. In this action the Claimant ("Mylan") seeks revocation of European Patent (UK) No. 0 762 888 ("the Patent") and a declaration of non-infringement. The First Defendant ("Yeda") and the Second Defendant ("Teva") are respectively the proprietor of, and the exclusive licensee under, the Patent. The Patent relates to a material known as copolymer-1 which was first described in 1971. Teva sells a product which it claims is protected by the Patent under the trade mark Copaxone (non-proprietary name glatiramer acetate) for the treatment of relapsing-remitting multiple sclerosis ("MS"). The purpose of this action is to enable Mylan to clear the way for the launch of its own generic glatiramer acetate in the United Kingdom.

2. The action raises a large number of issues. These can be broadly summarised as follows;

    i) whether the claims are entitled to the first claimed priority date of 24 May 1994 or whether they are only entitled to the application date of 23 May 1995;

ii) whether the Patent is invalid for obviousness over the prior art;

iii) whether the Patent is invalid for obviousness as making no technical contribution, but rather being an arbitrary selection from the known copolymer-1 material;

iv) whether the Patent is invalid for insufficiency because the claims are ambiguous;

v) whether the Patent is invalid for insufficiency on classical grounds;

vi) whether the Patent is invalid for insufficiency because it makes no technical contribution;

vii) whether the Patent is invalid for added matter; and

viii) whether the sale of Mylan's glatiramer acetate product would infringe any of the claims of the Patent.

3. Partly as a result of the nature of the invention claimed in the Patent and partly as a result of the very broad range of issues, the action has involved expert evidence from experts in an unusually wide range of disciplines. The result was a trial lasting 12 days (spread over 13 days, not including the court's pre-reading time). It follows that this judgment is necessarily rather long. (For comparison, the combined length of the parties' written closing submissions is 947 paragraphs and 266 pages.)

4. It is convenient to mention at this point that there has been parallel litigation in other countries, and in particular the USA.

Technical background

5. As indicated above, the action involves a number of different areas of science and technology. In this section I will introduce the technical background topic by topic.

Multiple sclerosis

6. MS is an autoimmune disease. Autoimmune diseases are ones in which the body's immune system malfunctions and is no longer able to make the distinction between the body's own and foreign antigens. The result is that the body's immune cells attack structures in the body itself. In MS there is an inflammatory response that leads to the removal of the sheath around nerves. As this sheath is comprised of the protein myelin, this process is referred to as "demyelination". Without the insulation provided by the myelin sheath, the nerve cells are not able to function correctly and control motor functions or to receive and relay information from the sensory systems. As MS progresses, it causes multiple lesions or scleroses to form on the brain and spinal cord, hence the name. MS is a chronic and progressive disease. The neurological effects, progression and disabilities associated with the disease are diverse. They include cognitive, motor and sensory impairments.

7. The clinical hallmarks of MS typically start in young adulthood. MS is usually characterised by episodes of neurological symptoms (called "relapses") which often recover (or "remit"). This is referred to as "relapsing-remitting" MS (previously

referred to as "exacerbating-remitting" MS). Over time, however, there is less recovery after relapses, leaving patients with increasingly persistent deficits. At about the age of 40, the relapses become less frequent and the patient enters a phase of "secondary progression" in which he or she experiences slow accumulations of disability between relapses. A much rarer form of MS is "primary progressive" MS. This resembles the secondary progressive disease, but without the preceding relapses.

8. The causes of MS were not known in 1994, and are still not known even today. Amongst the possible candidates are viral infections, genetic susceptibility to immune disorders, trauma, inadequate blood supply to the brain, diet, climate and other environmental factors. There is evidence, however, that its causes are complex and multifactorial, with factors such as the environment and the genetic susceptibility of the individuals implicated.

Experimental allergic encephalitis

9. The most widely used animal model for MS in 1994 was experimental allergic encephalitis ("EAE"). EAE is an autoimmune disease which resembles MS. It can be induced in a number of animal species, including mice, rats, guinea pigs, rabbits and primates, by the injection of brain or spinal cord tissue. The encephalitic agent was identified in the early 1960s as myelin basic protein ("MBP"), thus enabling EAE to be induced by administration of MBP. The immune response destroys the myelin in the central nervous system and the animals show increasing symptoms of neurological failure.

Treatments for MS

10. Until the early 1980s, MS was considered largely untreatable. Initially, general immune suppressants (such as corticosteroids) were used without much success. In 1981, it was shown that interferon β-1b injected into the spinal fluid could reduce the rate of attacks of the disease. A Phase III trial of interferon β-1b in subcutaneous form reported positive results in 1993. β- interferon (under the trade marks Betaferon and Betaseron) was licensed in the USA in 1993 and in Europe in 1995 as the first disease-modifying drug to be approved for MS. The second drug to be approved for MS was copolymer-1.

Copolymer-1

11. Copolymer-1 is a synthetic polypeptide. 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. Copolymer-1 (sometimes referred to as "cop-1" or "cop 1") was developed in the late 1960s by Professor Ruth Arnon, Professor Michael Sela, Dr Dvora Teitelbaum and colleagues at the Weizmann Institute of Science ("WIS") in Israel. Yeda is WIS's commercial exploitation arm.

12. Copolymer-1 was initially developed in order to induce EAE in an animal model so that the disease mechanism could be studied. For this reason it was designed to mimic MBP. However, copolymer-1 failed to induce EAE. The WIS 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 is one of the items of prior art relied upon by Mylan.

Teitelbaum 1971

13. The disclosure of Teitelbaum 1971 is accurately and conveniently summarised in the abstract:

> "Three random basic copolymers of amino acids were tested for their effect on experimental allergic encephalomyelitis (EAE). One of these copolymers denoted as Cop 1, composed of alanine, glutamic acid, lysine and tyrosine, with a molecular weight of 23 000, showed a marked suppressive effect on the disease. The intravenous administration of Cop 1 in physiological saline, as late as 5 days following the challenge with the disease-inducing dose of the basic encephalitogenic protein, reduced the clinical incidence of EAE from 64 % in the control group to 22 %; the histological lesions were also decreased both in prevalence and in severity. The suppressive effect on the disease attained by the synthetic copolymer is of the same order of magnitude as that previously reported for the basic encephalitogen.
>
> The effect of the copolymers appears to be specific, since neither an acidic amino acid copolymer, nor unrelated basic proteins, had any protective action. On the other hand, a second batch of Cop 1 showed activity identical to that of the first batch. The potential applicability of this non-encephalitogenic and non-immunosuppressive material is discussed."

14. The preparation of copolymer-1 is described as follows:

> "**2.3. Copolymers**
>
> Four different random copolymers of amino acids were used in this study. Three were rich in basic amino acids, whereas the fourth one was an acidic copolymer. They were prepared from the N-carboxyanhydrides of the respective amino acids according to Katchalski and Sela [11].
>
> **2.3.1. Copolymer 1**
>
> Cop 1 was prepared from the N-carboxyanhydrides of tyrosine [12], alanine [13], γ-benzyl glutamate [14], and ε**,** N-trifluoroacetyllysine [15] (Table 1). The polymerization reaction was carried out at room temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl groups of the glutamic acid was carried out with hydrogen bromide in glacial acetic acid [16], and was followed

> by the removal of the trifluoroacetyl groups from the lysine residues by 1 M piperidine [171] A second batch of this polymer was prepared in an identical manner. The molecular weight and amino acid composition of these polymers are listed in Table 1."

15. The "molecular weights" for Batch I and Batch II of copolymer-1 set out in Table 1 are 23,100 and 22,800 respectively. The method by which these were determined is described in paragraph 3.7 as follows:

> "The average molecular weights of the polymers were determined, in a Spinco model E ultracentrifuge, from sedimentation and diffusion measurements, as described earlier [24], and by the approach to equilibrium technique of Yphantis [29]."

16. The molar ratios of the amino acids for Batch I and Batch II of copolymer-1 set out in Table 1 are 6.0:1.9:4.7:1.0 and 6.7:2.1:4.2:1.0 (alanine:glutamic acid:lysine:tyrosine) respectively. Paragraph 3.8 describes the method by which the amino acid analyses were carried out as follows:

> "Were carried out in a Beckman-Spinco automatic amino acid analyzer, Model 120-B, after hydrolysis of the samples under reduced pressure in constant boiling hydrochloric acid (6N) for 22 h [28]."

17. Teitelbaum 1971 also describes the preparation of copolymer-2 and copolymer-3 from seven and 12 different amino acids respectively. The best results were obtained with copolymer-1. As indicated in the abstract, the two batches of copolymer-1 were found to have very similar activities: see paragraph 4.5 and Table 8.

Techniques for testing copolymer-1

18. A number of techniques have been used to test the efficacy and safety of copolymer-1 apart from clinical trials. The four which are relevant for present purposes are as follows.

19. *Suppression of EAE.* As indicated above, copolymer-1 was originally identified as an inhibitor of EAE. The biological activity of copolymer-1 can be expressed in terms of % suppression of MBP-induced EAE.

20. *Mouse lethality test.* In the past it was common to test the toxicity of chemicals by some form of test which involved administering the chemical to animals such as mice and observing the fatality rate in the animals. One such test is a safety test for biologics and biotechnology-derived products described in the Ninth Supplement to the 22nd revision of the US Pharmacopia. This involves taking five mice, injecting them with a test solution of the product and observing them for 48 hours. If at the end of 48 hours all of the mice survive and not more than one shows outward symptoms of an adverse reaction, then the test is satisfied. If one or more mice die, or if more than one shows symptoms of an adverse reaction, the test is repeated with 10 mice. As discussed below, the Patent employs a version of this test, but without the repetition.

21. *RBL degranulation test.* Basophils are a type of white blood cell that circulate in the blood. Mast cells are functionally similar to basophils, but reside in the connective tissue (such as the skin, peritoneum and lungs) and mucosa (such as the intestine and nose). Basophils and mast cells are both involved in the development of Immunoglobulin E (IgE)-mediated allergic reactions (also known as immediate-type hypersensitivity). Initial exposure to an allergen induces B-cells to produce specific IgE antibodies which bind to the surface of mast cells and basophils. Upon subsequent exposure to the same allergen, the allergen binds and cross-links the surface-bound IgE antibodies. This initiates a cascade of intracellular events leading to the release of chemical mediators such as histamine and serotonin – a process called "degranulation". These chemical mediators elicit a variety of inflammatory reactions, recognised clinically as allergy.

22. Rat basophilic leukemia (RBL) cells such as the RBL-2H3 cell line have long been used as an *in vitro* model for the initiation and development of immediate-type hypersensitivity. The cells are cultured in the presence of a radiolabelled chemical mediator (for example serotonin) and IgE antibodies derived from an animal which has been immunised with the relevant allergen. The chemical mediator is taken up by the cells and concentrates in their granules. Addition of the allergen triggers degranulation, which can be quantified as a percentage figure, reflecting the amount of chemical mediator released as compared with the total amount of chemical mediator loaded into the cells at the start of the experiment.

23. Mast cells and RBL cells can also be induced to degranulate by triggers other than allergen-induced cross-linking of IgE antibodies. This process (referred to as IgE-independent degranulation) was a recognised phenomenon in 1994, based largely on studies conducted *in vitro* rather than experiments *in vivo*. It was known that such degranulation could be triggered by a variety of polybasic secretagogues, including compound 48/80, mastoparan, substance P, vasoactive intestinal peptide and somatostatin. RBL cells and mucosal mast cells are not as sensitive to such compounds as peritoneal mast cells, however.

24. Whereas RBL degranulation was an accepted and commonly used method for evaluating IgE-mediated release of secretory granules in 1994, this was not the case for assessing IgE-independent degranulation. Nevertheless, the Patent employs RBL degranulation for this purpose.

25. *Guinea pig skin irritation test*. In this test guinea pigs are injected with the test sample intradermally. The diameter of the local inflammatory reaction in the skin is measured two and 24 hours later.

Clinical trials of copolymer-1

26. There have been a number of clinical trials of copolymer-1. The relevant ones for present purposes are as follows.

27. *Abramsky 1977*. This trial involved four patients in the terminal stages of MS and three patients with a related condition. It was reported in Abramsky *et al*, "Effect of a synthetic polypeptide (Cop 1) on patients with multiple sclerosis and with acute disseminated encephalomyelitis", *J. Neuro. Sci.*, 1977, 31(3), 433-438. The authors reported some improvement in vision and speech capacity and no side effects.

28. *Bornstein 1982*. This was a two-year, open-label, uncontrolled trial involving 12 patients with chronic progressive MS and four patients suffering from the relapsing-remitting form of the disease. It was reported in Bornstein *et al*, "Multiple sclerosis: trial of a synthetic polypeptide", *Ann. Neur.*, 1982, 11(3), 317-319. The results were encouraging, but no more than that. No undesirable side effects were noted.

29. *Bornstein 1987*. This was a single-centre, double-blind, randomised, placebo-controlled trial involving 50 patients, all suffering from relapsing-remitting MS. It was reported in Bornstein *et al*, "A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis", *N. Eng. J. Med.*, 1987, 317(7), 408-414. It provided evidence of efficacy and safety of copolymer-1 in the treatment of this form of the disease.

30. Bornstein 1987 is another item of prior art relied on by Mylan. It begins by describing copolymer-1 in the following terms:

> "Cop 1 is synthesised by the random polymerisation of L-alanine, L-glutamic acid, L-lysine and L-tyrosine in the ratio of 6:0:1.9:4.7:1.0 (molecular weight, 14,000 to 23,000). It was one of a series of polypeptides prepared to simulate myelin basic protein, a natural component of the myelin sheath.[1-3]"

Reference 1 is Teitelbaum 1971.

31. The preparation and characterisation of copolymer-1 is described as follows:

> "Cop 1 was first prepared at the Weizmann Institute of Science, Rehovot, Israel,[1] and later by the Bio-Yeda Company in Rehovot. All batches were analyzed for their amino acid composition, molecular weight, cross-reactivity with myelin basic protein, and suppression of experimental allergic encephalomyelitis in guinea pigs. Suppression was expressed as the difference in the percentage of diseased animals between the group treated with Cop 1 and the controls. The 12 batches from the Weizmann Institute had a suppression rate ranging from 10 to 80 percent (average, 33.5 percent); the rate for 14 batches produced by Bio-Yeda ranged from 10 to 75 percent (average, 40.6 percent). In an attempt to reduce inflammatory reactions at injection sites, we used an in vitro method to evaluate cell damage (basophil degranulation) by serotonin release.[18] All the batches in this study produced releases of less than 30 percent.
>
> Cop 1 was dissolved in bacteriostatic saline at a concentration of 20 mg per millilitre. Sterile single-dose vials containing 1 ml of bacteriostatic saline alone of the Cop 1 solution were stored at -20°C until they were used. Each patient received a monthly supply of 32 vials and patient compliance were monitored by a clinical assistant under the direction of the statistician responsible for the randomization of patients (see Study Design below)."

32. Side effects were monitored in two ways. First, by blood and urine analyses which revealed no apparent changes in the functions of the liver, spleen, kidney, bone marrow, gastrointestinal tract, heart or lungs. Secondly, by self-evaluation of symptoms by patients. Two patients had a patterned, transient reaction (consisting of flushing, sweating, palpitations, tightness around the chest, difficulty in breathing and anxiety) lasting from 5-15 minutes with no residual difficulties. Other patients experienced localised reactions at the injection site including soreness, itching and swelling (all statistically significant) and redness (not statistically significant). Other generalised reactions (headache, nausea, vomiting etc.) are said to have been reported "with comparable frequencies in each group".

33. The data are summarised in Table 4:

Table 4. Percentages of Patients Reporting Side Effects.

Symptom	Placebo (N = 23)	Cop 1 (N = 25)
Local		
Soreness*	35	92
Itching†	22	64
Swelling*	17	88
Redness	48	76
Other	35	36
Other		
Headache	39	32
Nausea	17	24
Vomiting	4	4
Dizziness	30	40
Constipation	30	40
Sweating	26	28
Rash	17	24
Palpitations	13	24
Cramps	9	12
Faintness	13	20
Joint pain	39	40
Gastrointestinal discomfort	22	12
Appetite loss	13	20
Drowsiness	26	20
Other	17	28

*P<0.001 for the difference between placebo and Cop 1.
†P<0.01 for the difference between placebo and Cop 1.

34. The conclusion drawn by the authors at 414 is that:

> "Undesirable side effects – primarily local irritation at injection sites and rare transient vasomotor responses [i.e. the patterned reaction] – were well tolerated".

35. *Bornstein 1991*. This was a two-centre, double-blind, randomised, placebo-controlled trial involving 106 patients, all suffering from chronic progressive MS. It was reported in Bornstein *et al*, "A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis", *Neurology*, 1991, 41, 533-539. The trial failed to show any statistically significant difference in efficacy as between copolymer-1 and placebo.

36. *Phase III trial*. This was a multi-centre trial involving 251 patients diagnosed with relapsing-remitting MS. The trial was discussed in Johnson, "Experimental therapy of

relapsing-remitting multiple sclerosis with copolymer-1", *Ann. Neur.*, 36 Supp., S115-117 ("Johnson 1994"), which is the third item of prior art relied on by Mylan. The results of the trial were announced by the lead investigator Dr Kenneth Johnson at the annual meeting of the American Neurological Association ("ANA") in San Francisco on 10 October 1994. They were published in full in July 1995 in Johnson *et al*, "Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial", *Neurology*, 1995, 45(7), 1268-1276 ("Johnson 1995"). Treatment resulted in a significant reduction in relapse rate and a reduced chance of worsening disability.

37. In December 1996, the United States Food and Drug Agency approved Copaxone for use in the treatment of relapsing-remitting MS, based on the results of Bornstein 1987 and the Phase III trial. It was subsequently approved for use in Europe.

38. *Comi 2001*. This was a multi-centre trial involving patients with primary progressive MS. The results were published in Comi *et al*, "European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects on glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing-remitting multiple sclerosis", *Ann. Neur.*, 2001, 149(3), 290-297.

39. *Wolinsky 2007*. This was a multi-centre trial involving patients with primary progressive MS. The results were published in Wolinsky *et al*, "Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial", *Ann. Neur.*, 2007, 63, 14-24.

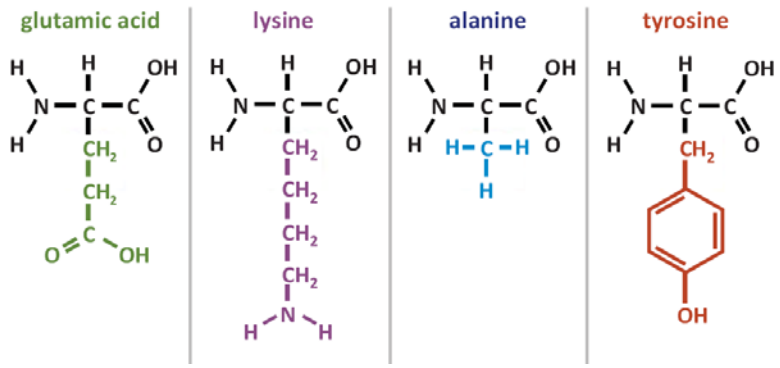
40. *Comi 2009*. This was a multi-centre trial involving patients with clinically isolated syndrome. The results were reported in Comi *et al*, "Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial", *Lancet*, 2009, 374, 1503-1511 ("Comi 2009").

41. It is important to note that, whereas Bornstein 1987 and the other early trials, including Bornstein 1991, reported use of copolymer-1 with a molecular weight in the region of 14,000 - 23,000 Daltons, the Phase III trial and the other later trials reported use of material with a molecular weight in the region of 7,000 Daltons.

Synthetic polypeptides

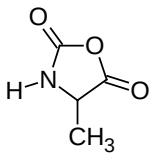
42. A polymer is a large molecule made from building blocks known as monomers. A homopolymer is formed by polymerisation of a single monomer. A copolymer is formed by polymerisation of two or more different monomers. A random copolymer is one in which the different monomers are incorporated into the chain in random order.

43. Proteins are copolymers of amino acid monomers connected through peptide bonds. Naturally-occurring proteins consist of up to twenty different amino acids in a defined sequence and length. Synthetic polypeptides can be made in the laboratory from the same amino acids. All amino acids have the same general backbone structure, but they vary in terms of their side chain. The four amino acids that make up copolymer-1 are shown below:



44. There are a variety of chemical and biological methods for forming peptide bonds between amino acids. Some chemical methods are focussed on making polypeptides of pre-determined sequence. This requires stepwise addition of amino acids to the growing polypeptide chain. Synthetic polypeptides can also be made by random polymerisation of suitably activated amino acid monomers known as *N*-carboxyanhydrides (NCAs) as described in Teitelbaum 1971 (see paragraph 14 above).

45. NCAs are cyclic molecules in which the carboxy group is activated and the amine group is masked. The NCA derivative of alanine is shown below:



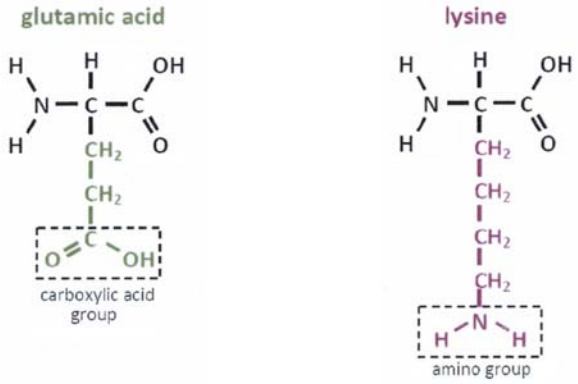
46. An initiator is needed to commence polymerisation. Addition of an amine initiator to the reaction forms an amide bond between the initiator and the carboxylic acid and also unmasks the amine group of the NCA. As part of this mechanism, the unmasked amine group can then react with another NCA molecule and unmask the amine group on that molecule. The reaction continues in this way until all NCAs are consumed. Amine-initiated polymerisation of NCAs dates from the late 1940s. Dithethylamine was a commonly-used initiator in 1994.

47. Synthetic polypeptides made in this way differ from proteins in that they comprise mixtures of different species. Use of a single NCA generates a mixture of polypeptides which differ only in terms of chain length. Polymerisation of more than one NCA generates a mixture of polypeptides which vary both in chain length and sequence. If each NCA in the reaction mixture reacts at the same rate, the sequence of the polypeptide will be random. If some react faster than others, they will tend to get incorporated into the growing polypeptide chains preferentially.

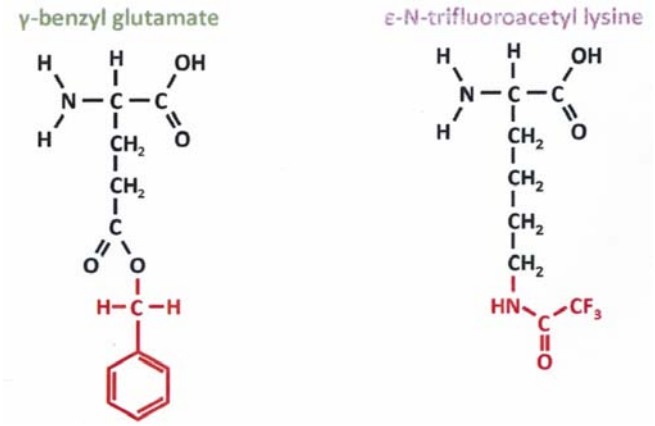
48. In 1994 varying the amount of initiator added was the standard way of controlling the length (and hence the weight) of the resulting polypeptides. The more initiator used, the more chains will be initiated and the quicker the monomer supply will be depleted, leading to a larger number of shorter chains. Lower amounts of initiator will lead to a smaller number of longer polypeptide chains.

49. The side chains of certain amino acids can themselves be reactive, leading to unwanted side reactions during the polymerisation process. For example, glutamic

acid contains a carboxylic acid group in its side chain and lysine contains an amino group:



50. In order to prevent polymerisation via reactive side chains, the latter can be masked using a protecting group which is removed after completion of the polymerisation step. In 1994 it was well known that glutamic acid could be protected by a benzyl group and lysine by a trifluoroacetyl ("TFA") group:



51. Once the protected copolymer has been synthesised, the benzyl group protecting the glutamic acid can be removed with hydrogen bromide (HBr) in glacial acetic acid. The TFA group protecting the lysine can be removed with piperidine. It is standard practice to perform such deprotection reactions for the minimum time necessary to achieve the desired result in order to minimise unwanted side reactions.

Amino acid analysis

52. Techniques for determining the amino acid composition of polypeptides were well known in 1994. In order to do so, polypeptides are broken down into their constituent amino acids, usually by use of aqueous acids to cleave the peptide bonds. Once this has been done, the amount of each amino acid can be measured, by either ion exchange chromatography (IEC) or high performance liquid chromatography (HPLC). In the IEC method, the retention time of each amino acid is determined by running known amino acid standards through the column. As the amino acids exit the

column, they are derivatised with a compound that provides colour, such as ninhydrin. In the HPLC method, they are derivatised prior to chromatography, for example with phenylisothiocynanate to form phenylthiocarbamyl (PTC) derivatives which absorb in the UV. In both methods the amount of each amino acid can be quantified by the absorbance of light in a spectrophotometer. The response of the spectrophotometer can be calibrated against the response of a known amount of a known amino acid, allowing the amount in the sample to be calculated.

Average molecular weights of polymers

53. For a single polypeptide or protein where only one molecular species exists, the molecular weight can be reported in the same way that it can for a small molecule such as water i.e. as a single molecular weight expressed in Daltons or kiloDaltons. In the case of a polymer which consists of a variety of species of differing molecular weights, however, there will be a distribution of molecules of different molecular weights within a sample of polymer. The molecular weight distribution of the polymer can be described in terms of several different average molecular weights.

54. The most widely used average molecular weights are the number average molecular weight (M_n) and the weight average molecular weight (M_w). A third kind is the z-average molecular weight (M_z). These are defined as follows:

$$M_n = \frac{\sum_i M_i N_i}{\sum_i N_i} \qquad M_w = \frac{\sum_i M_i^2 N_i}{\sum_i M_i N_i} \qquad M_z = \frac{\sum_i M_i^3 N_i}{\sum_i M_i^2 N_i}$$

where N_i is the number of molecules of molecular weight M_i. M_n represents the total weight of the sample divided by the total number of molecules. As the molecular weight values are squared and cubed in M_w and M_z respectively, larger molecules make a greater contribution to these averages.

55. For synthetic polymers comprising many polymer chains of different compositions and lengths, and thus different molecular weights, M_w is always greater than M_n. The divergence between these two values (M_w/M_n) is the standard measure of the breadth of the molecular weight distribution. This ratio is referred to as the polydispersity index (PDI). The closer the polydispersity index is to 1, the narrower the molecular weight distribution. A polymer consisting of a single species, each molecule having the same chain length and hence weight, is said to be "monodisperse".

56. In addition to M_n, M_w and M_z,, two other quantities are used to characterise the molecular weights of polymers. The first is the viscosity average molecular weight (M_v), which is determined by viscosity measurements. The second is the peak molecular weight (M_p), which is determined by size exclusion chromatography (see below).

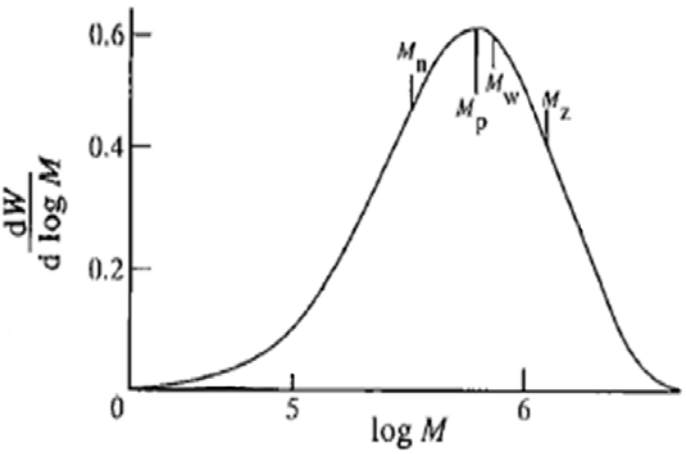
57. There are a number of techniques for measuring one or more of the average molecular weights of polymers. Some of these techniques yield an "absolute" measurement of one or more average molecular weights, but the results may differ depending on the technique used. Other techniques rely on calibration by reference to standards, which

have themselves been subjected to absolute analysis, thereby providing a "relative" measure of molecular weight as compared with the calibration standards.

Size exclusion chromatography

58. Size exclusion chromatography (SEC), referred to as "gel filtration chromatography" (GFC) or "gel permeation chromatography" (GPC) in older texts, is a technique that was developed in the 1950s, and it was a standard analytical technique by 1994. It separates molecules on the basis of their size in solution (referred to as "hydrodynamic volume"). The sample is passed though a column packed with a porous separation gel. The gel beads in the column have pores that allow molecules to enter to varying degrees depending on a particular molecule's size. Small molecules enter the beads to a greater degree and thus take longer to pass through the column. Larger molecules bypass the small pores and therefore exit the column earlier. The length of time it takes for the polymer to pass through the column is called the retention or elution time. The concentration of polymer exiting the column over time is typically measured using an ultraviolet (UV) or refractive index (RI) detector. The raw output of an SEC analysis is therefore a plot of the detector response versus elution time (referred to as a chromatogram).

59. Calibration of the column with an appropriate set of standards of known molecular weight (discussed below) is used to convert the data from the chromatogram into the molecular weight distribution of the polymer. The analysis is carried out using appropriate software. The same software can be used to calculate the M_n, M_w, M_z etc. Reproduced below is an illustrative example of a molecular weight distribution (note that this one is plotted on a log scale):



60. In this figure the position of M_n, M_w and M_z, have been marked on the distribution. So too has M_p. This is the molecular weight corresponding to the peak in the chromatogram, and hence the peak in the molecular weight distribution.

61. As well as being used as an analytical technique, SEC can also be used as a preparative technique to separate a polymer into fractions, each consisting of polymer components of similar molecular weights.

SEC mobile phase

62. The mobile phase or eluent is the solvent in which the sample is dissolved in order to be passed down the column. It must fulfil two requirements. First, it has to dissolve the sample. Secondly, it has to ensure that the sample is separated in the column on the basis of size only i.e. "non-size" interactions are avoided. There are two main types of non-size interactions: (a) ionic interactions and (b) hydrophobic interactions.

63. In 1994 there were well-known techniques to minimise non-size interactions. For ionic interactions, the usual techniques were either to adjust the pH of the eluent or, more commonly, to increase the ionic strength of the eluent. The former technique works by using pH adjustment to remove the ionic charges on the column and/or the sample. The latter technique works by using the ions in the eluent to counteract the charges on the column. It was generally expected that increasing the ionic strength would succeed in removing ionic interactions. In relation to hydrophobic interactions, the usual technique was to add a water soluble organic solvent to swamp out any hydrophobic interactions that might occur between the sample and the column. This too would be generally expected to eliminate such interactions.

SEC calibration

64. The hydrodynamic volume of a polymer can loosely be regarded as a measure of its physical size in solution. However, physical size and molecular weight do not necessarily equate with one another. Thus, two chemically distinct polymers with the same molecular weight may have different sizes in solution and elute at different times from an SEC column. Likewise, two chemically distinct polymers having different molecular weights but the same size in solution may elute together. Further, solution conditions such as pH can affect the size and shape of a polymer, especially if the polymer is made up of monomers having a positive or negative charge. Accordingly, it is necessary to calibrate the SEC column in a way which allows a correlation to be drawn between elution time and molecular weight.

65. Calibration is performed by taking samples of known or determined molecular weights and passing them through the column in order to establish the time or elution volume at which they exit the column. This permits the creation of a plot of retention time (or elution volume) against molecular weight. This is usually referred to as a calibration curve. Once the column has been calibrated, the accuracy of the calibration can be tested by checking the values for M_n and M_w produced by the column against values obtained by absolute methods. A number of different methods of constructing a calibration curve were known in 1994.

66. *Calibration using narrow standards.* This is the most common form of calibration used in SEC. It uses standards of known molecular weight and narrow molecular weight distribution to analyse the unknown sample. Where the sample has a narrow distribution (that is to say, a PDI of less than 1.1), M_n and M_w are approximately equal to M_p. It is therefore possible to construct a calibration curve based on assigning the known molecular weight for each standard to the chromatogram peak. Such standards are usually obtained commercially. It is desirable for the standards to be of the same material as the sample being analysed, or as chemically similar as possible to it in terms of the properties which affect hydrodynamic volume size, namely polymer backbone, functional groups and conformation. If the sample and standards are not

well matched, then the result obtained will not be accurate, but will provide a "molecular weight" relative to the standard used. In 1994 there were only a limited number of commercially available standards suitable for use in aqueous SEC. The main ones were proteins, polythene oxides (PEOs), polythene glycols (PEGs) and dextrans.

67. *Calibration using narrow self-standards.* Where appropriate standards are not commercially available, one possibility is to prepare "self-standards" by making (by fractionation or synthesis) narrow molecular weight distribution samples of the material being analysed, which span the range of molecular weights expected in the sample to be analysed, and measuring the average molecular weight values for each fraction using absolute techniques. In practice this approach is rarely used because of the work involved in making the standards. Although laborious, however, it is work of a routine nature.

68. *Single broad standard calibration*. Calibration can also be carried out with a single broad standard of the polymer being analysed. This can be done in two ways, known respectively as integral and linear. The integral method requires the preparative fractionation of the broad standard and subsequent characterisation of each fraction using absolute techniques so as to obtain molecular weight information about the entire distribution. This is extremely time consuming and rarely used.

69. The linear method requires a broad standard with two known average molecular weights (M_n and M_w) obtained using absolute techniques. The column is calibrated with narrow standards. Then the broad standard is run and the average molecular weights obtained using the narrow standards are compared to the known absolute values. The calibration curve is then adjusted in an iterative process until the calculated values fit the known values. Provided it is linear, the new calibration curve can be used to determine the molecular weights for unknown samples of the same type and having the same molecular weight range.

70. *Universal calibration*. This involves using a calibration curve based on hydrodynamic volume (the product of intrinsic viscosity and molecular weight). Universal calibration can be conducted in two ways. First, a calibration curve can be constructed by plotting the log of the product of molecular weight and intrinsic viscosity against retention time. Determination of the intrinsic viscosity of both the sample and the standard allows accurate determination of the sample's molecular weight. This requires an online viscometer, an expensive piece of equipment which not every laboratory had in 1994, but was nevertheless fairly widely available. Secondly, calibration can be conducted by determination of the "Mark-Houwink coefficients". These constants are the slope and intercept of the plot of log molecular weight against the log of intrinsic viscosity. These coefficients can then be used to determine molecular weight directly from intrinsic viscosity.

Experimental error

71. It is a fact of scientific life that most forms of experimental analysis and testing have some degree of experimental error associated with them. In considering this question, it is importantly clearly to distinguish between four different concepts. In doing so, I will use what I understand to be standard terminology. As the evidence in this case revealed, however, it needs to be appreciated that this terminology is not universally

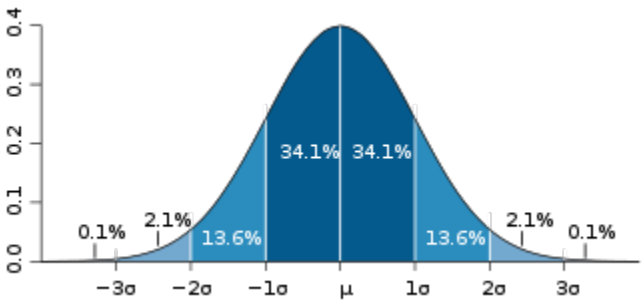
shared. Sometimes it is apparent from the context that one or more of these terms is being used in a different sense.

72. *Accuracy*. The accuracy of an experimental result refers to how close it is to the "true" result. It should be appreciated that in some contexts there is no "true" result, because the experimental technique is an entirely relative one, and therefore it is strictly meaningless to speak of the accuracy of the experimental result. This would be the case, for example, for an average molecular weight obtained by SEC calibrated using inappropriate narrow standards.

73. *Precision*. The precision of an experiment refers to the degree of scatter in the experimental results when performing replicate measurements of the same sample. An experiment may be accurate yet imprecise (where there are large random errors but no systematic errors), or precise yet inaccurate (where there are no random errors but the results are biased by a systematic error).

74. A common convention in science is to express accuracy and precision implicitly by means of significant figures. Under this convention, when not explicitly stated, the margin of error is understood to be one-half the value of the last significant place. Thus reporting a result as (say) 123.0 implies a lower margin of error than reporting it as 123.

75. In statistics, precision is quantified by the standard deviation (σ) of the data from the mean (μ). A low standard deviation indicates that the data points tend to be very close to the mean, whereas high standard deviation indicates that the data points are spread out over a large range of values. In a normal distribution, the distribution can be divided into bands, each of which has a width of one standard deviation as shown below (source Wikipedia):



76. It is common to express the precision of an experimental measurement in terms of its relative standard deviation (sometimes called the "coefficient of variation") expressed as a percentage. This is obtained by dividing the standard deviation by the mean and multiplying by 100. The lower the percentage, the more precise the measurement.

77. In addition to expressing the variability of a dataset, standard deviations are commonly used to measure confidence in statistical conclusions. Thus the fact that 95% of a normal distribution lies within two standard deviations of the mean provides the basis for the conventional measure of statistical significance of $p < 0.05$, but it is not necessary to go into the details of this for present purposes.

78. It is possible to distinguish between three different measures of precision. The purest measure of precision refers to repetitions of the same experiment by the same experimenter at the same time. It is more common, however, to distinguish between repeatability and reproducibility.

79. *Repeatability*. The repeatability of an experiment refers to the extent to which repetitions of the same experiment by the same experimenter on different occasions yield the same result. A highly repeatable experiment yields essentially the same result time after time when performed by the same experimenter. Repeatability is often expressed in terms of relative standard deviation, in which case the lower the percentage the higher the repeatability. It is also possible to express repeatability in terms of the percentage difference between the experimental result and the "true" value (which also provides a measure of accuracy), and again the lower the percentage the higher the repeatability.

80. *Reproducibility*. The reproducibility of an experiment refers to the extent to which repetitions of the same experiment by different experimenters yield the same result. A highly reproducible experiment yields essentially the same result when performed by different experimenters. (It will be appreciated that this may depend on the extent to which the different experimenters use the same equipment and conditions.) Again, reproducibility may be expressed in terms of relative standard deviation or percentage difference from the "true" value.

The skilled team

81. A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and he or she reads it knowing that its purpose is to describe and demarcate an invention. He (or she) is unimaginative and has no inventive capacity. In some cases the patent is addressed to a team of persons with different skills.

82. In the present case there is no fundamental dispute as to the identity of the skilled team to whom the Patent is addressed, but there are certain differences as to the level of expertise of some members. 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.

83. The main differences between the parties concern the synthetic chemist and the analytical chemist with expertise in amino acid analysis. So far as the synthetic chemist is concerned, the Defendants contend that he would have experience of polypeptide chemistry, since the Patent relates to a known synthetic polypeptide, namely copolymer-1. This contention is supported by Prof Sampson. Mylan contends that such experience is not necessary. This contention is supported by Prof Hunter. While I accept Prof Hunter's evidence that a person with sufficient experience in synthesising polydisperse polymers should be able to make copolymer-1 even if he did not have experience with polypeptides, I think it is clear that experience in polypeptide synthesis would be an advantage. Accordingly, I agree with the Defendants that the relevant member of the team would be likely to have at least some experience of this. As counsel for Mylan submitted, however, this makes little difference to the reasoning below.

84. So far as the analytical chemist with knowledge of amino acid analysis is concerned, Mylan contends that he would have experience in undertaking such analyses himself. This contention is supported by the evidence of Prof Kent. The Defendants contend that he would only need to have experience in interpreting amino acid analyses, since the actual analysis could be contracted out. This contention is supported by the evidence of Prof Sampson. The real difference between the parties, however, is not as to whether the analysis could be contracted out or not. Plainly it could be. What matters is the level of expertise of the analytical chemist in interpreting the results. So far as that is concerned, I consider that he would be likely to have a level of expertise intermediate between that of Prof Kent (who, as discussed below, is a leader in the field) and that of Prof Sampson (who, as discussed below, had relatively little experience of the technique).

The expert witnesses

85. The expert witnesses called by the parties do not precisely correspond to the five disciplines I have identified as comprising the skilled team. Furthermore, there is not a precise correspondence between Mylan's witnesses and the Defendants' witnesses, in particular since one of the Defendants' witnesses did double duty as discussed below. Yet further, there is some overlap between some of Mylan's witnesses. Still further, both counsel submitted that a witness called by the other side possessed greater expertise on a topic than another witness called by that side. Nevertheless, for convenience I will put the experts into pairs based on the skilled team. In each case, I will refer to Mylan's witness first.

86. Before doing so, a general point which is convenient to note here is that a number of the experts had previously given evidence in the US proceedings. Both counsel submitted that the other side's witnesses who had done so had become entrenched in their views as a result. I think that there is some truth in this, and I have borne this factor in mind in assessing the relevant witnesses' evidence.

The clinicians

87. *Dr Coles*. Since 2004 the Rev Dr Alasdair Coles has been a university lecturer in Clinical Neuroimmunology at the University of Cambridge. Since 2008 he has been Honorary Consultant Neurologist at Addenbrooke's Hospital and Peterborough City Hospital. Having studied medicine at Oxford, he held various junior medical posts from 1990-1994. These included nine months at the National Hospital for Neurology and Neurosurgery, working under a renowned expert in MS. From 1994-1997 he undertook a PhD the aims of which were to test an experimental drug called Campath-1H (now called alemtuzumab) as a treatment for MS and to understand its mechanism of action. He has continued to work with alemtuzumab since then, two Phase III trials of which were completed in 2011.

88. Dr Coles runs a research group focussed on studying the immunology of MS and its treatment. He supervises a weekly clinic for people with MS who are taking part in scientific studies and trials. He runs a NHS multi-disciplinary neuroimmunology clinic at Addenbrooke's Hospital, with another neurologist, a rheumatologist and a psychiatrist. He also does a weekly NHS clinic for patients with general neurological conditions, including MS, at Peterborough City Hospital. Dr Coles is Medical Advisor to the Multiple Sclerosis Society, a member of the grant review panel of the Multiple Sclerosis Society and International Advisory Board Member of the International Society for Neuroimmunology.

89. Importantly for the purposes of the present case, Dr Coles has been intimately involved in the design, execution and analysis of clinical trials, including 11 clinical trials in the field of MS. Despite this, counsel for the Defendants submitted that no weight should be given to the opinions he expressed in his report about the clinical trials of copolymer-1 having regard to the evidence of the statisticians. I must consider the statistical evidence, and its impact on Dr Coles' evidence, below. In general, however, I consider that Dr Coles was well qualified to consider the clinical trials data and to express opinions about it from a clinical perspective. Indeed, I found Dr Coles to be an impressive witness: he had a great command of his subject and he was very clear and precise in his evidence. On the other hand, he was somewhat forthright in his opinions.

90. *Prof Schellekens*. Prof Hubertus Schellekens has been Professor of Pharmaceutical Biotechnology at Utrecht University since 2009, having been Professor of Medical Biotechnology from 2006. Prof Schellekens qualified as a doctor in 1973. He then trained in medical microbiology and was awarded a PhD for work on interferon in 1980. Since then he has had a varied career in which he has combined a clinical practice with studies in microbiology, recombinant DNA and the activities of biotechnology derived products in animal models and clinical trials. In 1980 he joined the Primate Centre in the Netherlands. From 1990 to 1996 he was a medical microbiologist at a hospital in Delft. In 1996 he joined Utrecht University as Director of its Central Animal Laboratory Research Facility. Since the late 1980s his principal research interest has been the pre-clinical and early clinical development of biopharmaceuticals, particularly focussing on the immunogenicity of therapeutic proteins. For the last 30 years, Prof Schellekens has written articles on scientific issues for Dutch newspapers, and has written on MS more than once.

91. Although he has done some work on β-interferon, Prof Schellekens is not an expert in MS and has no direct experience of treating patients with MS. He himself said that, as a medical microbiologist who spends half of his day in the laboratory, he was not regarded by other clinicians as a serious clinician. Knowledge of MS has been part of Prof Schellekens' professional life, but no more than that of the average medical microbiologist choosing a scientific career in therapeutic proteins.

92. In these circumstances counsel for Mylan submitted that Dr Coles was better qualified than Prof Schellekens to express opinions about the clinical trials of copolymer-1 from a clinical perspective. I accept that submission. Furthermore, no doubt for that reason, I found him less impressive as a witness even after making full allowance for the fact that he gave evidence in English, which is not his mother tongue.

The toxicologists

93. *Prof Kimber*. Prof Ian Kimber is Professor of Toxicology and Assistant Dean for Business Development at the Faculty of Life Sciences at the University of Manchester since 2007. He graduated with a degree in Biology from the University of Manchester and subsequently was awarded an MSc and a PhD in Immunology from the same university. From 1983 to 2000 he was successively Head of Immunology, Senior Scientist, Section Head and Head of Research at the Central Toxicology Laboratory run successively by ICI, Zeneca, AstraZeneca and Syngenta. In 2000 he was made Syngenta's Global Head of Toxicology Research. In 2005 he was made Principal Scientist and was appointed a Director of the Syngenta Biopharmaceuticals Business with responsibility for Immunology, Allergy and Inflammation. Prior to leaving Syngenta in 2007, he held the position of Principal Fellow and Head of Research at the Central Toxicology Laboratory.

94. Although Prof Kimber has published no less than 1,435 papers and other publications, he has very little experience of the RBL degranulation assay and none of the mouse lethality assay employed in the Patent. On the other hand, he did have experience of the guinea pig skin irritation test. I regret to say that, for reasons that will appear, I was unimpressed by the distinction which Prof Kimber drew between association and correlation when considering the experimental data in this case.

95. *Prof Baird*. Prof Barbara Baird is the Horace White Professor and Chair of the Department of Chemistry and Chemical Biology at Cornell University. She gained a BA in Chemistry from Knox College in 1973, an MS from Cornell University in 1975 and a PhD in Chemistry from Cornell in 1979. After a postdoctoral fellowship in the Immunology Branch of the National Cancer Institute, she returned to Cornell University as an Assistant Professor of Chemistry, and was promoted to Associate Professor in 1986, and full Professor in 1991. Over the last 30 years, her research has focused on the cellular responses of the immune system and, particularly, the cellular mechanisms that can lead to hypersensitivity reactions.

96. Prof Baird has significant experience of using degranulation tests, including the RBL degranulation test, to measure cellular initiation of immune system reactions. She accepted that she was not an expert in the mouse lethality assay or the guinea pig skin irritation test, and said that she would defer to Prof Kimber in relation to the latter.

The synthetic chemists

97. *Prof Hunter*. Prof Christopher Hunter FRS is Professor of Chemistry at the University of Sheffield and head of the Sheffield Centre for Chemical Biology. He completed his degree in Chemistry in 1986 and undertook a PhD in Chemistry in 1989, both at the University of Cambridge. He was then a lecturer in bioorganic chemistry at University of Otago for two years. Since then, he has been successively Lecturer in Organic Chemistry, a Lister Institute Research Professor, Head of Organic Chemistry, an EPSRC Senior Research Fellow and Professor of Chemistry at Sheffield. He has received a number of prestigious prizes and awards, leading to his election as a Fellow of the Royal Society in 2008 at the age of 43.

98. He has experience in a diverse range of subject areas including organic synthesis, inorganic chemistry, supramolecular polymer synthesis and peptide and protein chemistry. His research interests on polymers have included synthesis of polyethylene glycol peptide block copolymers for tissue engineering applications in skin reconstruction, synthesis of peptide cross-linked polyacrylamide hydrogels for applications in biosensors and supramolecular synthesis and characterisation of a new class of porphyrin coordination polymers.

99. As well as giving evidence on questions of synthetic chemistry, Prof Hunter gave evidence about the characterisation of polymers, in particular by SEC, and related questions of interpretation of the Patent. In this respect his evidence overlapped with that of Dr Hunt. In my view this overlap could and should have been avoided by those instructing him and Dr Hunt.

100. Prof Hunter was another impressive witness. In his case, his evidence was made all the more impressive by the moderation with which he expressed himself.

101. Counsel for the Defendants submitted that Prof Hunter was a much more able chemist than the relevant member of the skilled team. Counsel for Mylan riposted by reminding me of what Jacob LJ said in *Technip France SA's Patent* [2004] EWCA Civ 381, [2004] RPC 46:

> "11. … sometimes the requirement that the skilled man be uninventive is used by counsel for a patentee in an attempt to downgrade or dismiss the evidence of an expert called to say that a patent is obvious—'my witness is more nerdlike than his' is the general theme. I do not find this a helpful approach. It is frequently invoked and Mr Waugh Q.C. invoked it in this case in an effort to downgrade Rockwater's expert evidence on obviousness given by Professor Witz. Mr Waugh said his witness, Mr Nash, was more appropriately qualified than Professor Witz, and that the latter, because he had patents in his name, 'was of an inventive turn of mind'.
>
> 12. I must explain why I think the attempt to approximate real people to the notional man is not helpful. It is to do with the function of expert witnesses in patent actions. Their primary function is to educate the court in the technology—they come as teachers, as makers of the mantle for the court to don. For

> that purpose it does not matter whether they do not approximate to the skilled man. What matters is how good they are at explaining things."

102. For the reasons given by Jacob LJ, the fact that Prof Hunter is a distinguished scientist does not in itself detract from his evidence as to the obviousness of the claimed inventions. As Jacob LJ pointed out in numerous judgments, what matters are his reasons for holding that opinion. Nevertheless, it will be necessary to consider whether the skilled person would have approached the prior art with quite the same scientific rigour and clarity of mind as Prof Hunter did.

103. A separate point made by counsel for the Defendants was that Prof Hunter has less experience in peptide synthesis than Prof Kent. He suggested that it was odd that Prof Hunter had been asked to give evidence on this subject rather than Prof Kent, and submitted that an adverse inference should be drawn from this. As counsel for Mylan pointed out, however, counsel for the Defendants had the opportunity to cross-examine Prof Kent on the subject, but did not so. In those circumstances no inference can be drawn as to what he might have said if asked.

104. *Prof Sampson*. Prof Nicole Sampson is Professor of Chemistry at the State University of New York at Stony Brook. She received a BSc in Chemistry from Harvey Mudd College in 1985, and a PhD in Chemistry from University of California at Berkeley in 1990. Following her PhD, she conducted postdoctoral research at Harvard University from 1991 to 1993. Since then she has been successively Assistant Professor of Chemistry, Associate Professor of Chemistry and Professor of Chemistry at Stony Brook. She has received a number of honours and awards.

105. Prof Sampson addressed both the issues of synthetic chemistry and those of amino acid analysis. So far as the synthetic chemistry issues are concerned, she was well qualified to do so.

The analytical chemists (amino acid analysis)

106. *Prof Kent*. Prof Stephen Kent is Professor of Chemistry, Professor of Biochemistry and Molecular Biology and Professor in Institute for Biophysical Dynamics at the University of Chicago. He earned a BSc in Chemistry and Biochemistry from Victoria University of Wellington, an MSc in Chemistry and Biochemistry from Massey University and a PhD in Organic Chemistry from the University of California, Berkeley. From 1974-1981, he was a post-doctoral fellow and Assistant Professor at the Rockefeller University in New York. Since then, he has held a string of positions in academia in industry, including Senior Research Associate at California Institute of Technology from 1983 to 1989 and Professor of Macromolecular and Cellular Structure and Chemistry at the Scripps Research Institute from 1991 to 1996. For the past 30 years he has consulted in the fields of peptide and protein chemistry for numerous pharmaceutical and biotechnology companies, several of which he helped start or founded. He has received a number of awards and honours in the field of peptide and protein chemistry.

107. Of particular relevance to his evidence in this case, Prof Kent has extensive experience concerning the amino acid analysis of peptides and proteins, which he used routinely for a period of over 20 years. Indeed, on his account, while he was at

CalTech he ran the world's leading research group in the area. As noted above, he also has wider experience of peptides and proteins, including polypeptide synthesis.

108. Counsel for the Defendants submitted that Prof Kent had an unduly narrow approach. This submission did not concern Prof Kent's technical evidence, however, but his approach to the interpretation of the Patent, to which much of his evidence was really directed. That is ultimately a matter for the court.

109. *Prof Sampson*. Prof Sampson had much less experience of amino acid analysis than Prof Kent. She had never conducted such an analysis herself, and her experience was limited to sending samples out for analysis and interpreting the results. Counsel for Mylan submitted that she was less well qualified to assist the court with regard to amino acid analysis. I accept that submission, but as I have already commented, I do not consider that the relevant member of the skilled team would have as much experience as Prof Kent. Furthermore, like Prof Kent, much of Prof Sampson's evidence on this topic was really directed to the interpretation of the Patent.

110. Counsel for Mylan submitted that it was surprising that Prof Sampson had been asked to give evidence about this topic given that Prof Grant had more expertise in it than she did. To that I give the same answer as he gave to counsel for the Defendants' submission about Profs Hunter and Kent: he did not cross-examine Prof Grant on the topic.

The analytical chemists (SEC)

111. *Dr Hunt.* Dr Barry Hunt retired in 2007 from his position as Senior Experimental Officer and Assistant Director of the Polymer Centre at Sheffield University. He obtained an MSc and PhD in Polymer Science from Lancaster University in 1970 and 1976 respectively. He was a Research Officer in Polymer Chemistry at Lancaster University from 1967 to 2000 and Senior Experimental Officer at Sheffield from then until his retirement. He was Deputy Director of Lancaster's Polymer Centre from the early 1990s to 2000, and helped establish Sheffield's Polymer Centre when the former closed. He spent 40 years primarily focussed on running a laboratory for characterisation and analysis of polymers. He has extensive experience of SEC, having edited a book on the subject on 1989, as well as other relevant analytical techniques.

112. *Prof Grant*. Prof Gregory Grant is Professor of Biochemistry in Medicine and of Developmental Biology at the School of Medicine at Washington University in St Louis, Missouri. He received a BSc in Biochemistry from Iowa State University in 1971 and a PhD in Biochemistry from the University of Wisconsin, Madison in 1975. He then conducted three years of postdoctoral research at the Washington University School of Medicine. He became a Research Assistant Professor at Washington University in 1978, an Assistant Professor in 1982, an Associate Professor in 1989 and a full Professor in 1995.

113. Although he stated in his first report that, from the outset of his career as an analytical biochemist in the 1970s, a key part of his research had involved the characterisation of polypeptides using SEC, it turned out that he had less experience of SEC than that appeared to suggest.

114. Counsel for Mylan submitted that Prof Grant was clearly uncomfortable at points in his evidence. I accept that submission. I was particularly unimpressed by his refusal to accept that a graph he had produced (in exhibit GAG8 discussed below) was the same as a plot of scaled x(M) against M, as demonstrated by Prof Hunter, despite accepting that it looked the same as Prof Hunter's plot of scaled x(M) against M and that there was nothing wrong with Prof Hunter's calculations. Nevertheless, I do not regard this as undermining the value of other parts of his evidence.

The statisticians

115. In addition to the five disciplines identified above, both sides called a statistician for reasons that I will discuss below.

116. *Dr Altmann*. Dr Daniel Altmann is a Senior Lecturer in Medical Statistics at the London School of Hygiene & Tropical Medicine and Honorary Lecturer in the Department of Neuroinflammation at the Institute of Neurology. He obtained a BA in Philosophy from Bristol University in 1972, a PhD in Philosophy from Oxford University in 1978 and an MSc in Statistics at LSHTM in 1999. After several research fellowships, he became Lecturer in Medical Statistics at LSHTM in 2002 and Senior Lecturer in 2008.

117. For the last 10 years his research has arisen almost entirely from a close collaboration with the Nuclear Magnetic Resonance ("NMR") unit at the Institute of Neurology, which primarily focusses on research into multiple sclerosis. His work with the NMR unit has involved statistical collaborations on a number of studies on the pathogenesis of multiple sclerosis, as well as a number of clinical trials into potential therapies for multiple sclerosis. As part of this work, he had contributed to the design and analysis of individual studies, as well as undertaking statistical supervision of nearly 50 clinical research fellows. He has co-authored around 70 scientific papers in the field of multiple sclerosis or multiple sclerosis-related conditions.

118. Through no fault of his own, Dr Altmann was put in a position that he should not have been placed in. Dr Coles requested that two statistical analyses of the incidence of adverse effects of lower molecular weight copolymer-1 compared to higher molecular weight copolymer-1 be carried out for the purposes of his first report. Mylan's solicitors instructed Dr Altmann to carry out those analyses. They then proceeded to serve a witness statement from Dr Altmann as part of Mylan's first round of evidence in which he described the statistical analyses he carried out. It is obvious that the reason why they took the course of serving a witness statement from Dr Altmann was that Mylan had only sought and obtained permission to call five experts, and Dr Altmann would have been a sixth. To try and camouflage the fact that Dr Altmann's evidence was really expert evidence, his witness statement was drafted so as merely to report the results of his analysis. Thus it contained no overt expression of opinion on the part of Dr Altmann as to suitability of the method of analysis he used (an analysis of risk ratios) or as to the significance of his analyses.

119. The Defendants served an expert report from Prof Sasieni in answer to Dr Altmann in which he said that in his opinion "the available clinical trial data do not make it possible to determine the question of whether lower molecular weight [copolymer-1] has fewer side effects than higher molecular weight [copolymer-1]". Mylan then served an expert report from Dr Altmann in reply in which he expressed his

agreement with this, saying that in his view "statistical evidence relating to the available clinical trial data cannot answer the question of whether differences in the copolymer-1 compound give rise to differences in adverse effects".

120. At the beginning of the trial Mylan finally sought and obtained permission to call Dr Altmann as an expert. The Defendants applied for his evidence to be excluded on the grounds that (i) his analyses constituted an experiment for which no notice had been given and (ii) his evidence was of no probative value given his agreement with Prof Sasieni. I refused that application for the reasons given in a ruling at the time.

121. Dr Altmann and Dr Coles explained in cross-examination that, at the time of preparing their witness statement and first expert report respectively, they had had no direct communication with each other. Dr Altmann also said he had expressed reservations to Mylan's solicitors as to the conclusions that could be drawn from his analyses prior to completing his witness statement. Those reservations were not passed on to Dr Coles at the time, and Dr Altmann did not see Dr Coles' first report until after it had been signed and served.

122. In my judgment it is plain that Dr Altmann's evidence in his first witness statement was expert evidence for which proper permission should have been obtained. That would have been so even if Dr Altmann was fully satisfied that his analyses could be relied upon for the purposes which Dr Coles sought to rely upon them. Furthermore, in the absence of the important reservation expressed by Dr Altmann in his expert report, the impression was wrongly given by Dr Altmann's witness statement, particularly when read together with Dr Coles' first report, that Dr Altmann considered that his analyses could be relied upon to support Dr Coles' conclusions. In the end, no harm was done because Dr Altmann's position was made clear in his expert report and by his oral evidence. That position should have been revealed at the outset, however.

123. The overall effect of the clinical and statistical evidence is a separate question which I shall consider below.

124. *Prof Sasieni*. Professor Peter Sasieni is Professor of Cancer Epidemiology and Biostatistics at Queen Mary University of London, Director of the Cancer Prevention Trials Unit, Honorary Professor at LSHTM and Vice-Director of the Department of Health Policy Research Unit on Cancer Awareness, Early Diagnosis and Screening. He has a BA in mathematics from the University of Cambridge (1984) and a PhD in biostatistics from the University of Washington (1989). He was a Research Fellow at the Imperial Cancer Research Fund (later Cancer Research UK) from 1989 to 2002 and has been a Professor in the Wolfson Institute of Preventive Medicine at QMUL since 2002. He has designed and analysed several clinical trials, mainly in the field of cancer, and has published extensively in both statistics and medicine. Little challenge was made to his evidence.

Factual witnesses

125. In addition to the experts listed above, the Defendants adduced evidence from two factual witnesses.

126. *Prof Arnon*. Professor Ruth Arnon is Paul Ehrlich Professor Emeritus of Immunology, a Professor at the Weizmann Institute of Science and President of the Israel Academy of Sciences and Humanities. She received a Masters degree in biochemistry from Hebrew University in 1954. In 1960, she was awarded a PhD in biochemistry by WIS. The subject of her PhD was the chemical basis of the antigenicity of proteins. It culminated in the first synthetic molecule to have immunogenic properties. The PhD was jointly supervised by Professor Ephraim Katchalski-Katzir and Professor Michael Sela. After post-doctoral work at the Rockefeller University in New York, she returned to WIS in 1963. She was appointed an Associate Professor of Immunology in 1971 and Professor of Immunology in 1975. Over the years, she has held several positions at WIS, including Head of the Chemical Immunology Department, Dean of the Faculty of Biology and Vice-President.

127. Prof Arnon was one of the authors and inventors of, among many other publications, (i) Teitelbaum 1971, (ii) US 550, (iii) Bornstein 1987 and (iv) the Patent. Her evidence was mainly concerned with the making of the invention described and claimed in the Patent and the subsequent development of Copaxone to the point where it was approved by the FDA. She was not required to attend for cross-examination.

128. *Dr Pinchasi*. Dr Irit Pinchasi joined Teva in 1986 and left at the beginning of 2009. She has a Bachelor's Degree in Biology, a Master's Degree in Biochemistry, and a PhD in Neurobiochemistry, all from Tel-Aviv University. After her PhD, she held a post-doctoral position at WIS. When she joined Teva, she was appointed as a Project Manager with responsibility for, among other things, the copolymer-1 project. As such, she was responsible for coordinating all the various activities relating to the development of copolymer-1 as a drug for MS. She remained in that role until Copaxone was placed on the market in the US in 1997.

129. Dr Pinchasi's evidence was mainly concerned with the development of Copaxone by Teva. She was a straightforward witness. She had little or no knowledge of some matters counsel for Mylan wished to ask her about, but that was not her fault.

Common general knowledge

130. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[115]. That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6].

131. In the present case there is a fair amount of common ground with regard to the common general knowledge of the skilled team, but there are also a number of differences between the parties. Save with regard to one specific topic, neither side suggested that there was any material difference with regard to the common general knowledge as between the two dates which are relevant for the purposes of this action, namely May 1994 and May 1995.

MS

132. It is common ground that the matters set out in paragraphs 6-8 above were (save for the references to the present state of knowledge) common general knowledge.

EAE

133. The use of the EAE model as described in paragraphs 9 and 19 was common general knowledge.

Treatments for MS

134. In May 1994 it was well known that MS could be treated with interferon as described in paragraph 10 above and that copolymer-1 was undergoing a Phase III trial.

The Phase III trial

135. It is common ground that there had been no report of any results from the Phase III trial by May 1994. As noted in paragraph 36 above, the results were announced at the ANA meeting in October 1994 (during the priority interval so far as the Patent is concerned), but not fully published until July 1995 (after the filing date of the Patent). There is a dispute as to whether the results announced in October 1994 would have been part of the common general knowledge of the clinician in the skilled team in May 1995. It should be appreciated that the announcement is not relied upon by Mylan as a pleaded item of prior art in itself.

136. Dr Coles' evidence in his reports was that he had not attended the meeting in person, but that news of the results had filtered back to him via colleagues. He remembered hearing that the results were positive, in that copolymer-1 reduced relapse rate and the accumulation of disability compared to placebo in a relapsing-remitting population. He said that this had made a big impact in the field since it led clinicians to anticipate that a second treatment for MS was likely to become available. It was his opinion that the headline results would have been common general knowledge among clinicians with an interest in MS by May 1995. He supported this opinion by reference to an article in *Annals of Neurology* published in that month.

137. In cross-examination, it emerged that, for the purposes of his evidence on obviousness, Dr Coles had assumed that the skilled person would either have been present at the meeting or have access to a fairly full transcript and copies of the slides (although in re-examination he said that his opinion would be the same even if the skilled person had only heard about the headline results, as suggested by his reports). After Dr Coles had given evidence, Mylan served a hearsay notice in respect of (i) copies of drafts of Dr Johnson's slides disclosed by Teva and (ii) copies of an article published in *Scrip* on 18 October 1994 reporting on the presentation. The Defendants did not object to this notice being served out of time.

138. As counsel for the Defendants pointed out, it is not surprising that Teva received drafts of the slides, since Teva were the sponsors of the Phase III trial. There is no reason to think that anyone else did. Nor is there any evidence as to what actual slides were presented. As counsel observed, there would seem to be a greater number of slides than could readily be presented in 15 minutes. Given the timing of the service of the hearsay notice, neither party has been able to adduce evidence from anyone who attended the meeting. In short, there is no proper evidence as to the content of Dr Johnson's presentation.

139. As for the *Scrip* article, Dr Coles did not suggest that he had read this or that he would have expected other clinicians in the field to have become aware of the presentation by that route.

140. Prof Schellekens gave evidence that he was not present at the ANA meeting and that he may have heard news through contacts, but he had no recollection of when and how he first heard the results of the trial. In any event, his involvement in the MS field at the time was limited.

141. My conclusion on the evidence as a whole is that 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.

142. Counsel for the Defendants submitted that, even if the headline results were known as I have found, they would not have been generally regarded as a good basis for further action. In my view, this question is more conveniently considered in the context of obviousness.

Immunogenicity of tyrosine

143. The Defendants contend that it was common general knowledge to the clinician that the immunogenic properties of polypeptides were relatively insensitive to the amount of tyrosine present. The evidential basis for this contention is two-fold. First, Prof Schellekens expressed the opinion that it was well known to those who had an interest in the immunogenicity of polypeptides that the scientists at WIS had shown in the 1960s that this was the case. This proposition was not put to Dr Coles, however. In any event, I was not persuaded by Prof Schellekens' evidence that this was common general knowledge. He did not refer to any textbook or other literature to support his opinion. Furthermore, he explained that, although he had not trained as an immunologist, he had specialised in the immunogenicity of therapeutic proteins for the last 20 years. In those circumstances I accept that the WIS work was well-known to him and others like him, but I do not accept that this establishes that it would be well-known to the clinical member of the skilled team.

144. Secondly, Prof Arnon said that she and Prof Sela had shown that the immunogenicity of samples of polytyrosyl gelatins containing 5% and 10% tyrosine was essentially the same, citing their paper "Studies on the Chemical Basis of Antigenicity of Proteins 2. Antigenic Specificity of Polytyrosyl Gelatins", *Biochem. J.*, (1960), 75, 103-110. The latter point was put to Prof Kent, who agreed that he had no reason to contradict Prof Arnon's evidence. Neither Prof Arnon's evidence nor the cross-examination of Prof Kent suggested, however, that this work would have been common general knowledge to a member of the skilled team in 1994, still less that the skilled person would have regarded it as applicable to the immunogenicity of tyrosine.

Synthetic polypeptides

145. It is common ground that the matters set out in paragraphs 45-51 above were common general knowledge in May 1994.

146. It is also common ground that it was *not* common general knowledge that the standard method for deprotection of the benzyl group, namely by use of HBr in glacial acetic acid, could cause cleavage of the polypeptide into smaller molecules. There is a minor dispute as to the extent to which this was known at all which I will consider below.

Amino acid analysis

147. It is common ground that amino acid analysis as described in paragraph 52 above was common general knowledge. It is also common ground that it was well known that there was a degree of variation in the results of amino acid analysis performed using those methods. There is a dispute as to the extent of this. Prof Sampson said these methods had "a precision of 11.4 – 26.4% for each amino acid" (by which I understood Prof Sampson to mean that the relative standard deviation should be in this range). Prof Kent said that he would expect any laboratory with the capability to conduct amino acid analysis to achieve "reproducibility of ±5% or better" (by which I understood Prof Kent to mean that the experimental result should not differ from the true result by more than 5% of the true result).

148. It is important to be clear as to the issue in this respect. The issue is not what level of accuracy, precision, repeatability or reproducibility was in fact attained either generally in analysing polypeptides or specifically in analysing copolymer-1. Rather, the issue is what degree of experimental error the skilled reader of the Patent would expect there to be in an amino acid analysis of copolymer-1 from his common general knowledge. The relevance of this issue is that it bears upon an issue of construction considered below.

149. Prof Sampson's evidence was based not upon her personal experience, but upon a paper by Crabb *et al*, "A collaborative amino acid analysis study from the Association of Biomolecular Resource Facilities", *Curr. Res. Prot. Chem.*, 1990, 49-61. This was a "round robin" study in which 36 "core facilities" (laboratories which were members of the Association) participated. The participating laboratories used 43 instruments of various different makes. They also used two different chemical methods (involving ninhydrin and PTC respectively). The participating laboratories were asked to analyse differing quantities of two unidentified samples, one pre-hydrolysed and one not. The authors analysed the results for accuracy (calculated as average % error for all amino acids measured except two) and "precision" (calculated as average % standard deviation). For the unhydrolysed sample, the average % error ranged from 9% (5 μg analysed) to 15% (0.2 μg analysed) for all responses and the average % standard deviation ranged from 21% to 29.4% for all responses. For the pre-hydrolysed sample, the corresponding figures were 15% (4 μg analysed) to 20% (0.1 μg analysed) and 16% to 25.7%. As the authors commented at 53, surprisingly it was found that there was a greater error with the pre-hydrolysed sample, although the "precision" was superior. As the authors also pointed out at 53, the data are not separated into intra- and inter-laboratory data i.e. the results for "precision" conflate repeatability and reproducibility. The authors concluded at 61:

> "In order to attain the high quality performance sought by the majority of the survey respondents (i.e. less than 10 % error), better approaches and methodologies for hydrolysis and amino acid analysis must be found that can routinely deliver the accuracy that is required."

150. The figures quoted by Prof Sampson are the lowest and highest figures for average % standard deviation of the pre-hydrolysed sample (11.4% for analysis of 4 μg using ninhydrin and 26.4% for analysis of 0.1 μg using PTC). As Prof Kent pointed out, strictly speaking, the more appropriate figures for the purposes of the present case are the ninhydrin ones (since reference 28 to Teitelbaum 1971 shows that a ninhydrin method was used). For the same reason, the unhydrolysed data should be used. The average % standard deviation figure for analysis of 4 μg of the unhydrolysed sample using ninhydrin was 20%.

151. Prof Kent made a number of points about the relevance of the Crabb paper to the analysis of copolymer-1. First, he pointed out that the amount of sample was small, compared to that which could be used for copolymer-1. Secondly, the study was designed to look at high sensitivity analysis of micro amounts of sample. Thirdly, the sample had a relatively complex amino acid composition compared to copolymer-1 with only four amino acids. I accept these points, but in my view what is more significant is his observation in paragraph 9 of his second report concerning the authors' conclusion:

> "As reflected in the Crabb paper, the core facilities at the time recognized that they were not achieving these generally accepted standards [namely, a reproducibility of typically better than 5%] for the reproducibility in amino acid analysis of peptide and protein samples."

When asked about this in cross-examination, he accepted that these laboratories were not attaining the desired performance of less than 10% error referred to in the Crabb paper, and explained:

> "What I found was that during that time people were throwing away accuracy in favour to being able to do relatively inaccurate analyses on small amounts of sample. It never made a lot of sense to me."

152. Prof Kent's evidence in his reports was partly based on his own experience and partly based on two papers. The first was Moore and Stein, "Chromatographic Determination of Amino Acids by the Use of Automatic Recording Equipment", *Methods in Enzymology*, 1963, 6, 819-831. This says at 827 that the results of a representative analysis should agree to within about 3% with the true values. The second paper was Ogden and Földi, "Amino acid analysis: an overview of current methods", *LC_GC*, 1987, 5(1), 28-40. The authors state at 34 that "The IEC method itself has proved reliable and accurate, with reproducibilities (CVs) between 1% and 2% achieved routinely at sample loads of 10 nmol amino acid … equivalent to ~10 μg of a 15 kDa protein"." In relation to the HPLC method, they state at 36 that "Coefficients of variation between 2.5% and 4.3% are typically obtained with protein hydrolysate standards … With plasma, the CV for double determinations is 3.2%-6.1% …"

153. In addition, Mylan place reliance upon certain Teva disclosure documents which Prof Kent said, and Prof Sampson accepted, showed that in December 1995 Teva was able to achieve a repeatability of 2% (relative standard deviation) and a reproducibility of

less than 5% (percentage difference) as between two laboratories when analysing 10-20 μg of copolymer-1 by HPLC.

154. My conclusion from this evidence is that the skilled analyst would know that in principle amino acid analyses should have the reproducibility stated by Prof Kent, namely ±5% or better; but he would also be aware that in practice many laboratories did not achieve such a low level of experimental error for the reason given by Prof Kent which I have quoted in paragraph 151 above.

Average molecular weight

155. It is common ground that the matters I have set out in paragraphs 53-57 above were common general knowledge. There is a sharp dispute, however, as to whether the skilled SEC analyst would regard peak molecular weight (M_p) as an average molecular weight. The evidence of both Prof Hunter and Dr Hunt in their first reports was that M_p was (i) not an average molecular weight and (ii) not referred to as such. The evidence of Prof Grant in his second report was that M_p (i) was an average molecular weight and (ii) was frequently referred to as "peak average molecular weight".

156. So far as the first point is concerned, Prof Grant said (a) that "average" included mean, median and mode, and (b) that M_p was the mode of the molecular weight distribution in an SEC analysis. Prof Hunter, to whom most of the Defendants' cross-examination on this topic was directed, agreed with (a) as a matter of mathematics and with (b) as a description of the SEC experiment (although, as he explained, care is needed about this, since the mode of the molecular weight distribution is only the same as the mode of the chromatogram if the calibration curve is linear). He did not agree, however, that M_p was an average molecular weight. He pointed out that M_n, M_w and M_z are all properties of the material, whereas M_p is a feature of the SEC experiment. He explained that it is important to distinguish between polymers which are close to monodisperse and those which are polydisperse. In the case of the former, one can approximate M_p to M_n and M_w. In those circumstances it is commonplace to take M_p as representing the "molecular weight" of the polymer. Indeed, this is the whole basis of calibration using narrow standards. In the case of the latter, one cannot use M_p quantitatively to characterise the polymer, although one can use it in a relative manner.

157. In relation to the second point, Prof Grant exhibited to his second report eight papers in which the term "peak average molecular weight", or similar expressions, had been used. More were produced by the Defendants for the purposes of cross-examining Prof Hunter and Dr Hunt. It is manifest that many of these papers had been located by means of electronic searches for the term "peak average molecular weight", or similar expressions. They covered a long period of time (1971 to 2007) and an astonishing range of subject matter (in fields such as coated gold nanoclusters, extracts from oak heartwood, the drying properties of metathesised soybean oil and polymers used for dental prostheses), but none of them was concerned with measuring the average molecular weight of a protein or polypeptide. Prof Hunter was cross-examined on a number of these papers. He accepted that they showed use of the term "peak average molecular weight", or similar expressions, by their authors. He did not accept that any of them showed use of M_p as an average molecular weight accurately to characterise a polydisperse polymer. Dr Hunt's evidence was to similar effect: he accepted that the

term "peak average molecular weight" was sometimes used, including to describe polydisperse polymers, but did not agree that that was an appropriate or correct use of terminology.

158. As counsel for Mylan submitted, what is most telling is that not a single textbook was produced describing M_p as an average molecular weight. To the contrary, extracts from a number of textbooks on SEC are in evidence, all of which are to the opposite effect. For example, section 1.4 of Billingham, *Molar Measurements in Polymer Science* (Kogan Page, 1977) entitled "Definitions of average molar masses" explains the definitions of M_n, M_w and M_z and also refers to M_v. It does not refer to M_p, which is discussed elsewhere. When I asked Prof Grant about this, he mentioned (having thought about the matter overnight) a chapter in *Remington's Pharmaceutical Sciences*. It turned out that he was referring to a chapter entitled "Statistics" by Randolph and Ciminera (it is not clear to me from which edition), an extract from which was appended to a Teva document describing an SEC method. But this made no reference to "peak average molecular weight", or indeed to SEC at all. All it showed was that, for a normal distribution, the mean coincides with the peak (as shown in the illustration below paragraph 75 above).

159. My conclusion from the evidence as a whole is that the skilled person would not consider M_p properly to be described as an average molecular weight. Nevertheless, he would be aware that M_p was sometimes referred to, albeit inaccurately, as an average molecular weight.

SEC

160. By the end of the trial there was little dispute that the matters I have set out in paragraphs 58-70 above were common general knowledge. There was dispute, however, as to two matters.

161. The first was whether a further method of calibration was common general knowledge. This is calibration using a range of broad self-standards. Where the PDI is greater than 1.1, it cannot be assumed that M_n and M_w are approximately the same as M_p. It follows that the molecular weight of the chromatogram peak cannot simply be assigned on the basis of an absolute measurement of M_n and M_w. Prof Grant suggested in his reports that there were well-known methods for calculating M_p on the basis of an adjustment to M_n and/or M_w, referring to two books and a paper. Dr Hunt disagreed with this in his second report. Counsel for the Defendants submitted that Dr Hunt had accepted it in cross-examination, while counsel for Mylan submitted that the materials relied on by Prof Grant did not support his assertion except where the chromatogram peak is a log normal distribution, in which case one can take the square root of M_n and M_w as M_p.

162. The answer given by Dr Hunt which was relied on by counsel for the Defendants was given in relation to a passage in Dawkins, "Calibration Procedures in Gel Permeation Chromatography", *Br. Polym. J.*, 1972, 4, 87-101 at 90-91. That passage concerns the case where the peak is log normal, and it states that where this is not the case "M_{peak} is not calculated simply". In cross-examination Prof Grant accepted that the books he had referred to and the passage in Dawkins at 90-91 were describing the case where the peak is log normal, but nevertheless suggested that there was an iterative process for assigning it in other cases. In re-examination he identified this as a procedure

described in Dawkins at page 92. This passage was not put to Dr Hunt in cross-examination, and concerns the use of M_v. Accordingly I am not satisfied that the iterative process was common general knowledge.

163. The second was the reproducibility of SEC measurements. Prof Grant's evidence was that the variability was in the range 5-10%. Dr Hunt exhibited a number of papers reporting round robin studies which had been carried out to assess this. One dating from 1995 reported reproducibility of 16-18% for M_n and 7-10% for $M_{w,}$ while another dating from 1996 reported reproducibility of 9-18% for M_n, M_w and M_z. These date from after the relevant date, however. Moreover, Dr Hunt agreed in cross-examination that 5-10% (perhaps more for M_n) was a reasonable figure for what the skilled person would have had in mind.

164. Prof Grant was asked in cross-examination about some Teva documents suggesting that the experimental error Teva experienced was greater than this. I agree with counsel for the Defendants that this is beside the point. What matters is what the skilled person would expect as a matter of his common general knowledge.

The Patent

Background to the invention

165. The specification begins at [0001] by stating that copolymer-1 is a synthetic polypeptide analog of MBP which has been suggested as a potential therapeutic agent for MS, referring to Teitelbaum 1971 and another paper. In [0002] the specification records that copolymer-1 was shown to suppress EAE, referring to Teitelbaum 1971 and US 550, and to be beneficial for patients with relapsing-remitting MS, referring to Bornstein 1987.

166. Paragraph [0003] states:

> "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, respectively. It is synthesised by chemically polymerising the four amino acids forming products with average molecular weights of 23,000 daltons (US Patent No. 3,849,550)"

167. Paragraph [0004] says that it is the object of the invention to provide an improved composition of copolymer-1. Neither this paragraph nor the summary of the invention which follows expressly identifies the nature of the improvement. I shall return to this point below.

Summary of the invention

168. Paragraphs [0005]-[0008] are consistory clauses corresponding to claims 1-4. As such they are directed to the improved composition of copolymer-1 and its use in the treatment of MS. As the specification and the claims make clear, however, the Patent also describes and claims a process for the synthesis of copolymer-1.

Brief description of the drawings

169. Paragraph [0009] states:

> "Figure 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40kDa. Figure 2 shows similar data relating to the molar fraction."

170. I reproduce Figures 1 and 2 below:

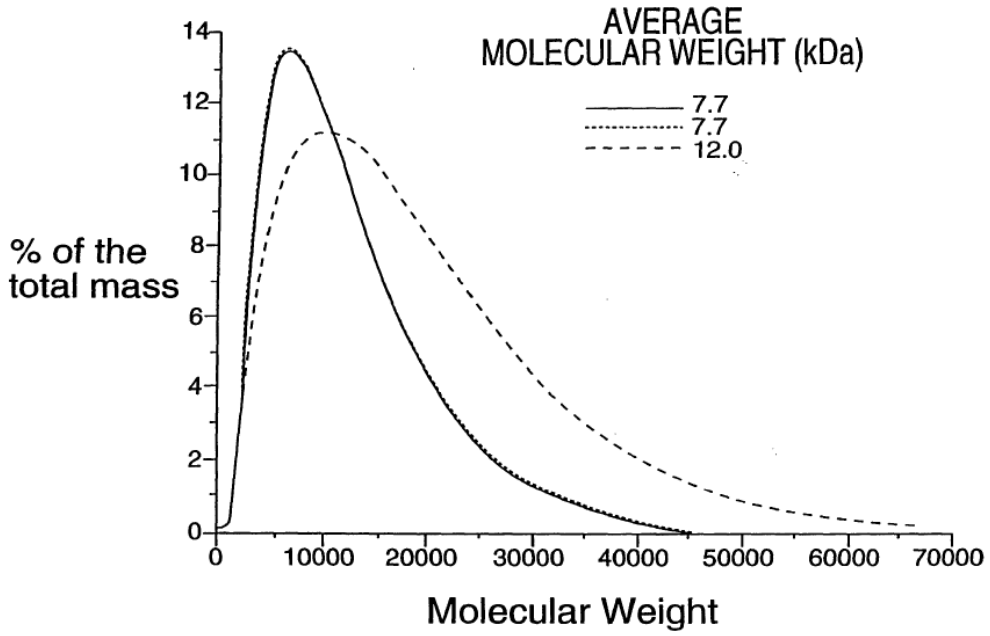


FIG. 1

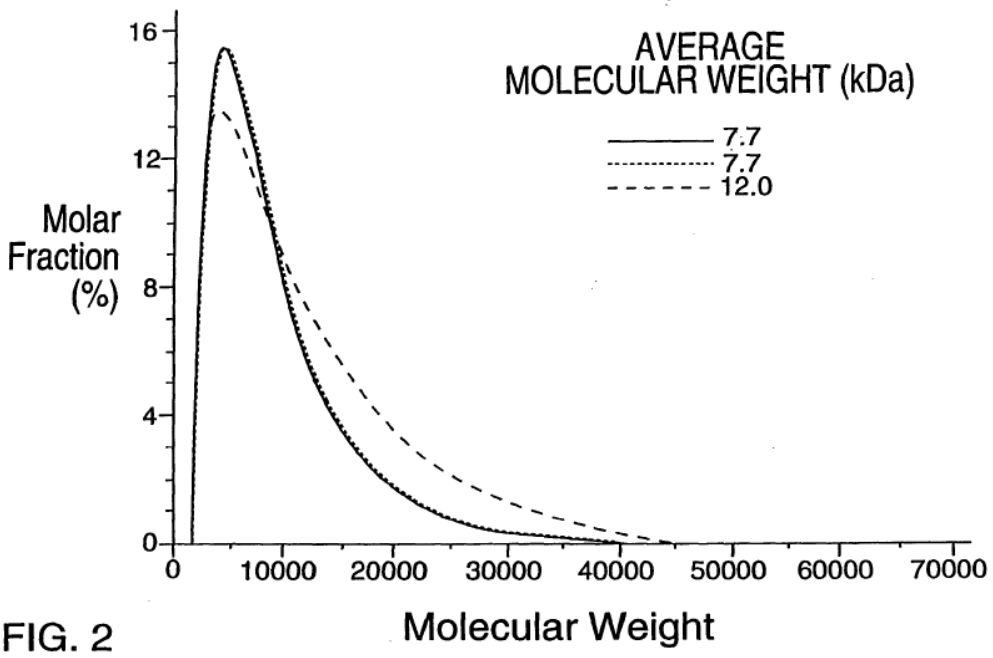


FIG. 2

171. Neither Figure 1 nor Figure 2 is expressly referred to in the remainder of the description. In particular, none of the Examples expressly refers to either Figure.

Detailed description of the invention

172. Paragraph [0010] states that the invention relates to a composition of copolymer-1 which contains less than 5%, preferably less than 2.5%, of species of copolymer-1 having a molecular weight of 40 kDa or more. Paragraph [0011] states that the invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa. Paragraph [0012] states that, in addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 kDa, in particular ones having an average molecular weight of about 4 to about 8 kDa and of about 6.25 to about 8.4 kDa.

173. At [0013] the specification says that copolymer-1 may be prepared by methods known in the art, such as the process disclosed in US 550, in which NCAs of alanine, tyrosine, benzyl-protected glutamic acid and TFA-protected lysine are polymerised with diethylamine as an initiator and then the blocking groups removed with HBr in acetic acid and piperidine.

174. Paragraph [0014] says that copolymer-1 with the required molecular weight profile can be obtained by methods known *per se*, including fractionation by chromatography, partial acid or enzymatic hydrolysis followed by dialysis or ultrafiltration and preparing the desired species while the amino acids are still protected. It then states:

> "A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. "

Finally, it says that the compositions of the invention may be formulated by conventional methods.

175. The specification then describes four examples. 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.

176. 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."

177. 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.

178. 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".

179. 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".

180. 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."

181. 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.

182. 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

183. 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."

184. Example 3 describes the preparation of TFA-copolymer-1. The reader is told that this is prepared in two steps. In the first step the NCAs of tyrosine, alanine, benzyl-protected glutamic acid and TFA-protected lysine are polymerised using diethylamine as initiator as described in Teitelbaum 1971, yielding protected copolymer-1. In the second step, the benzyl protecting groups are removed by treatment with 33% HBr in acetic acid at room temperature for 6-12 hours, yielding TFA-copolymer-1.

185. Example 4 is divided into two sections. The first describes the preparation of TFA-copolymer-1 and the second the preparation of "low toxicity" copolymer-1. In the first section the polymerisation step again follows the method described in Teitelbaum 1971. The specification continues:

> "[0033] Protected copolymer-1 is treated with HBr in glacial acetic acid which removes the omega benzyl protecting groups from the 5-carboxylate of the glutamate residues and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7000±2000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-28ºC a test reaction is performed on every batch at different time periods for example, from 10-50 hours.
>
> [0034] The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7000±2000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26ºC the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoro-acetyl-copolymer-1."

186. In the second section of Example 4, TFA-copolymer-1 is deprotected using piperidine, yielding copolymer-1.

The claims

187. The claims fall into four groups. First, three product claims directed to the improved copolymer-1 composition:

> "1. A copolymer-1 fraction wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight over 40 kDa and wherein 75% of said fraction is within a molecular weight range from 2 kilodaltons to 20 kilodaltons.
>
> 2. The copolymer-1 fraction according to Claim 1, wherein said copolymer-1 has an average molecular weight of 4 to 8 kilodaltons.
>
> 3. The copolymer-1 fraction according to Claim 1, wherein said copolymer-1 has an average molecular weight of 6.25 – 8.4 kDa."

188. Secondly, three composition for use claims as follows:

> "4. A composition for use in the treatment of multiple sclerosis, wherein said fraction contains less than 5% species of copolymer-1 having a molecular weight of over 40 kilodaltons, and 75% of said copolymer-1 in said fraction is within a molecular weight range of 2 kilodaltons to 20 kilodaltons.
>
> 5. The composition for use in the treatment of multiple sclerosis according to Claim 4, comprising a pharmaceutically effective amount of a copolymer-1 fraction, where said copolymer-1 fraction has an average molecular weight of 4 to 8 kilodaltons and a pharmaceutically acceptable carrier.
>
> 6. The composition for use in the treatment of multiple sclerosis according to Claim 4, comprising a pharmaceutically effective amount of a copolymer-1 fraction, where said copolymer-1 fraction has an average molecular weight of 6.25 to 8.4 kilodaltons and a pharmaceutically acceptable carrier."

189. Thirdly, claims directed to the method of controlling the molecular weight of copolymer-1:

> "7. A method of manufacturing copolymer-1 having over 75% of its molar fraction within the molecular weight range from 2 to 20 kilodaltons, comprising:
>
> reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1,
>
> wherein said reaction takes place for a time and at a temperature predetermined by a small scale reaction,

> treating the said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form crude copolymer-1 and
>
> purifying the said crude copolymer-1 to result in pure copolymer-1 having over 75% of its molar fraction within the molecular weight range 2 to 20 kilodaltons.
>
> 8. The method of Claim 7, wherein said protected copolymer-1 is reacted with hydrobromic acid for 10-50 hours at a temperature of 20-28°C.
>
> 9. The method of Claim 8 wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours and at a temperature of about 26°C.
>
> 10. The method of Claim 7 wherein said pure copolymer-1 has a molecular weight of 5-9 kilodaltons."

190. Finally, two independent Swiss-style claims:

> "11. Use of copolymer-1 fraction, wherein said copolymer-1 has an average molecular weight of 4 to 8 kilodaltons, in manufacture of a medicament for treatment of multiple sclerosis.
>
> 12. Use of copolymer-1 fraction, wherein said copolymer-1 has an average molecular weight of 6.25 to 8.4 kilodaltons, in manufacture of a medicament for treatment of multiple sclerosis."

Construction

191. In *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8 at [5] the Court of Appeal summarised the general principles applicable to the construction of patent claims as follows:

> "One might have thought there was nothing more to say on this topic after *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 9. The judge accurately set out the position, save that he used the old language of Art.69 EPC rather than that of the EPC 2000, a Convention now in force. The new language omits 'the terms of' from Art.69. No one suggested the amendment changes the meaning. We set out what the judge said, but using the language of the EPC 2000:
>
> [182] The task for the court is to determine what the person skilled in the art would have understood the patentee to have been using the language of the claim to mean. The principles were summarised by Jacob LJ in *Mayne Pharma Pty Ltd v Pharmacia Italia SpA* [2005] EWCA Civ 137 and refined by Pumfrey J in *Halliburton Energy Services Inc v Smith International (North Sea)*

Ltd [2005] EWHC 1623 (Pat) following their general approval by the House of Lords in *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 9. An abbreviated version of them is as follows:

(i) The first overarching principle is that contained in Article 69 of the European Patent Convention.

(ii) Article 69 says that the extent of protection is determined by the claims. It goes on to say that the description and drawings shall be used to interpret the claims. In short the claims are to be construed in context.

(iii) It follows that the claims are to be construed purposively - the inventor's purpose being ascertained from the description and drawings.

(iv) It further follows that the claims must not be construed as if they stood alone - the drawings and description only being used to resolve any ambiguity. Purpose is vital to the construction of claims.

(v) When ascertaining the inventor's purpose, it must be remembered that he may have several purposes depending on the level of generality of his invention. Typically, for instance, an inventor may have one, generally more than one, specific embodiment as well as a generalised concept. But there is no presumption that the patentee necessarily intended the widest possible meaning consistent with his purpose be given to the words that he used: purpose and meaning are different.

(vi) Thus purpose is not the be-all and end-all. One is still at the end of the day concerned with the meaning of the language used. Hence the other extreme of the Protocol - a mere guideline - is also ruled out by Article 69 itself. It is the terms of the claims which delineate the patentee's territory.

(vii) It follows that if the patentee has included what is obviously a deliberate limitation in his claims, it must have a meaning. One cannot disregard obviously intentional elements.

(viii) It also follows that where a patentee has used a word or phrase which, acontextually, might have a particular meaning (narrow or wide) it does not necessarily have that meaning in context.

(ix) It further follows that there is no general 'doctrine of equivalents.'

(x) On the other hand purposive construction can lead to the conclusion that a technically trivial or minor difference between an element of a claim and the corresponding element of the alleged infringement nonetheless falls within the meaning of the element when read purposively. This is not because there is a doctrine of equivalents: it is because that is the fair way to read the claim in context.

(xi) Finally purposive construction leads one to eschew the kind of meticulous verbal analysis which lawyers are too often tempted by their training to indulge."

192. In the present case, two further principles are relevant. The first is that, as Chitty J said in *Lister v Norton Brothers & Co* (1886) 3 RPC 199 at 203, a patent "must be read by a mind willing to understand, not by a mind desirous of misunderstanding". Binnie J delivering the judgment of the Supreme Court of Canada added in *Whirpool Corp v Camco Inc* [2001] FSR 46 at [49(c)] that "a 'mind willing to understand' necessarily pays close attention to the purpose and intent of the author." It follows that, as Pumfrey J said in *Halliburton Energy Services Inc v Smith International (North Sea) Ltd* [2005] EWHC 1623 (Pat), [2006] RPC at [60] "over-meticulousness is not to be equated to carefulness. Care in working out what the patentee was aiming at when he chose the words he used is absolutely necessary."

193. The second is that 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, as discussed below.

194. In the present case there are a series of questions of construction, some of which are relevant to issues of validity and some of which are relevant to issues of infringement. This is not a case where there is a squeeze between validity and infringement, however.

Copolymer-1

195. Each of the claims requires the presence or production of "copolymer-1". The Patent states at [0003] that "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." What is the meaning of "approximately 6:2:5:1"? Mylan's primary contention is that, for the reasons explained below, the word "approximately" covers compositions in which the molar fraction of any single amino acid does not differ from 6:2:5:1 by more than ±10%, with the result that Mylan's product does not infringe. 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. The Defendants' contention is in essence that the word "approximately" means what it says, and 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, however, 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. These broad contentions generated a number of sub-issues and a considerable volume of evidence.

196. It is convenient to begin with two points that are common ground. The first is 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. Accordingly, the burden of interpretation would primarily fall on the analytical chemist with expertise in amino acid analysis and the synthetic chemist. Prof Kent addressed this issue for Mylan, while Prof Sampson addressed it for the Defendants.

197. The second is that the skilled reader would look at the documents cited in the Patent to see if they gave assistance as to what was meant by "approximately 6:2:5:1".

198. The first sub-issue concerns the impact of the variability in amino acid analysis. I have already considered what degree of experimental error the skilled analytical chemist would expect there to be in an amino acid analysis of copolymer-1 from his common general knowledge. My conclusion was that he would know that in principle such analyses should have a reproducibility of ±5% or better, but that he would also be aware that in practice many laboratories did not achieve such a low level of experimental error. It follows that the skilled reader would appreciate that the inventors might well be intending to allow for a greater degree of experimental error in amino acid analysis than ±5%.

199. The second sub-issue concerns the impact of the variability in the synthesis of copolymer-1. Prof Kent expressed his opinion very precisely and concisely in paragraph 5.12 of his first report as follows:

> "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 …"

200. So far as the variability in the synthesis of copolymer-1 is concerned, neither side suggested that the skilled team would be aware from their common general knowledge what degree of variation in the molar ratio of the four amino acids should be expected. The synthetic chemist would be aware from his common general knowledge, however, of the general nature of a random copolymer like copolymer-1, namely that it is a mixture of chain lengths and chain sequences. Furthermore, the skilled team would see from the Patent that copolymer-1 even according to the invention has a fairly broad molecular weight distribution. In my view this casts considerable doubt on Prof Kent's approach, since the skilled team would not expect repeat syntheses to produce the same composition. In any event, as noted above, it is common ground that the skilled team would not rely simply on their reading of the Patent and their common general knowledge, but would look to the cited prior art for any guidance on this point.

201. This takes me to the third sub-issue, which is what the skilled team would get from those documents. As noted in paragraph 16 above, Teitelbaum 1971 discloses two batches of copolymer-1 whose molar ratios are 6.0:1.9:4.7:1.0 and 6.7:2.1:4.2:1.0 respectively. US 550 discloses "by way of example only" a composition whose molar ratio is 6:2:4.5:1. As noted in paragraph 29 above, Bornstein 1987 discloses copolymer-1 with a molar ratio of 6.0:1.9:4.7:1.0 i.e. the same as Teitelbaum 1971 Batch I. The following table compares the differences in amino acid molar fractions expressed as percentages between these compositions and one whose composition is exactly 6:2:5:1:

	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%

202. The Defendants, supported by Prof Sampson, say that the skilled reader would conclude that all of the compositions disclosed in Teitelbaum 1971, US550 and Bornstein 1987 had molar ratios of "approximately 6:2:5:1". A number of points are made in support of this contention, which may be summarised as follows. First, the specification describes what is disclosed in these documents at [0001]-[0002] as "copolymer-1" before going on to define "copolymer-1" as having a molar ratio of "approximately 6:2:5:1" in [0003]. Secondly, the skilled reader would note that Teitelbaum 1971 states that Batches I and II were prepared "in an identical manner",

and would take the resulting molar ratios as indicating the variability of the synthesis. Thirdly, the skilled reader would note that Teitelbaum 1971 describes Batches I and II as having "identical" (abstract) or "similar" (paragraph 4.5) activity. Fourthly, the skilled reader would note that, as can be seen from the table above, the proportions vary significantly, although not wildly. In this regard, it is common ground that the variation in the proportion of lysine in Teitelbaum 1971 Batch II from that in a composition of exactly 6:2:5:1 exceeds Prof Kent's 10% threshold: on Prof Kent's approach to the comparison (as to which see below), it is 16%.

203. Mylan, supported by Prof Kent, says that the skilled reader would not conclude from these documents that the variability in any single amino acid could exceed $\pm$10%. A number of points are made in support of this contention. First, the skilled reader would place most weight on Bornstein 1987, since this was the landmark study establishing the efficacy of copolymer-1 in humans and since it was the nearest in time to the Patent. The skilled reader would note that the composition used for this trial corresponded to Batch I of Teitelbaum 1971, and would presume that there was some reason for this. Secondly, and by contrast, the skilled reader would note that Teitelbaum 1971 Batch II is not reported to have been used in a study involving human beings, and indeed is not referred to at all in any of the other cited publications. Thirdly, the skilled reader would not think that it was possible to draw any meaningful conclusion as to the variability of the synthesis of copolymer-1 from the limited information in Teitelbaum 1971. Fourthly, the skilled reader would note that there was no change in the proportion of tyrosine between Batch I and II in Teitelbaum 1971. Thus, even if the skilled reader concluded that Teitelbaum 1971 told him something useful about the variability of the synthesis of copolymer-1, he would understand that the variability did not affect the proportion of tyrosine. Fifthly, the skilled reader would note that tyrosine is present in a lower relative amount than the other amino acids, and so any variation in tyrosine would be expected to be lower on an absolute basis. Lastly, the skilled reader would think that the molar ratio of Batch II was better described as approximately 7:2:4:1.

204. So far as this sub-issue is concerned, I find the points relied on by the Defendants more persuasive than those relied on by Mylan. So far as Mylan's first two points are concerned, none of the documents identify any reason why Bornstein 1987 used a composition corresponding to Teitelbaum 1971 Batch I and not Batch II, and Teitelbaum 1971 suggests that Batch II should be equally efficacious in humans. As to the third point, the information given by Teitelbaum 1971 is limited, but it is the most pertinent information on this point. As for the fourth and fifth points, these are driven by Mylan's non-infringement argument, which is based on the proportion of tyrosine in its product. It is not legitimate to construe the claim by reference to the alleged infringement, however. Furthermore, these points are inconsistent with Prof Kent's 10% interpretation, which involves treating all the amino acids in the same way. Yet further, the tyrosine proportion of Batches I and II is not identical, as can be seen from the table above. (Both molar ratios have tyrosine as one because both ratios are normalised with respect to tyrosine.) In any event, I do not think the skilled reader would conclude from Teitelbaum 1971 that the variability in tyrosine, at least in relative terms, was necessarily less than the variability in the other amino acids. The skilled reader would be more likely to conclude that the fact that the proportion of tyrosine was more similar in Batches I and II than, say, the proportion of lysine was down to chance. As to the last point, I accept that one can describe the molar ratio of

Batch II as being 7:2:4:1, but I do not agree that it follows that the skilled reader would not regard it as being "approximately 6:2:5:1."

205. This takes me to the fourth sub-issue, which concerns the immunogenicity of tyrosine. As noted above, the Defendants contend that the skilled team would have been aware from their common general knowledge that the immunogenicity of a substance like copolymer-1 was not sensitive to the proportion of tyrosine present, but I have not accepted that. Mylan, supported by Prof Kent, contends that the skilled team would have drawn the opposite conclusion from US 550. This states at col. 1 l. 69 – col. 2 l. 7:

> "Compositions according to the present invention comprise a basic copolymer with a net positive electrical charge, comprising a suitable quantity of an amino acid of positive electrical charge, such as lysine or arginine, in combination with a lesser quantity of an amino acid with a negative electrical charge, such as a glutamic acid or aspartic acid, possibly with an amino acid adapted to confer immunogenic properties, such as an aromatic amino acid."

Mylan says that the skilled reader would conclude from this that a significant change in the proportion of tyrosine (i.e. more than 10%) would be likely to change the activity or side effects of copolymer-1.

206. In my view this argument places more weight on the passage than it can bear. The passage is simply a general description of the constituents of copolymer-1. It does not purport to give any guidance to the reader as to the effect on the immunogenicity of copolymer-1 of changes in the proportion of tyrosine to the other three acids.

207. The fifth sub-issue concerns the manner in which differences in molar ratios should be assessed. The evidence and arguments in relation to this sub-issue became very elaborate during the course of trial. The core of the dispute, however, concerns two questions. The first question is 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). For convenience I will refer to these as "relative difference" and "absolute difference" respectively. Take, for example, a sample in which the molar fractions expressed as percentages are 42.7, 14.4, 33.6 and 9.2 (as in Mylan's batch GMA2 referred to below). The relative difference in tyrosine compared to a molar ratio of 6:2:5:1 is 29.6% (9.2 – 7.1 as a percentage of 7.1), whereas the absolute difference in tyrosine is 2.1% (9.2 – 7.1). Prof Kent supported the former approach, whereas Prof Sampson supported the latter approach.

208. The second question is whether, if the latter approach is taken, the skilled reader would proceed to make a comparison based on the total absolute difference, as Prof Sampson advocated. Thus it was Prof Sampson's opinion that batch GMA2 was "approximately 6:2:5:1" because the total absolute difference in the four amino acids compared to exactly 6:2:5:1 is 4.5, whereas in the case of Teitelbaum 1971 Batch II the total absolute difference is 12.

209. I do not intend to trawl through all of the different arguments and illustrations which were raised by the parties in relation to this sub-issue, because in my view they tended to obscure the position rather than illuminate it. Rather, I will concentrate on what appear to me to be the key points.

210. In my view, if one accepts Prof Kent's premises, then the logic of his approach is impeccable. As explained above, those premises are in essence that (a) "approximately" caters for variability in both amino acid analysis and synthesis, (b) the variability in amino acid analysis is $\pm$5% for each amino acid and (c) that figure should be doubled to allow for variability in synthesis. Logically, it follows from those premises that, if one is attempting to decide whether or not a particular molar ratio exceeds the 10% limit, then it is the relative difference in each amino acid that matters.

211. In addition, Prof Kent's approach is supported by the fact that, as Prof Sampson accepted, the conventional approach to questions of repeatability and reproducibility in amino acid analysis is to look at the molar fraction for each amino acid, i.e. the relative difference. Indeed, as counsel for Mylan submitted, it is striking that neither the papers such as Crabb nor Teva's disclosure documents that are in evidence adopt the approach of looking at the absolute difference. Furthermore, as Prof Kent pointed out, looking at the absolute difference ignores the relative abundance of the amino acid. This is particularly significant in the case of the least abundant, namely tyrosine. Finally, Prof Sampson's approach of comparing the total absolute differences of all four amino acids seems to have very little logic to it at all. Prof Sampson sought to justify it in her oral evidence by drawing an analogy with comparisons between proteins, but I did not find this persuasive.

212. In my opinion there are two problems with Prof Kent's approach, however. The first concerns premise (b). For the reasons given above, I consider 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. The second problem concerns premise (c). For the reasons given above, I consider that 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. Accordingly, the skilled reader 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.

213. In these circumstances, I agree with Prof Sampson that the skilled reader would proceed to consider what the different numbers represented in terms of amino acids in the polymer chain. Prof Sampson included two illustrations of this in her first report, which I will take in reverse order. The first compares an illustrative copolymer-1 chain comprising 70 amino acids (which would have a molecular weight of about 7 kDa) having a molar ratio of exactly 6:2:5:1 with an illustrative copolymer-1 chain comprising 70 amino acids having the molar ratio of Teitelbaum Batch II:

214. The second compares an illustrative copolymer-1 chain comprising 70 amino acids having a molar ratio of exactly 6:2:5:1 with an illustrative copolymer-1 chain comprising 70 amino acids having the molar ratio of batch GMA2:

215. Prof Kent's evidence when asked about these illustrations in cross-examination was that they were oversimplifications of complex mixtures. He went on to say:

> "...that would equate, I think, to a difference of about one and a half tyrosines and that is a problem when you try and illustrate it with a monodisperse illustration. You cannot have non-integral numbers of amino acids. In the real mixture you can and you do."

216. I do not accept this. It is quite true that the mixture is complex in that it contains chains of varying length and varying amino acid sequences as well as varying proportions of amino acids. Variations in length and sequence are relatively unimportant for this purpose, however, since what we are concerned with is the molar ratio of the four amino acids taken as an average across the mixture. It is also quite true that the average reflects the presence of a variety of different species in terms of amino acid proportions. The real mixture does not contain chains with non-integral numbers of amino acids, however. On the contrary, each chain has an integral number of amino acids. Thus in my opinion, provided it is kept firmly in mind that they are a simplification of a more complex situation, Prof Sampson's illustrations are helpful in showing the effect of changes in molar ratio in terms of numbers of amino acids.

217. This brings me back to the position with regard to tyrosine. As stated above, I agree with Prof Kent that one of the flaws of Prof Sampson's approach based on absolute differences is that it ignores the relative abundance of the amino acids and that this is particularly significant in the case of the least abundant, tyrosine. What Prof Sampson's second illustration shows, however, is that, precisely because tyrosine is the least abundant, a change in a single amino acid from lysine to tyrosine can result in a relative difference in tyrosine of 29.6% and change the molar ratio from 6:2:5:1 to 4.6:1.6:3.7:1.0. For this reason, I consider that the skilled reader would be inclined to accept a greater deviation, expressed in terms of relative difference, in the proportion of tyrosine as being encompassed by "approximately 6:2:5:1" than in the case of the other amino acids.

218. The final sub-issue arises out of the fact that Mylan's construction leads to the consequences that (a) Copaxone is not copolymer-1 within the meaning of the Patent and (b) nor is Mylan's product copolymer-1 within the meaning of the Patent even though Mylan and its manufacturer Natco Pharma Ltd ("Natco") both refer to it as copolymer-1. The Defendants submit that this is absurd. As counsel for Mylan pointed out, however, this amounts to an illegitimate attempt to construe the Patent by reference to products produced subsequently.

219. Drawing these threads together, my conclusions are as follows. 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 $\pm$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.

Fraction

220. Claims 1-6 and 11-12 refer to a copolymer-1 "fraction". Mylan contends that "fraction" means a sample obtained following a separation technique such as chromatography, and more specifically a sample of lower molecular weight obtained by removal of higher molecular weight species. The Defendants contend that it should be interpreted as not being so limited, but as meaning a sample obtained from something greater, whether by separation or by the process of claims 7-10, which involves splitting larger molecules into smaller ones.

221. Prof Hunter and Prof Grant were agreed that the conventional meaning of "fraction" in chemistry was a sample obtained following a separation technique, most typically chromatography. The issue is whether the skilled reader would understand that the term was being used in the Patent with that conventional meaning or was intended to have a wider meaning. In my judgment the skilled reader would understand that in the context of the Patent the term was being used with the wider meaning contended for by the Defendants for the following reasons.

222. The skilled reader would appreciate that the Patent was disclosing that there are benefits to lower molecular weight copolymer-1 fractions however they are obtained. Indeed, the summary of the invention in the Patent at [0005]-[0007] does not refer to the process at all. As I shall discuss in more detail below, paragraph [0014] discloses that copolymer-1 with the desired molecular weight profile can be obtained either by chromatographic separation or by the method which is further described in Example 4, that is to say, the method of claims 7-10. The skilled reader would understand that in the former method a population of lower weight molecules was separated from a population of higher molecular weight molecules, whereas in the latter method a population of higher molecular weight molecules was converted into a population of lower weight molecules. There is nothing in the specification to suggest to the skilled reader that, by use of the word "fraction", the inventors intended to limit the product claims to copolymer-1 obtained by the former method rather than the latter method. On the contrary, it suggests that the inventors had the opposite intention.

Average molecular weight

223. Claims 2, 3, 5, 6, 11 and 12 all use the expression "average molecular weight". Furthermore, it is common ground that "molecular weight" in claim 10 (and Example 4) would be understood by the skilled team to mean "average molecular weight". One of the major disputes in this action is as to how the skilled team would interpret this expression. The Defendants contend that the skilled team would understand it to mean M_p. Mylan contends that the skilled team would be unable to determine what type of average molecular weight was being referred to, and hence that the claims are ambiguous.

224. It is convenient to begin with two points that are common ground. The first is that the specification does not define or explain what is meant by the term "average molecular weight". In my view the skilled team would be very surprised that the inventors had failed to explain such a basic matter, and rather cross at being presented with such a puzzle to solve. After all, the inventors could easily have specified which type of average molecular weight they meant. As I have pointed out above, however, the skilled team is deemed to read the specification with a mind willing to understand it.

It follows that they would not throw up their hands when confronted with the problem, but would consider the specification with care to see if it was possible to work out what was meant by "average molecular weight".

225. The second point is that the skilled team would appreciate that the average molecular weight figures quoted in the Patent had been determined by SEC. It follows that the burden of interpretation would primarily fall upon the analytical chemist with knowledge of SEC. As I have noted above, Mylan's main witness on this issue was Prof Hunter, rather than Dr Hunt, but Prof Hunter had sufficient expertise in SEC for this purpose. It also follows that M_v can be ruled out as a possible candidate.

226. The Defendants contend that the skilled SEC analyst would approach the specification with the understanding that M_p was an average molecular weight. For the reasons given above, I have not accepted that contention, but I have nevertheless concluded that the skilled analytical chemist would be aware from his common general knowledge that M_p was sometimes inaccurately referred to as an average molecular weight. In my view it follows that, when trying to work out what the inventors meant by "average molecular weight", the skilled reader would consider the possibility that the inventors had used the expression to mean M_p, even if the reader started with the presumption that "average molecular weight" meant M_n, M_w or M_z.

227. Prof Grant gave a number of reasons for concluding that "average molecular weight" would be interpreted by the skilled reader as meaning M_p rather than any of the other possible candidates, such as M_n or M_w. First, it was Prof Grant's evidence that it was common practice for polypeptides and proteins to be described by a single molecular weight, and in many cases those values were M_p values determined by SEC. Prof Hunter agreed that this was so in the case of single proteins or monodisperse polypeptides, where $M_p = M_n = M_w$, but he was not able to speak to the position regarding polydisperse polypeptides. Nevertheless, he accepted that in general it was common practice for researchers to use the peak of a differential distribution (i.e. M_p) as a rough estimate of the "molecular weight" of their sample.

228. Secondly, M_p is usually determined by SEC. Given that the Patent provides no other information than that the measurement was by SEC, Prof Grant considered that the skilled reader's understanding would be that the "average molecular weight" was M_p. This evidence was predicated, however, on his view that the skilled reader would consider M_p to be an average molecular weight. Furthermore, I do not follow the logic of this point given that SEC also gives M_n, M_w and so on.

229. Thirdly, M_p can be read directly from a calibrated chromatogram. In contrast, the other types of averages require calculation and the Patent is silent about any such calculation. As both Prof Hunter and Dr Hunt pointed out, however, SEC instruments in 1994 generally had software which calculated all these values.

230. Fourthly, in traditional polymer chemistry, it is common practice for both M_n and M_w values to be quoted (or for one value to be given together with the PDI), so as to indicate the degree of polydispersity. Prof Grant's evidence was that it was much less common to report only one of M_n or M_w in the context of SEC, since that would give no information as to the breadth of the distribution. As Prof Grant accepted, however, if only M_p is reported, that gives no information as to the breadth of the distribution either.

231. Fifthly, the legends of Figures 1 and 2 identify the curves as being of samples of "average molecular weight" of 7.7 and 12.0 kDa. In the case of Figure 1, the peaks of the curves appear to be at approximately 7 and just over 10 kDa respectively. Prof Grant opined that this would support the skilled reader's view that the average in question was M_p. He gave an explanation for the discrepancies between the molecular weights quoted and the apparent peaks of the curves in Figure 1. This was that the Figure had been created by dividing the original chromatogram into a small number of slices and plotting a graph of the percentage of the sample attributable to a particular slice against the molecular weight of that slice. The accuracy of this method will depend on the number of slices of the chromatogram taken. When only a few slices are taken, the precise positioning of the peak of the molecular weight distribution will not necessarily correspond precisely to the peak of the chromatogram. In the case of Figure 1, the peak of the 7.7 kDa curve is at nearly 14% of the total mass of the sample. Unless this figure was created from a small number of wide slices, the area under the curve would be greater than 100%. In his second report Prof Hunter agreed that Figure 1 appeared to have been prepared in the manner described by Prof Grant and that this indicated that there was some error in the position of the peaks of the curves.

232. Prof Hunter's opinion was that it was unclear from the specification what was meant by "average molecular weight". His expectation was that this was a reference to either M_n or M_w. He did not think that it was M_p because he did not consider M_p to be an average molecular weight. In an attempt to ascertain whether "average molecular weight" meant M_n or M_w, he conducted an experiment using the Figures. This involved putting tracing paper over each Figure, marking the position of about 20 points on the curve, obtaining x and y values for these points using graph paper, converting every pair of sequential data points into the bars of a histogram and using the histogram to calculate the M_n, M_w and M_z values. In addition, he estimated the positions of each peak to obtain M_p. He subsequently repeated the exercise. The results were summarised by Prof Hunter in his first report as follows:

Analysis	**Figure**	**7.7 kDa sample**				
		PD	***M_n***	***M_w***	***M_z***	***M_p***
Original analysis	Fig 1	1.5	8.3	12.8	17.5	6.8
	Fig 2	1.4	9.3	13.3	17.4	-
Estimated ranges	Fig 1	1.5 ± 0.1	8.3 ± 0.5	12.8 ± 0.5	17.5 ± 1	6.8 ± 1
	Fig 2	1.4 ± 0.1	9.3 ± 0.5	13.3 ± 0.5	17.4 ± 1	-
Repeat analysis	Fig 1	1.5	8.4	12.9	17.8	6.7
	Fig 2	1.4	9.5	13.4	17.5	-

Analysis	**Figure**	**12 kDa sample**				
		PD	***M_n***	***M_w***	***M_z***	***M_p***
Original analysis	Fig 1	1.7	11.7	20.0	28.4	10.4
	Fig 2	1.5	12.3	18.1	23.1	-

Estimated ranges	Fig 1	1.7 ± 0.1	11.7 ± 0.5	20.0 ± 0.5	28.4 ± 1	10.4 ± 1
	Fig 2	1.5 ± 0.1	12.3 ± 0.5	18.1 ± 0.5	23.1 ± 1	-
Repeat analysis	Fig 1	1.7	11.8	19.9	28.0	10.1
	Fig 2	1.5	12.5	18.2	23.3	-

233. Prof Hunter's conclusion was that the M_n values he had calculated were closer to the values for "average molecular weight" quoted in the Patent than his M_w or M_z figures, or even M_p, but that there was a discrepancy between the values of M_n that he had calculated and the "average molecular weight" quoted in the Patent for the 7.7 kDa sample that he was unable to explain. Thus he considered it unclear what the Patent meant by "average molecular weight".

234. This experiment led to an elaborate dispute between Prof Hunter and Prof Grant. Before turning to that, however, it should be noted that in his first and second reports Prof Hunter proceeded on the basis, as discussed above, that M_p could be obtained by estimating the position of the peaks in Figure 1. In his third report, however, Prof Hunter came to the conclusion as a result of further analysis of the Figures undertaken by him in response to Prof Grant's second report that this was not correct. Prof Hunter proceeded to explain his analysis further in his fourth report in reply to Prof Grant's third report.

235. In summary, Prof Hunter explained in his third and fourth reports that there are two forms of differential molecular weight distribution, w(M) and x(M). w(M) represents the molecular weight distribution as a function of molecular weight M, while x(M) represents the log of the molecular weight distribution as a function of log molecular weight. Accordingly, it is usual to plot w(M) against M and x(M) against log M. If x(M) is plotted against M, the effect is that the curve acquires a high molecular weight tail and the peak also shifts. Standard equations can be used to calculate M_n and M_w from a plot of x(M) against log M or from a plot of w(M) against M. If x(M) is plotted against M, then an adjustment has to be carried out in order to determine M_n and M_w. A plot of x(M) against log M has the same shape as the chromatogram assuming that the calibration curve is linear, and hence the peak of such a plot is M_p. If the plot is of w(M) against M, however, a conversion must be carried out to estimate M_p.

236. Prof Hunter's opinion was that Figure 1 in the Patent is a plot of w(M) (multiplied by a scaling factor) against M. He accepted that there was no information in the Patent which made it clear whether Figure 1 was a plot of a scaled version of w(M) against M or a scaled version of x(M) against M. He believed that Figure 1 was of the former type because it was conventional to plot w(M) against M rather than x(M) against M, and the x axis in Figure 1 was labelled as "molecular weight". Furthermore, that would be particularly appropriate given the prominence of average molecular weight and molecular weight distribution characteristics in the Patent and would mean that one could read off from the curves the relative proportion of species present at any molecular weight.

237. In his second and third reports, Prof Grant disagreed with Prof Hunter's interpretation of Figure 1. His opinion was that Figure 1 was not a differential molecular weight

distribution at all. In exhibit GAG8 to his second report, Prof Grant enlarged on the explanation he had given in his first report of the way in which he thought that Figure 1 had been created (summarised in paragraph 231 above). As Prof Hunter demonstrated in his fourth report, however, what this process results in is a plot of x(M) (multiplied by a scaling factor) against M. As noted in paragraph 114 above, Prof Grant was reluctant to accept this; but he was unable to point to any error in Prof Hunter's analysis.

238. It follows that the difference between Prof Hunter's and Prof Grant's interpretation of Figure 1 is as to whether the y axis (labelled "% total mass") is a scaled version of w(M) or a scaled version of x(M). If the y axis is a scaled version of w(M), then the standard equations can be applied directly and produce the results set out by Prof Hunter in his first report and quoted in paragraph 232 above (although, as noted in paragraph 234 above, the figures for M_p require adjustment: these should read 11.7, 11.7, 21.3 and 20.8). If the y axis is a scaled version of x(M), then a conversion needs to be undertaken. Prof Hunter set out the relevant figures in exhibit CH11 to his third report. The upshot was that, on the latter basis, the best fit is with the average molecular weight being M_w, but there are still discrepancies.

239. So far as the science is concerned, I found Prof Hunter's analysis in his third and fourth reports and his explanations in cross-examination completely convincing, and I have no hesitation in accepting it. The issue which I have to decide, however, is not whether Prof Hunter's analysis or that of Prof Grant is the more scientifically accurate. The issue is how the skilled reader of the Patent would interpret the references to "average molecular weight". So far as that issue is concerned, I have come to the conclusion that counsel for the Defendants was correct to submit that Prof Hunter's approach to the figures does not represent the approach which the skilled reader would adopt even though it is scientifically sound. My reasons are as follows.

240. First, I am not persuaded that the skilled reader would think of conducting an experiment of the kind carried out by Prof Hunter in order to ascertain what the inventors meant by "average molecular weight". The experiment is a painstaking and time-consuming exercise. Furthermore, I think that there is force in the point made by both Prof Grant and counsel for the Defendants that the skilled reader would be doubtful that the Figures were sufficiently accurate to be used in this way. I do not consider that the skilled reader would view the Figures as purely schematic, but he would note two curiosities about them. The first is that, as I shall explain below, the Figures do not appear to be consistent with each other. The second is that, perhaps due to an artefact of reproduction, the spacing on the axes is uneven: on the x axis the distance between each 10,000 Da interval varies from 20.5 to 22 mm, while on the y axis the distance between each 2% interval varies from 14 to 15 mm.

241. Secondly, I agree with counsel for the Defendants that it is significant that even Prof Hunter thought until quite late in the day that it was possible to estimate M_p directly from the positions of the peaks in Figure 1 and that the discrepancy between the values observed and the values quoted in the Patent could be explained by the manner in which the Figure had been produced from the chromatogram.

242. Thirdly, it is also significant that Prof Hunter's analysis in his third report was heavily based on a paper by Shortt, "Differential Molecular Weight Distributions in High Performance Size Exclusion Chromatography", *J. Liq. Chrom.*, 1993, 16(16), 3371-

3391. Prof Hunter said that this paper was included in Teva's disclosure documents. He did not suggest that he was familiar with it prior to reading it for the purposes of preparing his third report. Furthermore, Shortt states that it reveals and corrects a number of "common errors in the literature", of which plotting x(M) against M is one. I am therefore not persuaded that the ordinary skilled SEC analyst using just his common general knowledge would arrive at the analysis which Prof Hunter finally arrived at. In this regard, it is telling that this analysis was undertaken by Prof Hunter and not Dr Hunt.

243. Fourthly, even if the skilled reader did undertake the experiment, I do not think he would draw the conclusion from it that Prof Hunter did. In my view he would be more likely to conclude that the experiment was flawed, probably because the Figures were not accurate enough to admit of such an analysis. This is not only because none of the averages calculated by Prof Hunter correspond with the values quoted in the Figures, but also the values obtained by Prof Hunter from Figure 1 and 2 differ substantially from each other.

244. Counsel for Mylan relied on the fact that, when confronted with Prof Hunter's analysis in cross-examination, Prof Grant said on several occasions that the skilled person would not know whether the y axis of Figure 1 was a scaled version of x(M) or a scaled version of w(M). Counsel argued that this confirmed that the Patent was ambiguous. I do not accept this argument. Prof Grant's answers have to be viewed in context, which was a discussion of the correctness or otherwise of Prof Hunter's analysis. Considered as a whole, the effect of Prof Grant's evidence was that the skilled reader would not analyse Figure 1 in that kind of depth at all. For the reasons I have just given, I agree with that assessment.

245. Finally, I must consider a separate argument advanced by counsel for Mylan. He submitted that one approach which the skilled team could take would be to note that the Patent contrasts the average molecular weight of the products of the invention with the average molecular weight of copolymer-1 in the prior art. This would suggest that the Patent was using the expression "average molecular weight" to mean the same thing as it meant in the prior art cited in the specification. Counsel submitted that this did not take the skilled team any further forward, however. If they looked at Bornstein 1987, they would see mention of a molecular weight, which must be an average molecular weight, but no indication of which average molecular weight is intended or how it was measured. If they looked at US 550, the position would be the same. If the skilled team looked at Teitelbaum 1971, the analyst would see from section 3.7 that the molecular weights, which are expressly stated to be average molecular weights, have been measured by ultracentrifugation techniques, citing references 24 and 29. Prof Hunter's opinion having considered those references was that the most likely interpretation was that Teitelbaum 1971 was referring to M_w. Prof Grant said this involved an incorrect assumption, and that it could be M_n, M_w or M_z. He did not suggest, however, that the skilled reader would conclude that Teitelbaum 1971 was referring to M_p.

246. Accordingly, counsel for Mylan argued that the skilled person who reviewed the prior art cited in the Patent would note that the authors of the prior art (who include three of the four inventors of the Patent, namely Prof Arnon, Prof Sela and Dr Teitelbaum) cite numbers for what are clearly average molecular weights without specifying whether they are M_n or M_w (or even M_z), but which do not appear to be M_p, and

would conclude that the inventors were doing the same thing in the Patent. Thus the skilled reader would be left in a quandary as to what the Patent meant by "average molecular weight". Indeed, this would undermine any suggestion that the Patent was referring to M_p.

247. While I acknowledge the force of this argument, I am not persuaded by it. The problem with it is that the skilled team would appreciate that the Patent is clear that the average molecular weights have been determined by SEC, but that there is no indication that SEC was used to determine the molecular weights quoted in the prior art. On the contrary, it is clear from Teitelbaum 1971 that at least in that case SEC was not used. Thus while the skilled team might well start with the presumption that the inventors were using the term "average molecular weight" in the same way as the prior art, they would realise upon reflection that that might well not be the case. Accordingly, they would be driven back to trying to work out what the term meant in the context of the Patent.

248. Although I confess that I have at times come close to concluding that the Patent is ambiguous, in the end I have come to the conclusion that the skilled team would interpret the Patent as using "average molecular weight" to mean M_p. In reaching this conclusion I have taken into account all the points considered above, but I have been most influenced by Prof Grant's first and fifth points and Prof Hunter's responses to them. In summary, it seems to me that the skilled analyst would be likely to approach the specification with the presumption that "average molecular weight" meant M_n or M_w (or possibly M_z), which would lead him to wonder which of these was intended. Upon consideration of the facts that the (i) the Patent specifies the use of SEC to determine the "average molecular weight", (ii) it gives a single "average molecular weight" and (iii) the values quoted in Figure 1 appear to correspond with the peaks shown allowing for the error introduced by the manner in which the skilled analyst would think that Figure 1 had been prepared, however, the skilled analyst would conclude that the inventors must be taking M_p, albeit somewhat inaccurately, as the average molecular weight of the copolymer.

Molecular weight distribution

249. There is a similar issue to the preceding issue in relation to claims 1 and 4. Claim 1 requires that less than 5% of the species of copolymer-1 have a molecular weight more than 40 kDa and that over 75% have a molecular weight between 2 and 20 kDa. The Defendants contend that the percentage is a molar fraction. Mylan contends that it is unclear whether it is a molar fraction or mass faction, and therefore that the claim is ambiguous. (Counsel for the Defendants submitted that this allegation was not open to Mylan since it had not been pleaded. In my judgment it is just about covered by the relevant paragraph of the Grounds of Invalidity, but in any event the Defendants did not object when the point was raised in Mylan's evidence but proceeded to deal with it on its merits.) The same point arises on claim 4.

250. The Defendants rely upon three arguments for interpreting the claim as referring to a molar fraction. The first is that it was Prof Grant's opinion that the use of the word "species" indicated that the patentee was referring to 5% of the molecules, i.e. 5% of the sample on a molar basis. As Prof Hunter pointed out and Prof Grant accepted, however, paragraph [0009] of the Patent states that Figure 1 shows "the proportion of species with molecular weight above 40 kDa" and Figure 1 shows mass fraction, not

molar fraction. Thus the use of the word species in claim 1 does not necessarily indicate a molar fraction.

251. The second argument is that this interpretation is consistent with paragraph [0011] and claim 7, both of which explicitly require that the copolymer-1 has over 75% of its molar fraction within the range of 2 and 20 kDa. Mylan's counter-argument is that there is a clear difference in wording between claim 1 on the one hand and paragraph [0011] and claim 7 on the other hand, which should be given effect to. In my opinion the skilled reader would take the view that this is another instance in which the claims of the Patent have been sloppily drafted (like the omission of "average" from claim 10 mentioned above, and the omission of "over" from claim 4 as discussed below). Accordingly, he would be more likely to think that claim 1 should be interpreted consistently with paragraph [0011] and claim 7 than he would to think that the difference in wording was intentional and significant.

252. The third argument is based on a comparison between what the specification says at [0020]-[0021] with what is shown in Figures 1 and 2. Professor Hunter's assumption was that Figures 1 and 2 showed the molecular weight analyses for the two batches described in [0020]-[0021]. Curiously, Prof Grant disagreed with this assumption. He gave three reasons for doing so. First, the Patent did not say this. That would not prevent the skilled team from reading the document and reaching their own conclusion, however, just as, on Prof Grant's own view, the absence of a definition of "average molecular weight" would not prevent the skilled team from concluding that that meant M_p. Secondly, the Figures show three batches whereas only two are described in [0020]-[0021]. But the Figures show two batches which have the same molecular weight distribution. This could be explained by the preparation of Batch A being repeated. Thirdly, Prof Grant said that he would expect that fractionation would lead to a narrower distribution than that shown for the 7.7 kDa sample in the Figures. But this evidence appeared to be based on his knowledge of copolymer-1 fractionation gained from his extensive exposure to Teva's disclosure documents.

253. As Prof Hunter noted in his first report, if one does assume that Figures 1 and 2 show the molecular weight analyses for the two batches described in [0020]-[0021], then it can be seen that the curve for the 7.7 kDa sample in Figure 2 goes to zero at 40 kDa, which fits the description of Batch A in [0020], whereas the corresponding curve in Figure 1 goes to zero at about 45 kDa. As Prof Hunter said, this suggests that the figures given in [0020] refer to molar fraction since Figure 2 is a plot of molar fraction whereas Figure 1 is a plot of mass fraction. (Although it is odd that the two curves should reach zero at substantially different points.) In the case of the 12 kDa sample, it is not clear whether the description in [0021] refers to the molar fraction plot or the mass fraction plot.

254. Despite his conclusion based on visual inspection of Figures 1 and 2 that the percentages in [0021]-[0022] related to molar fraction, Prof Hunter addressed this issue by means of another part of his experiment described above. I shall not set out the results of this part of the experiment, but the upshot was similarly inconclusive in that none of the percentages tallied with [0021]-[0022], although Prof Hunter's opinion was that on balance the results favoured the view that the percentages were mass fractions. Again, however, it seems to me that the skilled reader would not undertake such an experiment, or if he did, he would conclude that the Figures were not sufficiently accurate for the results to be reliable. Rather, I consider that the

skilled reader would adopt the approach that Prof Hunter did with his visual inspection.

255. For the second and third reasons, although not the first, I conclude that the Defendants' interpretation of claim 1 is correct. The same goes for claim 4.

256. An additional point which arises on claim 4 is that, as mentioned above, this says that "75%" of the fraction is in the range 2-20 kDa, whereas claims 1 and 7 say "over 75%" as do paragraphs [0005] and [0011] of the specification. The Defendants contend that the skilled reader would understand from the specification as a whole that claim 4 was intended to refer to "over 75%" and that the word "over" had been inadvertently omitted. I agree with this. Thus Prof Hunter admitted that he had not noticed that the word "over" was missing.

Predetermined by small scale reaction

257. Claim 7 requires that the reaction "takes place for a time and a temperature predetermined by small scale reaction". Mylan contends that this must be done for each batch, whereas the Defendants contend that it is sufficient if it is done once. It is common ground that the skilled reader would interpret this requirement in the light of paragraphs [0033]-[0034] of the specification. Mylan focuses on the statement in [0033] that "a test reaction is performed on every batch". The Defendants focus on the statement in [0034] that, after the results obtained in [0033] have been used to plot a curve of molecular weight against time, the time needed is calculated from the curve and "performed on larger scale reaction". In my judgment the skilled reader would understand from this that, once the small scale or test reaction had been performed to obtain the curve, the curve could be used repeatedly to produce the desired copolymer-1 material by larger scale reactions. The skilled reader would not consider that it was necessary to repeat the small scale reactions every time that a larger scale reaction was carried out. Nor is there any evidence that the skilled reader would consider that it was technically necessary to do this. On the contrary, Prof Hunter accepted that, once the appropriate reaction conditions had been determined on a small scale at the outset, then the skilled person would not need to carry out the test reaction each time unless there was some variation in the reaction conditions or the reagents that made this necessary. He was unaware of any variation in the process or starting materials that might necessitate repeating the small scale reaction. Prof Sampson's evidence was to similar effect.

Priority

258. Mylan contends that claims 2-3 and 5-12 are not entitled to the priority date of 24 May 1994 because they are not supported by matter disclosed in the priority document filed on that date ("the Priority Document"). For the purposes of these proceedings, the Defendants accept that claims 2, 5 and 7-11 are not entitled to priority. Thus the dispute for present purposes is over the entitlement of claims 3, 6 and 12 to priority.

259. Mylan also has a further attack on the priority of all the claims based upon the entitlement of Yeda to claim priority. Because of the late stage at which that point was raised, it was ordered to be tried later if need be. The consequence is that it will be necessary for me to consider the validity of claims 1 and 4, as well as claims 3, 6 and

12, both on the footing that they are entitled to priority and on the footing that they are not.

260. Returning to the present issue as to the entitlement of claims 3, 6 and 12, I summarised the relevant principles in *Intervet UK Ltd v Merial* [2010] EWHC 294 (Pat) at [180]-[183]. Neither side took issue with that summary.

261. Claims 3, 6 and 12 all require an average molecular weight of 6.25 to 8.4 kDa. In addition, claims 3 and 6 are to a fraction which has less than 5% of species of copolymer-1 having a molecular weight over 40 kDa and over 75% between 2 and 20 kDa. (In the case of claim 6, this assumes that claim 4 is to be interpreted as if it included the word "over".) Claim 12 does not include these limits.

262. The Defendants rely on the *in vivo* data in Example 2A and the *in vitro* data in Example 2B of the Priority Document to support their claim to priority. The relevant parts of the Priority Document are the same as the corresponding parts of the Patent. In summary, Example 2A states that two batches of 7.3 and 8.4 kDa with less than 2.5% of species over 40 kDa were subjected to the mouse assay and designated "non-toxic", whereas a higher molecular weight batch was designated "toxic". Example 2B of the Priority Document gives the results of the RBL assay for two batches of 6.25 and 7.3 kDa with less than 2.5% of species over 40 kDa as well as two higher molecular weight batches. Below the table of results is the statement which appears in the Patent at [0028] (see paragraph 182 above).

263. The Defendants contend that this teaches the skilled person that copolymer-1 having an average molecular weight of between 6.25 and 8.4 kDa is less toxic than higher molecular weight copolymer-1, and that this disclosure supports the claimed ranges. Mylan disputes this for five reasons. As will appear, there is some overlap between these reasons, but nevertheless it is convenient to consider them separately.

264. First, Mylan points out that there are no results for the 6.25 kDa batch in the mouse assay, nor for the 8.4 kDa batch in the RBL assay. While the reader might deduce that the 6.25 kDa batch would be non-toxic in the mouse assay, Mylan argues that it is not clear what the level of serotonin release would be in the RBL assay for the 8.4 kDa batch, still less what it would be for a sample of copolymer-1 with an average molecular weight of 8.4 kDa but with between 2.5% and 5% of species with molecular weight over 40 kDa.

265. In this connection Mylan relies on the evidence of Prof Baird and Prof. Schellekens. Prof Baird said that there was no direct correlation between RBL degranulation and mouse toxicity: they are correlated only in that they both show a similar trend. Prof Schellekens said that the mouse data and the RBL data were independent and that the Patent treated them as independent assays.

266. The Defendants argue that the skilled reader is taught that both 6.25 kDa copolymer-1 and 8.4 kDa copolymer-1 are less toxic than higher weight material, and that is enough. Whatever might be the position in relation to 6.25 kDa material, I cannot accept this argument in relation to 8.4 kDa material. The Priority Document does not directly and unambiguously teach the skilled reader that 8.4 kDa material is less toxic than higher molecular weight material, because it gives the reader no clear guidance as to the toxicity of 8.4 kDa material judged by the RBL test, still less as to what

conclusion should be drawn when the both tests are considered. By way of illustration, what conclusion is the skilled reader supposed to draw if a sample of 8.4 kDa material is non-toxic according to the mouse assay, but gives, say, 40% serotonin release in the RBL test?

267. Secondly, Mylan says that, although there is disclosure of results for the individual batches mentioned, there is no disclosure that all batches within the range of 6.25 to 8.4 kDa will give comparable results in these assays. Mylan argues that the skilled reader cannot deduce that directly and unambiguously.

268. In this connection Mylan particularly relies on Prof Baird's evidence concerning the RBL data in the Priority Document. In summary, this was to the effect that, although she thought one could make a prediction as to level of serotonin release for 8.4 kDa material by drawing a smooth curve through the four data points, there would be considerable uncertainty in the position of the curve. Furthermore, she made no allowance for the variability in the determination of average molecular weight by SEC.

269. The Defendants argue that this is immaterial and that what matters is the results that are disclosed in the Priority Document. In my view, this point supports Mylan's first point, but adds little to it. In essence, it simply confirms that the skilled reader cannot directly and unambiguously derive from the Priority Document any conclusion to the toxicity of 8.4 kDa material.

270. Thirdly, in relation to claims 3 and 6, Mylan points out there is no disclosure that any of the 6.25, 7.3 and 8.4 kDa batches had greater than 75% of species with a molecular weight of 2 to 20 kDa. Mylan argues that the skilled reader cannot derive this directly and unambiguously. The Defendants' response is that this is disclosed by the summary of the invention on page 2 of the Priority Document and the statement on page 4 that the invention is exemplified by the Examples. On this point, I think that the skilled reader reading the Examples in the light of those statements would take it to be implied that the batches satisfied that criterion.

271. Fourthly, again in relation to claims 3 and 6, Mylan points out that the disclosure is that each of the 6.25, 7.3 and 8.4 kDa batches had less than 2.5% of species with a molecular weight over 40 kDa. There is no disclosure of what the position would be with batches with between 2.5% and 5% of species over 40 kDa. Furthermore, in the discussion of the RBL test results, particular emphasis is placed on the significance of less than 2.5% over 40 kDa for toxicity. Accordingly, Mylan argues that there is no support for a claim to less than 5% over 40 kDa.

272. In this regard Mylan relies on the evidence of Prof Baird. She accepted that, if the skilled person were presented with a batch of copolymer-1 with an average molecular weight of 6.25 or 7.3 kDa, but where the percentage of species over 40 kDa was between 2.5 and 5%, the skilled person would have no means of predicting the percentage serotonin release based on the information in the specification.

273. The Defendants' only response to this argument is to rely on the fact that page 2 of the Priority Document states that it is a preferred feature of the invention that the composition contains less 5% of species over 40 kDa. In my view this does not answer Mylan's point. The Priority Document does not disclose, let alone directly and

unambiguously, that copolymer-1 having an average molecular weight of 6.25 to 8.4 kDa and between 2.5% and 5% species over 40 kDa is less toxic than higher molecular weight material. For the reasons discussed above, this lack of support is particularly acute in relation to 8.4 kDa material.

274. Fifthly, as to claim 12, Mylan points out there is no limitation on the molecular weight distribution. Mylan argues that a claim with no limit on the molecular weight distribution cannot be supported by the disclosure of the Priority Document, which is limited to materials with less than 2.5% over 40 kDa.

275. The Defendants' response to the fifth argument is the same to their response to the fourth argument, and my conclusion is the same.

276. For these reasons I conclude that none of claims 3, 6 and 12 are entitled to priority from the Priority Document.

Obviousness over the prior art

The law

277. A patent will be invalid if the invention is not a patentable invention (section 72(1)(a) of the Patents Act 1977). It will not be patentable if it does not involve any inventive step (section 1(1)(b)), that is to say, if the invention claimed was obvious to a person skilled in the art having regard to the state of the art at the priority date (section 3). The familiar structured approach to the assessment of allegations of obviousness first articulated by the Court of Appeal in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 was re-stated by Jacob LJ in *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37 at [23] as follows:

> "(1)(a) Identify the notional 'person skilled in the art';
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the 'state of the art' and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

278. In both *H. Lundbeck A/S v Generics (UK) Ltd* [2008] EWCA Civ 311, [2008] RPC 19 at [24] and *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28 at [42] Lord Hoffmann approved without qualification the following statement of principle by Kitchin J (as he then was) at first instance in the former case:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

279. When considering the fourth *Pozzoli* step, it is often relevant to consider whether what is claimed arises from taking steps which were obvious to try with a fair expectation of success. As Lord Hoffmann said in *Conor* at [42]:

> "In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case."

280. The primary evidence on the question of obviousness is that of properly qualified expert witnesses. Secondary evidence must be kept firmly in its place: *Mölnycke AB v Procter & Gamble Ltd* [1994] RPC 49 at 112 (Sir Donald Nicholls V-C). This does not mean that secondary evidence cannot sometimes be of considerable value: *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 at [75]-[85] (Jacob LJ). As Laddie J explained in *Pfizer Ltd's Patent* [2001] FSR 16 at [63]-[64], evidence of what actual researchers in the field were doing at the time may be persuasive, but must be examined with care to see if it sheds light on what the notional skilled person with common general knowledge and the prior art would do.

281. In assessing whether a claimed invention is obvious, it is always important, although difficult, to avoid hindsight. The fact that, after the event, it is easy to see how the invention could be arrived at by starting from an item of prior art and taking a series of apparently simple steps does not necessarily show that it was obvious at the time: *British Westinghouse Electric & Manufacturing Co Ltd v Braulik* (1910) 27 RPC 209 at 230 (Fletcher Moulton LJ), *Non-Drip Measure Co Ltd v Strangers Ltd* (1943) 60 RPC 135 at 142 (Lord Russell) and *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346 at 362 (Lord Diplock).

Obviousness of the product claims over Bornstein 1987

282. I have identified the skilled team and their common general knowledge above. Although claims 1-6 and 11-12 have a variety of different features, it is not necessary to distinguish between them for the purpose of considering Mylan's obviousness case based on Bornstein 1987. For this purpose, the core of the inventive concept can be taken to be copolymer-1 having an average molecular weight in the range 6.25-8.4 kDa with over 75% in the range 2-20 kDa and less than 5% over 40 kDa. The difference between Bornstein 1987 and this is that Bornstein 1987 does not disclose

copolymer-1 having those molecular weight characteristics, but only copolymer-1 having a "molecular weight" (i.e. an average molecular weight) in the range of 14-23 kDa. For different reasons, neither side contends that it matters for this purpose whether the skilled reader would understand Bornstein 1987 to mean M_n or M_w or M_p.

283. The starting point for Mylan's obviousness case is that it is common ground that, having read Bornstein 1987, the clinician would recommend that copolymer-1 should be developed further. It is also common ground that the skilled team would aim to make and develop copolymer-1 with an average molecular weight of 14-23 kDa. It is also common ground that the synthetic chemist would attempt to synthesise copolymer-1 by the method of Teitelbaum 1971.

284. It is Mylan's case that, for the reasons considered below, the synthetic chemist who set out to make copolymer-1 for such a project would proceed in a manner which would make development of the process claimed in the process claims of the Patent obvious. Mylan goes on to contend that the synthetic chemist would end up producing copolymer-1 with a lower average molecular weight than he was aiming for, and at least in some cases would produce copolymer-1 falling within the product claims.

285. The Defendants contend that, even if the synthetic chemist would discover the claimed process by taking obvious steps and would accidentally produce lower molecular weight copolymer-1, it does not follow that the product claims are obvious over Bornstein 1987. I agree with the Defendants. Bornstein 1987 gives the skilled team no reason whatsoever to develop copolymer-1 of average molecular weight lower than 14-23 kDa. On the contrary, it suggests that what they want is material in that weight range. Accordingly, if the synthetic chemist accidentally produced some copolymer-1 of lower average molecular weight, I consider that the skilled team would discard it as not being what was wanted. Accordingly, in my judgment the product claims are not obvious over Bornstein 1987 even if the claimed process is obvious. This is particularly true of claims 4-6 and 11-12.

Obviousness of the product claims over Johnson 1994

286. Johnson 1994 is only available as prior art in relation to claims which are not entitled to priority. The Defendants have conceded that claim 2, 5 and 11 are not entitled to priority, and I have held that claims 3, 6 and 12 are not entitled either. In addition, for the reason explained in paragraph 259 above, it is necessary to consider the validity of claims 1 and 4 on the footing that they are not entitled to priority.

287. I have introduced Johnson 1994 in paragraph 36 above, but I must now describe its disclosure. It is the text of a talk reviewing the development of copolymer-1 given by Dr Johnson at a symposium in Victoria, British Columbia, Canada in September 1993. It is fairly short, consisting of two pages, half of one of which comprises a figure reproduced from Bornstein 1987, together with two short questions and answers.

288. In the third paragraph, Dr Johnson says:

> "COP-1, a compound developed at the Weizman Institute in Israel, is composed of four amino acids – L-alanine, L-glutamic acid, L-lysine, and L-tyrosine - that are common in MBP. The

> sequence and length of the various polymers in COP-1 are random, with a molecular weight of approximately 7000. It is currently used in a therapeutic dose of 20 mg daily by subcutaneous injection."

289. He goes on to discuss Bornstein 1982, Bornstein 1987 and Bornstein 1991. He then says:

> "Following these three provocative human studies, there was a long delay before further clinical study could be carricd out with COP-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 standardized preparation of COP-1 that could be employed in further clinical trials. Problems with manufacture were not solved until 1991, when it was possible to initiate further studies of COP-1 in R/R MS."

290. The remainder of the talk discusses ongoing work on copolymer-1, and in particular the Phase III trial, stating that it was begun in October 1991 and is nearing completion.

291. The only difference between Johnson 1994 and the inventive concept is that Johnson 1994 does not disclose copolymer-1 having the precise molecular weight distribution called for by the claims, but only copolymer-1 having a "molecular weight" (i.e. average molecular weight) of 7 kDa. Again, neither side contends that it matters for this purpose whether the skilled reader would understand this to mean M_n or M_w or M_p. The Defendants do not dispute that, if the skilled team were to try to develop 7 kDa copolymer-1, they would be likely to produce something that fell within the claims.

292. Mylan's case is that, in the light of Johnson 1994 and the positive results from the Phase III trial announced at the ANA meeting in October 1994, the skilled clinician would recommend development of both copolymer-1 having an average molecular weight of 14-23 kDa and copolymer-1 having an average molecular weight of 7 kDa. This case is based on the evidence of Dr Coles, which proceeds in the following stages:

i) Dr Coles was asked to assume that one of the chemists in the skilled team would have brought it to his attention that Johnson 1994 reported that the Phase III trial was being conducted with copolymer-1 having a molecular weight of 7 kDa, whereas Bornstein 1987 reported use of copolymer-1 having a molecular weight of 14-23 kDa.

ii) Although he was aware of the headline results of the Phase III trial in May 1995, he would not have felt sufficiently informed about it to suggest that the skilled team develop 7 kDa copolymer-1 in preference to 14-23 kDa copolymer-1 given the results reported for the latter in Bornstein 1987 and elsewhere.

iii) On the other hand, he would not have wanted to miss the possibility that 7 kDa copolymer-1 had some advantage over 14-23 kDa copolymer-1 given the positive results in the Phase III trials.

iv) Therefore he would have recommended that both versions be developed.

293. The Defendants contend that this approach is based on hindsight. I agree with this. My main reasons are as follows.

294. First, Dr Coles made it clear in his reports that he did not think he would have noticed the difference in molecular weight between Bornstein 1987 and Johnson 1994 himself. At the time he had thought that the Phase III trial was testing the same drug as Bornstein 1987, and that was how the trials were discussed in the field. Indeed, he did not know that there had been a change in the molecular weight profile of copolymer-1 until he became involved in this case. This is consistent with the evidence of Prof Schellekens that it was highly unusual for a drug to change between Phase II and III trials and that the assumption of a person with experience in drug development would be that the same material was being used in both.

295. In cross-examination, Dr Coles was candid that he would not have been interested in either the amino acid composition or the molecular weight of copolymer-1. Furthermore, he said that he would not have been able to draw any useful conclusions from this information himself.

296. As noted above, Dr Coles was asked to assume that the difference in molecular weight had been pointed out to him by a chemist. No justification for this is advanced by Mylan. Johnson 1994 is not a paper directed to any of the chemists in the skilled team, it is directed to the clinician. Dr Coles did not suggest that he would have asked the chemist for help in understanding the paper. Prof Hunter said that he would have drawn the difference to the attention of the rest of the team, but he gave no reason for doing so.

297. In any event, the point remains that Dr Coles was simply not interested in the molecular weight of the copolymer-1. As counsel for the Defendants submitted, if the chemist had pointed out the difference in molecular weight to him, it is clear that Dr Coles' reaction would have been: "So what? I am not interested in that". It is only with the benefit of hindsight that the change can be seen to be important.

298. Even if the clinician had taken an interest in the information, I think Prof Schellekens was right to say he would have been confused by it given that he would have been aware from Bornstein 1987 that the copolymer-1 used in that trial had a higher molecular weight. The clinician would have wondered whether there had really been a change in the molecular weight of copolymer-1, and if so why.

299. Secondly, Dr Coles' analysis takes into account his knowledge of the headline results of the Phase III trial in May 1995. As noted above, there is a dispute as to whether these results were common general knowledge. I have concluded that the clinician would have known that the results were positive, in that copolymer-1 reduced relapse rate and the accumulation of disability compared to placebo in a relapsing-remitting population, but no more. Counsel for the Defendants submitted that the results would not have been regarded as a good basis for further action. In support of this, he relied

upon the evidence of Prof Schellekens that the clinician would wait until full publication of the results of the Phase III trial before deciding how to proceed. Counsel for Mylan submitted that the results would have been regarded as a good basis for developing the material which had been used in the Phase III trial and which had produced those results. In support of this, he relied upon Dr Coles' evidence in re-examination.

300. I agree with counsel for Mylan that the clinician would have regarded the headline results as a good basis for thinking that the material which had been used in the Phase III trial merited further development. I do not agree that it follows that the clinician would recommend the development of 7 kDa copolymer-1. As noted above, 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.

301. Thirdly, I consider that, if it is assumed that the difference in molecular weight was pointed out to the clinician, he took an interest in it and he was asked for a recommendation as to the way forward, the clinician would be more likely to recommend development of 14-23 kDa than 7 kDa copolymer-1. Johnson 1994 states that molecular weight of copolymer-1 is approximately 7 kDa, and later says that effort has been devoted to developing a standardised preparation, but it does not say that there has been any change in the molecular weight since the earlier trials. Indeed, the implication is the opposite. Thus it would be far from clear to the clinician that the material used in the Phase III trial did in fact have a molecular weight of 7 kDa. The clinician might well wonder if the statement in Johnson 1994 was a mistake.

302. Furthermore, as Dr Coles explained, his primary concern would have been not to endanger efficacy that had been established. The best evidence for efficacy pending publication of the full results of the Phase III trial remained Bornstein 1987. Furthermore, Bornstein 1987 explained that copolymer-1 had been designed to mimic MBP. Changing copolymer-1 from 14-23 kDa to 7 kDa would move it further away from MBP, and therefore might adversely affect efficacy.

303. Fourthly, as Dr Coles accepted, to take two materials forward for further clinical studies would be costly, although he pointed out that the expense would depend on the scale of the studies and expressed the opinion that the expense would be justified. The question, however, is whether the skilled team would have a sufficient expectation of success to justify the effort and expense of developing both 7 kDa copolymer-1 and 14-23 kDa copolymer-1. Having regard to how little was known about MS and the mechanism of action of copolymer-1 in May 1995, and having regard to the uncertainties as to whether 7 kDa copolymer-1 had really been used in the Phase III trial and, if so, why a change had been made to the molecular weight of the material, I do not consider that they would have a sufficient expectation of success to make this an obvious step to take.

304. Accordingly, I am not persuaded that Johnson 1994 would have made it obvious to develop copolymer-1 with an average molecular weight of 7kDa in May 1995.

Obviousness of the process claims over Teitelbaum 1971

305. The synthesis of copolymer-1 described in paragraphs 2.3 and 2.3.1 of Teitelbaum 1971 consists of four main steps:

    i) Synthesis of the four NCAs, on the basis of references 12-15.

    ii) Polymerisation of the NCAs at room temperature in anhydrous dioxane using diethylamine as initiator in accordance with reference 11. This is Katchalski and Sela, "Synthesis and Chemical Properties of Poly-α-Amino Acids", *Advan. Prot. Chem.*, 1958, 13, 243-492.

    iii) Removal of the benzyl groups protecting the glutamic acid residues using HBr in glacial acetic acid guided by reference 16. This is Ben-Ishai & Berger, "Cleavage of N-Carbobenzoxy Groups by Dry Hydrogen Bromide and Hydrogen Chloride", *J. Org. Chem.*, 1952, 17 (12), 1564-157.

    iv) Removal of the trifluoroacetyl groups from the lysine residues using piperidine following reference 17.

306. It should be noted that Katchalski, Sela, Ben-Ishai and Berger were all WIS scientists. In addition, Prof Sela was one of the authors of Teitelbaum 1971 and one of the inventors of the Patent.

307. The core inventive concept of the process claims is to select the reaction conditions for the HBr/glacial acetic acid deprotection step so that cleavage of some peptide bonds occurs as well as deprotection of the glutamic acid residues, thus enabling the molecular weight of the final copolymer-1 to be controlled. The difference between Teitelbaum 1971 and the process claims is that Teitelbaum 1971 does not disclose to the reader that the HBr/glacial acetic acid reaction can be used in this way.

308. Mylan does not contend that the skilled reader would know this from his common general knowledge. Mylan's case is that the synthetic chemist who tried to implement Teitelbaum 1971 would discover that the HBr/glacial acetic acid reaction resulted in a reduction in molecular weight, and that it would be obvious to take advantage of this to control the molecular weight of copolymer-1.

309. Mylan's case is based on the evidence of Prof Hunter. In a nutshell, the key point made by Prof Hunter is that the synthetic chemist would seek to characterise the intermediates obtained following the polymerisation step and the HBr deprotection step as fully as possible. As he put it in his first report, "It is standard procedure in synthetic chemistry to characterise the reaction products of each step in a synthetic pathway as fully as possible before moving on to the next step". It was Prof Hunter's opinion that, as a result, the synthetic chemist would notice the reduction in molecular weight of the product after the HBr deprotection step, would realise that this was causing cleavage of peptide bonds and would realise that he could take advantage of this to control the molecular weight of the copolymer-1. Prof Sampson disagreed with this.

310. *The polymerisation step*. Although the key dispute concerns the HBr deprotection step, it is necessary to begin by considering how the synthetic chemist would carry out the polymerisation step.

311. Although Teitelbaum 1971 discloses the quantities of the NCAs used to synthesise copolymer-1 of 23 kDa, it does not tell the reader how much initiator was used. So even if he is trying to make a 23 kDa product, the synthetic chemist would have to determine for himself the right level of initiator. The amount needed will depend on whether the chemist is aiming for a product with an M_n or an M_w of 23 kDa. Prof Sampson said that the chemist could calculate the amount of initiator expected to be required for a product with a given M_n, but she accepted that one could not calculate the amount of initiator required for a product with a given M_w without knowing the polydispersity. The same would be true if the average molecular weight is M_p.

312. Even in the case where calculation is possible, the synthetic chemist would know that it cannot be assumed that the reaction will behave perfectly, and accordingly the amount of initiator required will need to be determined experimentally. As Katchalski and Sela state at 283:

> "…it is still difficult to predict the average degree of polymerisation and molecular weight distribution of a polyamino acid derived from a given NCA under specified conditions. It is therefore advisable to determine experimentally the average molecular weight of any new batch of polymer prepared, by the standard procedures discussed in Section IV.3."

313. Prof Hunter's view was that the way in which to determine the right level of initiator was to run parallel reactions with a range of initiator concentrations and find out which concentration produced the desired 23 kDa product by plotting initiator concentration against molecular weight. He thought that between 5 and 10 parallel reactions would be required for this purpose. After the polymerisation reaction was complete, he would comprehensively analyse the intermediate reaction product by the following techniques: (a) analytical ultracentrifugation; (b) light scattering to corroborate his AUC results; (c) end-group analysis; (d) NMR; (e) mass spectrometry; (f) infrared spectroscopy; (g) UV/visible spectroscopy; (h) SEC; and (i) amino acid analysis. Prof Hunter accepted that it would take a week to get all the results back. He would then repeat these analyses after the HBr deprotection step and again after the piperidine deprotection step.

314. Prof Sampson did not, I think, dispute that running parallel reactions with a range of initiators would be a sensible way in which to proceed. She disagreed, however, that the synthetic chemist would characterise the intermediate reaction product in the manner suggested by Prof Hunter. Her view was that the extent to which a synthetic chemist would want to characterise the reaction products in a synthetic pathway depended on the purpose of the synthesis, what was known about the pathway and what was expected to occur. Since the polymerisation of NCAs was well established by 1994, she thought that the skilled person would not see the need to characterise the intermediate product as extensively as suggested by Prof Hunter. Rather, he would simply do the analyses that were necessary to confirm that the expected reaction had taken place. At the end of the polymerisation reaction, these would be thin-layer

chromatography (to check the reaction had gone to completion by looking for the absence of NCA monomers) and UV and NMR (to check that all the amino acids were present in the protected polymer). She thought that there was no reason why the skilled person would perform any molecular weight analysis on the intermediate product at this stage. Rather, the skilled person would only check the molecular weight of the product once the protecting groups had been removed. This was partly to save time and effort, but also because it was only at that stage that he would be able to make a comparison with Teitelbaum 1971.

315. Both experts were cross-examined at some length on their respective views and both defended those views clearly and persuasively. I have no difficulty in accepting that Prof Hunter would have proceeded in the manner he described, while Prof Sampson would have proceeded as she said. In my view it is clear that Prof Hunter's approach is the more scientifically rigorous of the two. That is not the question, however. The question is which approach represents that of the ordinary skilled synthetic chemist. In my judgment, Prof Sampson's approach does. For the reasons she gave, I do not think the ordinary skilled synthetic chemist would think it worth while to carry out the battery of analyses required by Prof Hunter's approach on each of 5-10 samples at each stage of the reaction.

316. Counsel for Mylan submitted that it was at least obvious to do as Katchalski and Sela recommended and to check the molecular weight of the product of the polymerisation step. I do not accept this. Katchalski and Sela recommends determining the molecular weight of "any new batch of polymer". It does not specify the stage at which this should be undertaken. Prof Sampson did not disagree that the average molecular weight of the copolymer-1 should be checked; her point was as to the stage at which the skilled person would do this.

317. Counsel for Mylan also relied upon a number of other factors as showing that it was at least obvious to check the molecular weight of the product of the polymerisation step, such as the fact that the skilled team would have in mind the need to obtain regulatory approval for the process and the fact that Bornstein 1987 indicates that there may be variability in the molecular weight of copolymer-1. I do not accept that these factors would have any significant impact on Prof Sampson's approach, however.

318. *The HBr deprotection step*. No conditions for this reaction are given in Teitelbaum 1971, but Ben-Ishai and Berger gives times of 3 hours, 12 hours and "overnight" for reactions to remove benzyl groups from various small molecules.

319. Prof Hunter's view was that, because one would not know how the reaction would take with copolymer-1, it would be necessary to establish this by experiment. Accordingly, the synthetic chemist would run the reaction for 24 hours, taking samples every hour (or every hour during the day with a sample the next morning), quenching the reaction and isolating the product for analysis by the nine methods referred to above.

320. Prof Sampson's view was that the synthetic chemist would simply follow Ben-Ishai and Berger and run the reaction for 3-12 hours. Indeed, she considered that he would choose the shorter of these times, at least initially, in order to avoid the risk of side reactions. In her view, he would only analyse the product of this reaction by UV and NMR to check that the benzyl groups had been removed.

321. Again, I accept that Prof Hunter would have done as he suggested, as would Prof Sampson. Again, I am impressed by the scientific rigour of Prof Hunter's approach. Again, however, it seems to me that Prof Sampson's approach represents the approach that the ordinary skilled synthetic chemist would adopt.

322. So far as the reaction time is concerned, it was common ground between Prof Hunter and Prof Sampson that deprotection reactions are generally run for the minimum amount of time to remove the protecting group, in order to minimise unwanted side reactions. In these circumstances I think that the skilled person would not run the reaction for longer than 12 hours. Furthermore, Prof Arnon's unchallenged evidence was that removal of the benzyl groups could in fact be achieved in a few hours, and certainly overnight. Thus success would be achieved within 12 hours.

323. Counsel for Mylan submitted that, even if the reaction was run for only 12 hours, then it was likely, in the light of the information in the Patent and Teva's disclosure, that there would be some cleavage of the peptide bonds and some reduction of the molecular weight of the resulting copolymer-1. I accept this, but it does not follow that the skilled person would either notice this phenomenon or appreciate its significance.

324. So far as the analysis of the product of this reaction is concerned, it is common ground that it was a well-known reaction by 1994, and so the skilled person would not be anticipating problems. In these circumstances, the skilled person would not think it worthwhile to undertake molecular weight analysis at this stage, even if he had undertaken it after the polymerisation reaction. This would be time consuming, and unnecessary for determining whether the deprotection reaction had gone to completion. Whereas UV and NMR would allow the skilled person to see the extent of loss of benzyl groups, molecular weight analysis would merely indicate that mass had been lost. It would say nothing about what had been lost. Thus it would also not provide useful information in relation to the deprotection reaction.

325. Counsel for Mylan relied on Prof Sampson's agreement that, if the synthetic chemist were alert to the fact that there was a risk of peptide bond cleavage as a result of the HBr deprotection reaction, then he would check for this. Prof Sampson did not agree, however, that the skilled person would be alert to this. She accepted that the skilled person would know that the presence of water in the reaction could lead to acid hydrolysis of the peptide bonds, but she considered that the skilled person would take care to ensure that the reagents were as anhydrous as possible.

326. In this connection Prof Hunter pointed out that Katchalski and Sela states at 410 that Blout and Idelson, "Polypeptides VI. Poly-α-L-Glutamic Acid: Preparation and Helix-Coil Conversions", *J. Am. Chem. Soc.*, 1956, 78, 497-498, reported "slight degradation of the polymer during the debenzylation". It was not established that this was common general knowledge, however. I agree with the Defendants that it is unlikely that the skilled person wanting to make copolymer-1 would pick up this passing reference in a different section of what is a very long paper. Even if he did, and pursued the cross-reference to Blout and Idelson, he would note that: (i) the reactions described there were not in acetic acid, but SO_2 and benzene; and (ii) the degradation was most likely to have been caused by the presence of water in the washing step.

327. Prof Hunter's evidence was that molecular weight analyses after the deprotection reaction would reveal additional mass loss to that expected by reason of the removal of the benzyl protecting groups. He considered that it would immediately be clear to him that the HBr in glacial acetic acid was causing partial cleavage of the peptide bonds, and he would appreciate that this could be used to control the molecular weight of the final product.

328. As counsel for the Defendants submitted, it is noteworthy that Mylan did not give Teitelbaum 1971 to a suitably qualified synthetic chemist and ask him to make copolymer-1 in accordance with it and the cited references. This is despite the fact that Prof Hunter offered to do this. Thus Mylan has not proved experimentally precisely what would occur if Prof Hunter's approach were to be followed.

329. Furthermore, if it was obvious that the molecular weight of a polymer like copolymer-1 could be controlled in this way, it is relevant to ask why it had not been reported earlier. Katchalski and Sela was published in 1958. Teitelbaum 1971 was published in 1971. As noted above, the HBr deprotection reaction was a well-known reaction by 1994. Yet there is no evidence that anyone appreciated that it could be used to control the molecular weight of the polymer prior to the present invention. Prof Hunter had no explanation for this.

330. Yet further, it is also noteworthy that it is not clear even now how the cleavage reaction occurs, particularly if it does not proceed by acid hydrolysis. Prof Hunter was able to postulate a plausible reaction mechanism, but accepted that he had no evidence to support it.

331. It may well be the case that Prof Hunter would have discovered that the HBr deprotection step could be used to control the molecular weight of copolymer-1 in the way that he postulated. It does not follow, however, that the ordinary skilled person would do so without inventive insight. I am not persuaded that he would. Even if it were obvious to analyse the molecular weight at each stage and hence to discover the unexpected loss of mass in the HBr deprotection step, which for the reasons I have given I doubt, I do not accept that it would have been obvious to the skilled person that he could take advantage of this phenomenon to control the molecular weight of the desired polymer. In my view, he would be more likely to regard the loss of mass in the way that Blout and Idelson and Katchalski and Sela did, namely as representing degradation of the polymer. Accordingly, rather than being inspired to exploit it, he would be more likely to view it as undesirable, and to respond by shortening the reaction time and/or redoubling his efforts to make the reagents anhydrous. The way in which he would have attempted to control the molecular weight was by varying the amount of initiator (or subsequent fractionation).

332. Counsel for Mylan argued that, even if the synthetic chemist were to adopt Prof Sampson's approach, he would still discover that the HBr deprotection step caused a reduction in molecular weight and would realise that this could be used to control the molecular weight of copolymer-1. I do not propose to go into the details of this argument. It suffices to say that I do not accept it for two reasons. First, I do not agree that, if Prof Sampson's approach were followed, the skilled person would be likely to discover that the HBr deprotection reaction caused a reduction in molecular weight. Secondly, even if he did, I do not agree that he would realise that he could capitalise on this to control the molecular weight of copolymer-1.

333. For these reasons I am not persuaded that the process claims were obvious.

Secondary evidence of non-obviousness

334. Counsel for the Defendants relied upon the history of the making of the invention as secondary evidence of non-obviousness. In my judgment this is of little relevance to the obviousness or otherwise of the product claims over Bornstein 1987 and Johnson 1994, but does provide some modest further support for my conclusion that the process claims were not obvious over Teitelbaum 1971. The short point is that Prof Katchalski, Prof Sela and a number of other distinguished WIS scientists had worked extensively in the field of synthetic polypeptides generally since the late 1940s, and some of them had worked on copolymer-1 since the work that was published in Teitelbaum 1971, yet none of them discovered that the reaction with HBr in glacial acetic acid could be used to control the molecular weight of the final product as well removing the benzyl protecting groups. That discovery was only made by Eliezer Konfino of Teva in the late 1980s. (It is a curious, but irrelevant, aspect of the case that all the inventions claimed in the Patent were made in the late 1980s, yet the Priority Document was not filed until May 1994).

Obviousness for lack of technical contribution

335. Quite separately from its conventional arguments that the claimed inventions are obvious in the light of the prior art, Mylan also argues that the product claims are obvious since copolymer-1 with the molecular weight characteristics called for by the claims is an arbitrary selection with no technical merit.

The law

336. I reviewed this aspect of the law of obviousness in some detail in *Sandvik Intellectual Property AB v Kennametal UK Ltd* [2011] EWHC 3311 (Pat) at [180]-[185]. Having considered T 939/92 *Agrevo/Triazoles* [1996] EPOR 171, *Abbott Laboratories Ltd v Evysio Medical Devices ULC* [2008] EWHC 800 (Ch), [2008] RPC 23, *Conor Medsystems Ltd v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28 and *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2009] EWCA Civ 1362, [2010] RPC 9, I concluded at [185]:

> "What these cases show is that the principles to be applied in determining whether a claimed invention is obvious are the same regardless of the field of the invention, but that the application of those principles can vary according to the circumstances of the case, including the field of the invention. An arbitrary selection from the prior art is not inventive, regardless of the field. Nevertheless this is a problem which is more likely to arise with claims to classes of chemical compounds for the reasons explained by the Board of Appeal in *Agrevo*. Where it is suggested that a claimed invention is obvious as being an arbitrary selection, the key question is whether the specification 'passes the threshold test of disclosing enough to make the invention plausible' as Lord Hoffmann put it in *Conor v Angiotech*, that is to say, to make it

> plausible that the selection has the technical significance claimed for it."

I went on to hold on the facts that claim 6 of the patent in suit was an arbitrary selection because (a) the specification did not make it plausible that the characterising feature of the claim had any technical significance and (b) subsequent evidence indicated the opposite.

337. In the present case both sides accepted as correct the statement of principle I have quoted from *Sandvik* so far as it went. Furthermore, it was common ground that, making due allowance for the difference in context, some assistance with regard to the concept of plausibility could be obtained from the decision of the Supreme Court in *Human Genome Sciences Inc v Eli Lilly & Co* [2011] UKSC 51, [2012] RPC 6 on the question of whether an invention is capable of industrial application, and in particular the statement of Lord Hope at [149]:

> "I would not quarrel with Jacob LJ's comment, after consulting the *Shorter Oxford English Dictionary*, that the sense ['plausibly'] conveys is that there must be some real reason for supposing that the statement is true: para. 111. The important point, however, is that the standard is not any higher than that."

338. Nevertheless, there was argument concerning two related points which had not been canvassed in *Sandvik*, namely the burden of proof and the role of evidence which post-dates the Patent.

339. *Burden of proof.* Counsel for Mylan cited a number of decisions of EPO Boards of Appeal as to the burden of proof, beginning with *Agrevo* itself. In that case the Board held at 2.6.1:

> "According to the appellant's [applicant's] submission, in a case such as this one, where the credibility of the alleged herbicidal activity [of the claimed compounds] is at issue, the burden of proof that the presence of the alleged herbicidal activity is not credible rests on the EPO, here the Board of Appeal. This submission is clearly contrary to the legal principle that anyone who alleges a fact has the onus of proving his allegation (in this case to the standard of the balance of probabilities) by appropriate evidence. … Thus, if neither the Examining Division nor the Board of appeal is in the position to discharge this burden to the above or to any other standard, and if it is evident that the number of compounds claimed is such that it is inherently unlikely that all of them, or at least substantially all of them, will possess the promised activity, then the burden of proof of that fact, namely the possession of that activity, can indeed rest only on the shoulders of the person alleging it."

340. The only other decision to which I consider it is necessary to refer is T 1797/09 *Unilever/Dish-wash compositions* (8 February 2012, unreported). In that case the Board held at 2.7:

> "The Board agrees with the Respondents insofar as a technical problem set out in a patent is considered to be credibly solved by a claimed invention if there exist no reasons to assume the contrary. In such circumstances, it is normally the Opponent's burden to prove the opposite or at least provide evidence casting doubt on the alleged solution of the problem. If no such evidence is provided, the benefit of doubt is given to the Patent Proprietor. However, if the Opponent succeeds to cast reasonable doubt on the alleged effect, the burden to proof its allegations is shifted to the Patent Proprietor (Case Law of the Boards of Appeal, 6th edition 2010, chapter VI.H.5.)."

341. Counsel for Mylan submitted that what these cases showed was that, where it was inherently unlikely that the claimed invention solved the technical problem addressed by it (as in *Agrevo*) or where the opponent adduced evidence which cast doubt on this (as in *Unilever*), the burden fell on the patentee to demonstrate on the balance of probabilities that the claimed invention did indeed solve the problem.

342. Counsel for the Defendants submitted that, where it is alleged that a patent is invalid on the ground of obviousness, the legal burden of establishing the facts relied on lies on the party alleging invalidity. Nevertheless, he did not really dispute that the evidential burden could shift to the patentee where it is inherently unlikely that the claimed invention solves the technical problem or the opponent adduces evidence which casts doubt on this. Rather, he emphasised that what matters is whether the patent discloses enough to make the invention plausible. This takes me to the next point.

343. *Evidence which post-dates the patent*. Counsel for Mylan submitted that there was a two-stage enquiry. First, it was necessary to consider the disclosure of the patent itself. If the patent when read with the skilled person's common general knowledge did not "disclose enough to make the invention plausible", i.e. 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. Secondly, even if the patent did make the invention plausible, however, it remained open to the other party to cast doubt on this by post-dated evidence.

344. I did not understand Counsel for the Defendants to dispute the first proposition, which is supported by the decision of the Board of Appeal in T 1329/04 *Johns Hopkins University School of Medicine/Growth differentiation factor-9* [2006] EPOR 8 at [12], which was cited by Lord Hoffmann in *Conor* at [33]-[35] (quoted in *Sandvik* at [182]), although he went on to distinguish *Conor* on the facts. It is also supported by several statements of principle by judges in this jurisdiction. It is sufficient for present purposes to cite three examples.

345. First, in *Richardson-Vicks Inc' Patent* [1995] RPC 568 at 581 Jacob J (as he then was) said:

> "Whether or not there was synergy demonstrated by experiments conducted after the date of the patent cannot help show obviousness or non-obviousness. Nor can the amended

> claim be better if only the components of the amended claim (as opposed to the unamended claim) can be shown to demonstrate synergy. The patent does not draw any such distinction and it would be quite wrong for later-acquired knowledge to be used to justify the amended claim."

This point did not arise in the Court of Appeal.

346. Secondly, in *Generics (UK) Ltd v H Lundbeck A/S* [2007] EWHC 1040 (Pat), [2007] RPC 32 at [235] Kitchin J (as he then was) said:

> "… A patentee cannot seek to bolster the inventive nature of his monopoly by relying on a discovery which he had not made at the time of the patent. That is the position here. At the date of the Patent, Lundbeck had not found that escitalopram was more efficacious or was effective in treating more patients than citalopram. Those discoveries were not made until some time later. They are nowhere hinted at in the specification and could not have been predicted from what is described. In these circumstances I do not believe that it is legitimate for Lundbeck to rely upon them in support of the alleged invention. "

Again this issue did not arise in the Court of Appeal or House of Lords.

347. Thirdly, in *HGS v Lilly* in the Court of Appeal [2010] EWCA Civ 33, [2010] RPC 14 at [92] Jacob LJ said in the context of industrial applicability:

> "I add, in passing, that I do not understand the reference to 'post-published evidence' to include post-published evidence establishing for the first time or adding to what the potential industrial application of the patented subject-matter may be. It is surely axiomatic that whatever the standard for susceptibility to industrial application may be, the information about it must be in the patent (supplemented if necessary by the common general knowledge of the time). Otherwise you could satisfy the Art.57 requirement by just identifying a compound in the patent and finding a use for it later. That would contravene, for example, Art.5(3) of the Directive. You cannot have a patent for an invention when only years later you or someone else finds out what it is for. The same principle as applied in *Johns Hopkins* concerning obviousness must apply also to Art.57."

348. Counsel for the Defendants took issue, however, with the second proposition. This raises an important point of principle. If a patent does disclose enough to make the invention plausible at the priority or filing date, can an opposing party came along 20 years later and say that, in the light of subsequently acquired knowledge, in fact the invention does not have the technical benefit that it appeared to have? As a matter of principle, it seems to me that the reasoning of the Board of Appeal in *Johns Hopkins* and of the English judges quoted above applies with equal force: just as a patent which does not make the invention plausible cannot be supported by post-dated evidence, then a patent which does make the invention plausible cannot be shown to

be obvious by post-dated evidence. Either way, the fundamental principle is that whether a claimed invention is obvious or not should be judged as at the priority or application date.

349. I acknowledge that it can be seen from the case law of the Boards of Appeal of the EPO that they do sometimes take post-dated evidence into account. Thus in both T 1336/04 *Novozyme/Cellulase* (unreported, 9 March 2006) and T 433/05 *Conjuchem/Fusion peptide inhibitors* (unreported, 14 June 2007), both of which are cited in *Case Law of the Boards of Appeal of the European Patent Office* (6th ed) at 176-177, the Board of Appeal took into account post-dated evidence which supported the disclosure in the patents. As I read those decisions, the Board considered that the disclosure in the patents was plausible and confirmed by the later evidence. The same applies to the decisions in T 898/05 *Zymogenetics/Hematopoietic Cytokine receptor* [2007] EPOR 2, T1452/06 *Bayer/Human epithin-like serine protease* (unreported, 10 May 2007) and T1165/06 *Schering/IL-17 related polypeptide* (unreported, 19 July 2007) cited in the judgment of Lord Neuberger in *HGS v Lilly* at [107(ix)]. I also acknowledge that I took post-dated evidence into account in *Sandvik* as confirming the conclusion I had reached on the basis of the disclosure of the patent that the invention did not confer any technical advantage.

350. 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.

351. Furthermore, to return to the first point, if the specification does make it plausible that the invention solves the technical problem, I do not consider that it is open to an applicant for revocation to rely upon post-dated evidence as casting doubt on this so as to place an evidential burden on the patentee to demonstrate affirmatively that the invention does solve the technical problem.

352. Finally, I would observe that it seems to me that the position is different in the case of evidence which is extrinsic to, but contemporaneous with, the Patent. Such evidence does not contravene the fundamental principle identified in paragraph 348 above.

The disclosure of the specification

353. As counsel for Mylan submitted, the starting point is to identify the technical advance claimed for the invention. Only then can one consider whether the patent discloses enough to make the invention plausible.

354. In the present case, the opening paragraphs of the Patent refer to the role of copolymer-1 in the treatment of multiple sclerosis as suggested by Teitelbaum 1971 and confirmed by Bornstein 1987. Paragraph [0004] states that the object of the

invention is to provide "an improved composition of copolymer-1". As noted above, there is no express disclosure of what is meant by "improved".

355. Counsel for Mylan submitted that it was plain from the preceding paragraphs and the rest of the specification that the improvement must relate to some aspect of the use of copolymer-1 in the treatment of multiple sclerosis. I did not understand counsel for the Defendants to dispute this.

356. Counsel for the Defendants submitted that the skilled team would appreciate that the nature of the improvement was reduced toxicity in the two assays described in the Patent. As Counsel for Mylan submitted, however, those assays had no intrinsic value in themselves. It is therefore necessary to consider what the skilled reader would understand to be their relevance.

357. So far as the mouse lethality assay is concerned, paragraph [0023] simply says that, if all the animals are alive and no adverse signs have been observed, the batch is designated "non-toxic". Applying this test, paragraph [0024] reports that the 7.3 and 8.4 kDa batches were non-toxic.

358. As for the RBL degranulation assay, paragraph [0025] states that this is used to screen out batches of copolymer-1 which "might elicit undesirable local and/or systemic side effects". Prof Baird accepted that this would be understood by the skilled person to be a reference to the side effects reported in Bornstein 1987, namely local irritation at the injection site and rare transient vasomotor responses respectively. Paragraph [0028] states that, when the percentage of high molecular weight species present is low, the serotonin release, indicative of toxicity, is low.

359. Counsel for Mylan submitted that it followed that the teaching of the specification was that copolymer-1 having the molecular weight characteristics claimed was improved in the sense that it caused less irritation at the injection site and a reduced incidence of systemic side effects as compared with the copolymer-1 used in Bornstein 1987. As he accepted, the specification does not state, nor would the skilled reader understand from his common general knowledge, that either assay is predictive of toxicity in humans. He submitted, however, that the specification necessarily implied that the improvement in toxicity was clinically meaningful, that is to say one which would influence the decisions of a clinician. Furthermore, he argued that the mere possibility of an improvement was not a technical advance in any real sense. Accordingly, if there was a technical advance, it must reside 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. I accept this analysis.

360. Thus the primary question to be addressed is whether the results reported in the Patent, read in the light of the skilled team's common general knowledge, make it plausible that copolymer-1 having the claimed molecular weight characteristics causes less irritation at the injection site and/or a reduced incidence of systemic side effects than copolymer having a molecular weight of 14-23 kDa.

361. *Example 2A.* In Example 2A, none of the mice injected with the 7.3 or 8.4 kDa copolymer-1 batches died or exhibited an adverse reaction, whereas three out of five mice injected with the 22 kDa copolymer-1 batch having more than 5% died.

362. Prof Kimber's opinion was that these results were not persuasive that there was any association between average molecular weight of copolymer-1 and toxicity. Prof Schellekens' opinion was that the results provided support for a correlation between molecular weight and toxicity, particularly when taken together with Example 2B.

363. Importantly, Prof Sasieni analysed the results, and concluded that they were statistically significant applying the conventional threshold of $p < 0.05$. Mylan did not challenge his analysis in cross-examination, and Prof Kimber accepted it. Accordingly, I consider that Example 2A does make it 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.

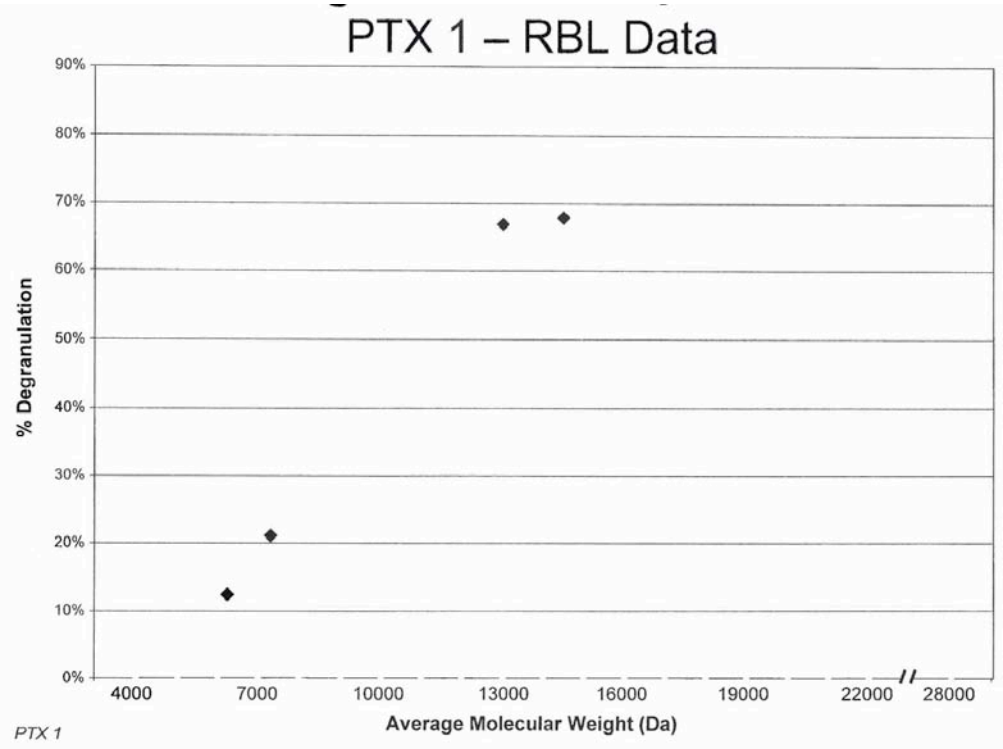
364. Although the mouse lethality test is not predictive of toxicity in humans, Prof Kimber accepted that it provided information about likely toxicity in humans and that (at least in the US Pharmacopeia version) it was commonly used for that purpose.

365. *Example 2B.* I have set out the results of the RBL degranulation test in Example 2B in paragraph 182 above. There was a lot of evidence as to significance or otherwise of these results. I do not intend to rehearse all of this evidence, although I have taken it all into account. Rather, I shall concentrate on what I consider to be the main points.

366. Counsel for Mylan submitted that the skilled team would approach the Patent's use of the RBL degranulation test with scepticism because of the common general knowledge that RBL cells were not as responsive to polybasic secretagogues as peritoneal mast cells. I do not think that Prof Baird went that far, but she did accept that the results would have to be treated with care. She also accepted that there were no controls as to spontaneous release or cell viability reported in the Patent.

367. Prof Kimber's opinion as stated in his first report was that the results did not provide any basis for an association between the molecular weight characteristics of copolymer-1 and RBL degranulation. In cross-examination, however, he distinguished between association and correlation, accepting that there was an association, but not a correlation. As stated above, I was not impressed by this evidence.

368. Prof Baird's opinion was that the results supported a correlation between the average molecular weight and percentage of higher molecular weight species of copolymer-1 and its toxicity as measured by RBL degranulation. In cross-examination she said that she assumed that the reported results were representative of further data which had not been reported, but as I understood her evidence her opinion was the same even if that was not the case. She exhibited a plot of the data points which I reproduce below, and said that it was possible to draw a curve through them:



369. Prof Baird accepted that there was some uncertainty as to where one drew the curve, particularly when one took into account the variability in the RBL data (9.9-14.9% for the 6.25 kDa batch and 16.8-25.2% for the 7.3 kDa). As counsel for Mylan submitted, this uncertainly gets even greater if one also takes into account the variability in SEC average molecular weight measurements.

370. Nevertheless, I consider that what matters for present purposes is the trend shown by the reported data. In my view this makes it 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.

371. Counsel for Mylan pointed out with some force that, even on that basis, the results do not support the claims. For example, claim 1 requires that more than 75% of the fraction is within a molecular weight range 2-20 kDa, but Example 2B is silent in this respect. Moreover, whilst claim 1 suggests that the critical threshold of species having a molecular weight of more than 40 kDa is 5%, the Patent does not disclose the actual % of such species in Example 2B. Thus 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 was occasioned by the difference in average molecular weight or the difference in % species over 40 kDa. Furthermore, the skilled person would have 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 %.

372. As can be seen, I have accepted similar arguments in the context of the issue as to priority. In my judgment, however, the position is different when it comes to obviousness. In the context of priority, the test of direct and unambiguous derivability is for good reason quite a strict one. In the context of obviousness, there is no reason

to apply such a strict test. On the contrary, the authorities discussed above make it clear that the test of plausibility is far from strict. I agree with Mylan that the results in Example 2B do not precisely support the limits in the claims, but I do not think that matters. The general trend disclosed by the results nevertheless makes it plausible that, as a general proposition, the claimed copolymer-1 is superior to copolymer-1 falling outside the claims. As with any such trend, there may be a degree of arbitrariness in where one draws the line between the two, but that cannot be fatal to the claims.

373. Counsel for Mylan also argued that, even if the Patent made it plausible that there was a meaningful association between molecular weight and RBL degranulation, it did not follow that this has any relevance in terms of toxicity *in vivo*. As noted above, RBL degranulation is not predictive of toxicity *in vivo*. Counsel for Mylan pointed out that the Patent merely stated that batches of copolymer-1 which evoked substantial degranulation "might" elicit undesirable local and/or systemic side efforts. He argued that this was not enough, since it amounted to presenting the skilled person with a hypothesis to investigate by experiment.

374. I do not accept this argument either. The Patent is clear that the RBL degranulation, like the mouse lethality assay, is being used as a screen to eliminate copolymer-1 that is potentially toxic in humans. Taken as a whole, Prof Baird's evidence was to the effect that, despite its limitations, the RBL degranulation test was a useful *in vitro* model for this purpose.

375. *Overall*. As noted above, Prof Schellekens' opinion was that, even though Example 2A and Example 2B did not feature precisely the same batches of copolymer-1, together they supported an association between molecular weight and toxicity. In my judgment, taken together, they disclose enough to make it plausible that copolymer-1 as claimed will cause less irritation at the injection site and/or a reduced incidence of systemic side effects than the higher molecular weight copolymer-1 used in Bornstein 1987.

Contemporaneous extrinsic evidence

376. Mylan relies upon extrinsic evidence which is contemporaneous with the Patent as demonstrating that copolymer-1 as claimed does not cause less irritation at the injection site and a reduced incidence of systemic side effects than copolymer having a molecular weight of 14-23 kDa, or at least as casting sufficient doubt on this to shift the evidential burden to the Defendants to prove that it does have the benefit. This consists of other experimental data and comments thereon recorded in Teva's contemporaneous disclosure documents. The Defendants contend that these materials support the conclusion drawn in the Patent rather than undermine it.

377. Although at earlier stages other documents were relied on, in Mylan's closing submissions reliance was confined to a single Teva document. This is a table of experimental results compiled in April 1994 ("the April 1994 Table"). The April 1994 Table contains results for (i) average molecular weight, (ii) percentage serotonin release in the RBL degranulation assay, (iii) mouse lethality and (iv) guinea pig skin irritation for a number of batches of copolymer-1, together with annotations in a mixture of English and Hebrew. Prof Kimber's first report includes a transcription

and translation of the April 1994 Table with added highlighting which I reproduce below:

Batch	Average MW	Peak III Select	RBL	Safety *in vivo*	Skin Irritation
123-094	6250	41.0	12.4	0/5	NT
123-090	**7300**	43.3	21	**0/5**	14±2.5 (14±1.2)
123-095	**8400**	40.8	25.6	**0/5**	11.6±1.5 (12±1.2)
04792	9245	43.9	31.3	0/5	13.8±1 (14±1.2)
04892	9600	44.2	50.5 (?)	0/5	NT
04992	9900	43.9	51.5 (?)	0/5	13.8±1.2 (14±1.2)
123-096	10,950	44.2	39.8	0/5	NT
04592	11,050	45.3	41.3	0/5	16±1.2 (16.4±0.8)
04692	11,900	15.8	41.7	0/5	NT
04492	12,150	47	47.6	0/5	18±1.8 (17.2±1)
196/2	13,000	45.7	66.9	0/5	16.2±1 (17±1.55)
196/1	14,500	44.66	67.8	0/5	15.6±0.8 (14.8±1)
186/1	**22,000**	47.29	60.3	**3/5**	NT

** Skin irritation: in mm, tested 2 hours (and 24 hours) after an intradermal injection*
NT = not tested
2 exceptional specimens. All the rest seem to align nicely (?)

378. The figures in red type are the data included in Example 2A of the Patent, while the yellow highlighting identifies the data included in Example 2B of the Patent. It is a curious historical fact that Yeda only included those data in the Patent when the other data were also available. Nevertheless counsel for Mylan did not submit that Yeda had cherry-picked only favourable results to put into the Patent. Rather he submitted that, whatever view one took of the RBL data, the more complete mouse lethality data recorded in the April 1994 Table and the guinea pig skin irritation data showed that copolymer-1 as claimed did not have the advantage claimed for it.

379. *Mouse lethality assay*. Counsel for Mylan pointed out that all of the batches of copolymer-1 in the April 1994 Table other than the 22 kDa batch were non-toxic according to the mouse lethality assay. He submitted that this demonstrated that the molecular weight ranges in the Patent were meaningless. I do not accept this submission for the following reasons.

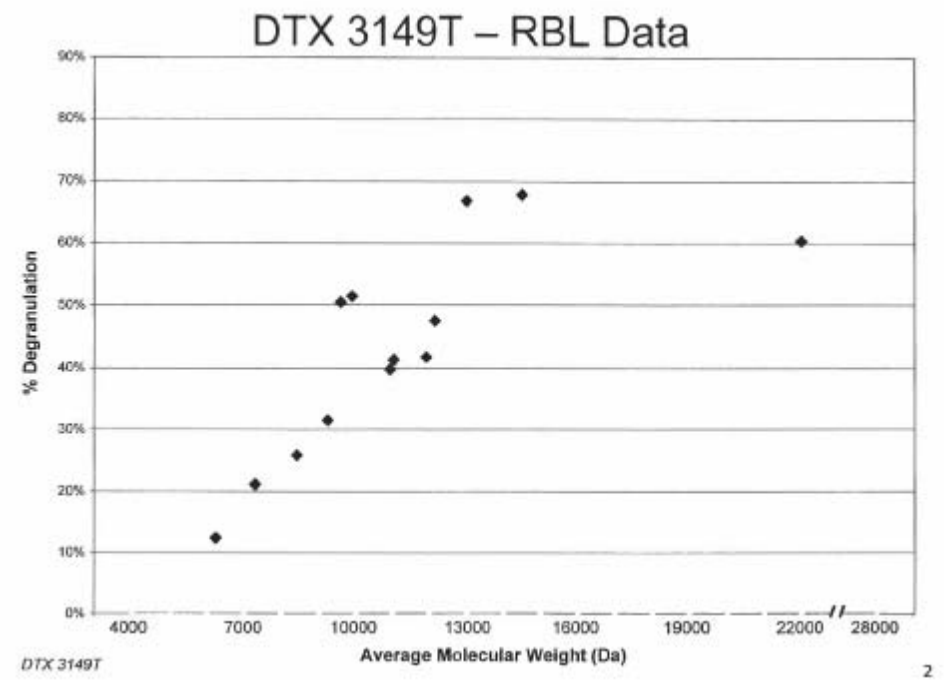
380. First, the data were analysed by Prof Sasieni. He noted that only three of these 65 mice in the 13 groups had a toxic reaction and those three mice were all in the group of five receiving the batch with the highest average molecular weight. His evidence was that, if one were to treat each mouse as independent, this result would be highly statistically significant. If, however, a more conservative approach were taken of treating the mice within each group as dependent, then the data only showed that the

one toxic response out of 13 was in the batch with the highest average molecular weight. This evidence was not challenged by Mylan.

381. Even on the more conservative approach, I consider that the data makes it plausible that there is an association between toxicity and molecular weight. I agree that the results for the batches of average molecular weight from 9.245 to 14.5 kDa do not support the limits in the claims. For the reasons given above, however, I do not regard this as an objection to the validity of the claims in the context of obviousness.

382. Secondly, Dr Pinchasi's evidence was that there was more mouse data available to Teva which demonstrated the correlation between molecular weight and toxicity in the mouse assay.

383. Thirdly, the mouse lethality data do not stand on their own. The April 1994 Table also includes additional RBL data. Although Mylan had contended that these data did not support the conclusion drawn in the Patent, that contention was rightly not pursued in closing submissions. Although Prof Kimber stated in his report that the data did not show a correlation between average molecular weight and RBL degranulation, in cross-examination he accepted that they showed an association while maintaining that there was a distinction between the two. Prof Baird's opinion was that the data did show a correlation in that the toxicity increased with molecular weight and then levelled off at a higher molecular weight. She acknowledged that there were two outliers at 9.6 and 9.9 kDa, but said that the trend of increasing RBL degranulation with increasing average molecular weight was nevertheless clear. Again she exhibited a plot of the data points and said that it would be possible to draw a curve through them:



384. Furthermore, Prof Sasieni analysed the RBL data in the April 1994 Table. He found that the data had a high Spearman's correlation coefficient (0.85) with a very low P-value (0.0002). His evidence was that this showed a strong association between the

percent serotonin release and the average molecular weight of the copolymer-1, and that this was extremely unlikely to be due to chance. Mylan did not challenge this evidence.

385. *Guinea pig skin irritation test*. There is little dispute that the guinea pig skin irritation data in the April 1994 Table do not show any correlation between the average molecular weight of the copolymer-1 and the skin irritation. The dispute is as to the significance of this. Prof Kimber's evidence was that the skin irritation test was more likely to reflect the ability of different batches of copolymer-1 to cause local injection site reactions in patients than either of the tests in the Patent. He did not suggest that it reflected the ability of copolymer-1 to cause systemic side effects, however.

386. As noted above, Prof Baird said that she would defer to Prof Kimber when it came to interpreting the skin irritation test data. Nevertheless, it was her opinion that the inconclusive results in the skin irritation data did not detract from the conclusion to be drawn from the RBL assay, with which she was very familiar. This is supported by the evidence of Dr Pinchasi that, although Teva performed the tests to see if there was a correlation between RBL degranulation and skin irritation, Teva concluded that the skin irritation test was less informative than the RBL degranulation test or mouse mortality assay and abandoned it.

387. Counsel for Mylan submitted that the effect of the skin irritation data was to place the burden on the Defendants to demonstrate that copolymer-1 having the molecular weight characteristics of the claims conferred an improvement in local injection site reactions compared to Bornstein 1987. I do not accept that submission. In my view the data in the April 1994 Table have to be considered as a whole. I consider that the mouse lethality data and the RBL degranulation data in the April 1994 Table are broadly consistent with the data reported in the Patent and that, taken together, they also make it plausible that copolymer-1 as claimed is less toxic than the copolymer-1 used in Bornstein 1987. I do not consider that the skin irritation data detract from this conclusion, particularly when it is borne in mind that the skin irritation data tell one nothing about systemic side effects.

Post-dated evidence

388. As well as the contemporaneous extrinsic evidence, Mylan relies upon subsequent clinical data as demonstrating that copolymer-1 as claimed does not cause less irritation at the injection site and a reduced incidence of systemic side effects than copolymer having a molecular weight of 14-23 kDa, or at least as casting sufficient doubt on this to shift the evidential burden to the Defendants to prove that it does have this benefit. For the reasons given above, I do not consider that it is open to Mylan to rely upon such evidence for this purpose. I must nevertheless consider the evidence, both in case I am wrong in that conclusion and because Mylan relies on the same evidence as demonstrating insufficiency. I shall do so under a number of headings.

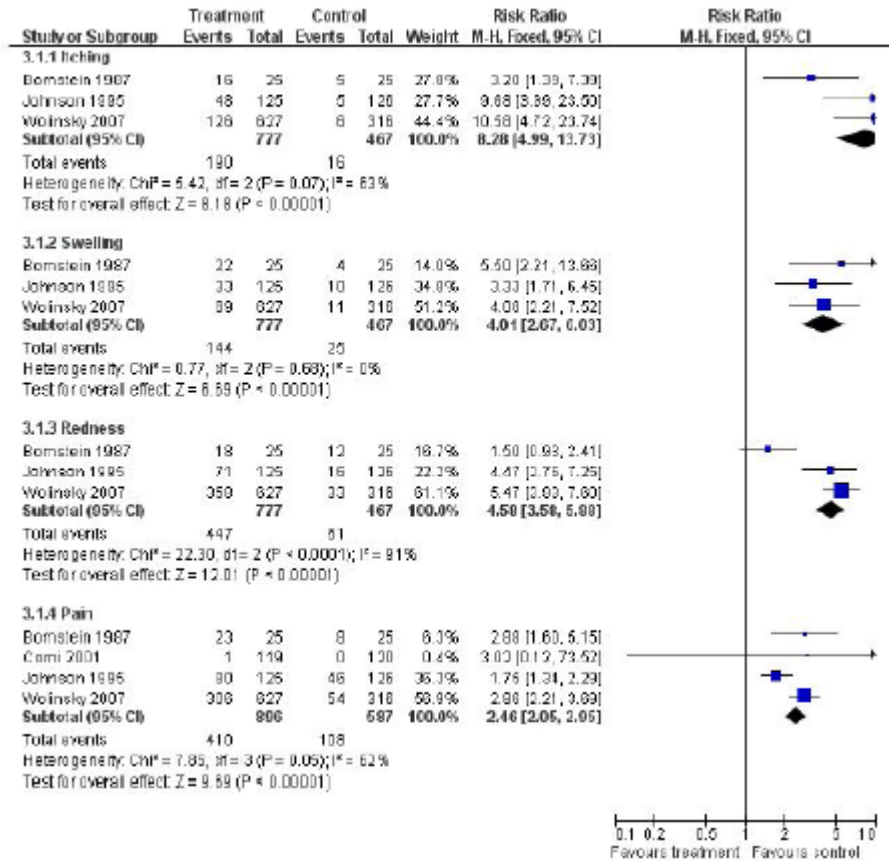
389. *The Cochrane Review*. The Cochrane Collaboration publishes systematic reviews of clinical trials in which the published data is subjected to meta-analysis. These reviews are highly regarded in the medical and scientific communities. An updated Cochrane review of copolymer-1 clinical trials was published in 2010: La Mantia *et al*, "Glatiramer acetate for multiple sclerosis (Review)", The Cochrane Collaboration, John Wiley & Sons, Ltd, 2010 ("the Cochrane Review"). The Cochrane Review was

aimed at determining "clinical efficacy and safety of glatiramer acetate in patients with MS". Six main outcomes were considered, of which the fifth was "incidence of any adverse events". The selection criteria for the review were all randomised or quasi-randomised controlled trials comparing copolymer-1 and placebo in patients with MS. Six trials met these criteria and were included: Bornstein 1987, Bornstein 1991, Johnson 1995, Comi 2001, Wolinsky 2007 and Filippi *et al*, "Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: A multicentre, double-blind, randomised, placebo-controlled study", *Lancet Neurology*, 2006, Vol 5, pp 213-220 ("Filippi 2006"). The last of these is not informative with regard to the question of the relative adverse effects of injectable copolymer-1, and can be disregarded for present purposes.

390. The Cochrane Review is instructive for the purpose of comparing the adverse effect profiles between the trials for three reasons. First, it assesses the quality of the trials under consideration. Secondly, it presents the trial data in a convenient way that allows easy comparison. Thirdly, it tests "heterogeneity" within the trials. Trials are considered homogenous if the differences between them arise by chance alone and heterogeneous if differences might be due to other factors (for instance, arising from a change in the molecular weight of the copolymer-1 being administered). The Cochrane approach is to test systematically for heterogeneity.

391. Figure 8 of the Cochrane Review, reproduced below, is an analysis of the results in relation to localised injection site adverse effects:

Figure 8. Forest plot of comparison: 3 Glatiramer acetate versus placebo: adverse effects, outcome: Localised to the injection site.



392. The comparison is expressed in the form of a Forest plot, where trial outcomes (represented by blue squares) are placed in relation to a vertical line called the "line of no effect". In a Forest plot, raw data for each observation is extracted from the clinical trial reports and re-plotted and re-analysed. The size of the blue squares indicate the number of patients involved in the study and the position of the blue squares on either side of the line of no effect indicate whether the treatment is favoured or the control is favoured. If a blue square falls on the right side of the line of no effect, this indicates a result in favour of the control, meaning that the adverse effect is seen more frequently in those patients being treated with copolymer-1 compared with placebo. The horizontal lines on either side of the blue squares indicate the 95% confidence intervals (that is to say, the "true" result may be found, with 95% confidence, somewhere within the area found between the upper and lower limits). If the horizontal lines (the confidence intervals) do not cross the line of no effect, this means that the observation is statistically significant. The black diamond is a summary of all of the data, with the confidence intervals indicated by the horizontal spread of the diamond. This is irrelevant for present purposes.

393. It can be seen from Figure 8 that copolymer-1 appeared to cause "itching" in fewer patients in Bornstein 1987 than in Johnson 1995 and Wolinsky 2007 (given that the blue square is closest to the line of no effect), but to induce "swelling" in more patients in Bornstein 1987 than in the other two trials. It is unlikely that either of these differences is statistically significant, however, because for both itching and swelling there are regions where the horizontal lines (the confidence intervals) for each of the blue squares overlap. This impression is supported by the formal test for heterogeneity, which leads to a p value > 0.05 ($p = 0.07$ and $p = 0.68$ in relation to "itching" and "swelling", respectively), i.e. they are homogeneous. Therefore, the Cochrane Review suggests that there is no difference between the itching and swelling induced by copolymer-1 in Bornstein 1987, Johnson 1995 and Wolinsky 2007.

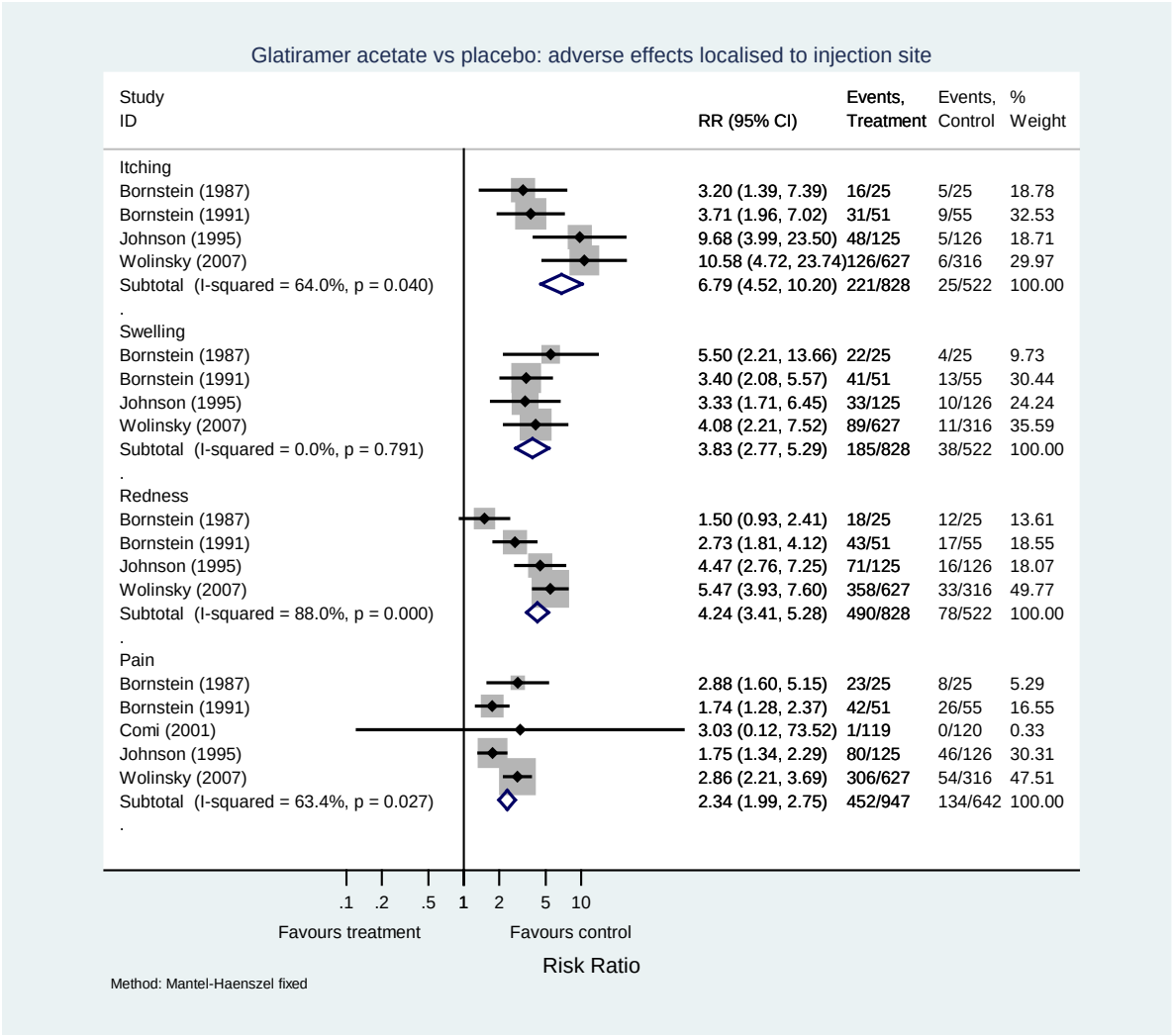
394. Similarly, for patients reporting pain after receiving copolymer-1, there is no difference between the trials, either visually or indicated by the test for heterogeneity, where $p = 0.05$.

395. A different picture emerges from the data for redness. While the copolymer-1 used in Johnson 1995 and Wolinsky 2007 caused redness in statistically significantly more patients than those on placebo, the confidence intervals for redness in Bornstein 1987 cross the line of no effect, which means it is not statistically secure that the copolymer-1 used in this trial is associated with redness. Furthermore, the fact that the confidence intervals of Bornstein 1987 lie outside of those of Johnson 1995 and Wolinsky 2007 means that there was statistically significantly less redness in Bornstein 1987 than in Johnson 1995 and Wolinsky 2007. The formal test for heterogeneity supports this interpretation ($p < 0.00001$), i.e. they are heterogeneous.

396. Analysis 3.2 of the Cochrane Review shows a comparison between the trials in terms of the systemic adverse effects experienced by patients. There is no evidence of a difference between the incidence of systemic effects between Bornstein 1987 and later studies. For instance, visually there appears to be no difference between the frequency of the patterned reaction between the trials. This is reinforced by the negative test for heterogeneity ($p = 0.64$), i.e. the trials are homogeneous in this respect.

397. *Dr Altmann's analyses*. At Dr Coles' request, Dr Altmann was instructed to incorporate data from Bornstein 1991 into the Cochrane Review's analysis of local injection site reactions and data from Bornstein 1991 and Comi 2009 into the Cochrane Review's analysis of the systemic reactions. (Comi 2009 did not include a detailed report of injection site reactions.)

398. The results of Dr Altmann's calculations in the case of local reactions are set out below:



399. Visually, the results suggest that itching was experienced by fewer patients in Bornstein 1987 and Bornstein 1991 (higher molecular weight copolymer-1) compared to Johnson 1995 and Wolinsky 2007 (lower molecular weight copolymer-1). The statistical test for heterogeneity across these trials is positive ($p = 0.040$), i.e. they are heterogeneous. As for swelling, the test for heterogeneity across these trials is negative ($p = 0.791$), i.e. they are homogeneous. Fewer patients experienced injection site redness in Bornstein 1987 and Bornstein 1991 compared to the other trials, and the test for heterogeneity across these trials is positive ($p = 0.000$), i.e. they are heterogeneous. The test for heterogeneity for "pain" is also positive ($p = 0.027$), but the profile of the frequency of pain across the trials does not differentiate lower molecular weight copolymer-1 from higher molecular weight copolymer-1. Pain is seen most frequently in Bornstein 1987 and Wolinsky 2007, whereas Bornstein 1991

and Johnson 1995 are in the lower incidence group. Overall, therefore, these results suggest that higher molecular weight copolymer-1 causes less itching and redness than lower molecular weight copolymer-1, while there is no evidence of any difference in relation to swelling or pain.

400. In the case of systemic reactions, incorporation of the additional data made no difference according to Dr Altmann's calculations. It remained the case that there was no evidence of a difference between higher molecular weight copolymer-1 and lower molecular weight copolymer-1.

401. In addition to these recalculations of the Cochrane Review analyses, Dr Altmann was instructed directly to compare the adverse effects as between Bornstein 1987 and Bornstein 1991 on the one hand and the later trials on the other hand. He found there was no statistical difference in the number of patients experiencing itching, swelling, redness, pain or the patterned reaction between the earlier and later trials.

402. *Prof Sasieni's analyses*. Dr Altmann, like the authors of the Cochrane Review, analysed the data in terms of "risk ratio", that is to say the ratio of the two proportions of patients reporting the relevant side effect in each arm of the trial. Prof Sasieni accepted that such an analysis was standard where the risks were small and it could be assumed that the risk ratio was independent of the underlying risk. In his opinion, however, this was not the situation in the present case. For example, in Wolinsky 2007 the risk of itching in patients on placebo was 1.9% and it was 10.6 times greater in patients on copolymer-1. In Bornstein 1987 20% of patients on placebo had itching. It was thus impossible for the relative risk to be 10.6 in Bornstein 1987: the most it could be would be 5.0 if all of the patients who received copolymer-1 reported itching.

403. Prof Sasieni therefore re-analysed the data in terms of "excess risk" or "risk difference", that is to say, the difference between the proportions of patients experiencing side-effects in each arm of the trial. The results of this re-analysis were as follows (Comi 2001 had to be excluded from the pain analysis for technical reasons):

	% Events GA	**% Events Placebo**	**Excess risk**	**Weighted average excess**	**Difference: Early vs. Late**	**95% Confidence Interval**	**p-value**
Itching							
Bornstein 1987	64.0	20.0	44.0	} 44.3	24.0	9.9 to 38.1	0.002
Bornstein 1991	60.8	16.4	44.4				
Johnson 1995	38.4	4.0	34.4	} 20.3			
Wolinsky 2007	20.1	1.9	18.2				
Swelling							
Bornstein 1987	88.0	16.0	72.0	} 61.6	50.0	37.2 to 62.7	<0.001
Bornstein 1991	80.4	23.6	56.8				
Johnson 1995	26.4	7.9	18.5	} 11.7			
Wolinsky 2007	14.2	3.5	10.7				

Redness							
Bornstein 1987	72	48	24.0	} 44.0	-2.1	-16.7 to 12.5	0.77
Bornstein 1991	84.3	30.9	53.4				
Johnson 1995	56.8	12.7	44.1	} 46.1			
Wolinsky 2007	57.1	10.4	46.7				
Pain							
Bornstein 1987	92	32	60.0	} 43.1	12.2	-2.2 to 26.6	0.105
Bornstein 1991	82.4	47.3	35.1				
Johnson 1995	64	36.5	27.5	} 30.9			
Wolinsky 2007	48.8	17.1	31.7				
Comi 2001	0.8	0	0.8	excluded			

404. This analysis indicates that, for itching and swelling, the excess risk was substantially and highly significantly greater in the two earlier Bornstein trials than in the later trials. For redness and pain, the differences in the excess risk were smaller and non-significant. Prof Sasieni also considered the patterned reaction data, and concluded that it was not possible to say that there was a difference in patterned reactions between the earlier and later trials whether analysed by relative risk or excess risk.

405. *The evidence of Dr Altmann and Prof Sasieni*. Notwithstanding the differences in their respective analyses, there was a considerable amount of common ground between Dr Altmann and Prof Sasieni. Importantly, as noted in paragraph 119 above, they were agreed that statistical analysis of the available clinical trial data did not make it possible to determine whether lower molecular weight copolymer-1 had fewer side effects than higher molecular weight copolymer-1. This is because none of the clinical trials were designed to compare the side effects of lower and higher molecular weight copolymer-1. In order to do that, a trial would have to be carried out involving the two products for which measurement of the adverse effects was the primary endpoint.

406. So far as the choice of risk ratio or risk difference was concerned, Dr Altmann did not accept that it was relevant or desirable to assume the treatment effect had to be independent of the underlying risk and therefore discount the risk ratio approach. He pointed out that the risk difference analysis was not free from difficulty either. For example, the copolymer-1 minus placebo risk difference for pain in Bornstein 1987 was 60%, but it was impossible for the risk difference in Bornstein 1991 to be the same because the placebo risk was 47.3% and the active risk could not be greater than 100%. He considered the risk ratio approach to be more intuitive and, in his experience, more frequently used as a measure of treatment effect than risk difference. Nevertheless, he did not believe that there were any statistical grounds for preferring risk difference to risk ratio or vice versa. The fact that the two approaches led to different conclusions in the present case was reflection of the well-known statistical problem of assessing heterogeneity. He therefore concluded that there was no clear statistical evidence of a difference in side effects between the earlier and later copolymer-1, since the risk ratio and risk difference approaches gave discordant results.

407. Prof Sasieni agreed that there were problems with both approaches, although he considered that these were fatal with risk ratio, but merely critical with risk

difference. It was his opinion that the correct approach applying the precautionary principle was to consider both analyses. The result was inconclusive.

408. *Dr Coles' evidence*. Dr Coles' opinion was that neither the result of the risk ratio analysis nor the result of the risk difference analysis was biologically credible. The risk ratio analysis suggested that higher molecular weight copolymer-1 caused less itching and redness than lower molecular weight copolymer-1. Dr Coles' view was that a true difference between the two would lead to a segregation in all four symptoms of itching, swelling, redness and pain, since they were due to the same pathological mechanism, namely inflammation. Thus he did not find it plausible that there should be a difference in only two of these symptoms. Similarly, the risk difference analysis suggested that lower molecular weight copolymer-1 caused less itching and swelling than higher molecular weight copolymer-1. Again, he did not find this plausible for the same reason. Accordingly, it was his opinion that these differences arose by chance and as a result of the idiosyncrasies of the statistical techniques.

409. Nevertheless, it was also Dr Coles' opinion that, given the clinical trials included 947 patients on copolymer-1 and 642 patients on placebo, there was enough data to assess whether there was in fact a clinically meaningful difference between the adverse effect profiles of higher and lower molecular weight copolymer-1. In his view, there was no such difference.

410. *Prof Schellekens' evidence*. Prof Schellekens' opinion was that the comparisons between clinical trials which Dr Coles and Dr Altmann had undertaken were "scientifically flawed" and "meaningless" because of six actual or potential differences between the trials. I was unconvinced by this evidence for the following reasons. First, for the reasons given above, I do not think that Prof Schellekens was well qualified to give it. Secondly, it emerged that he had not troubled to read the primary publications. Thirdly, he had considerable difficulty in justifying his criticisms in cross-examination. Fourthly, he had no coherent answer to the point that the authors of the Cochrane Review, which as noted above is a publication in a highly respected series, had adopted the same approach.

411. Prof Schellekens also disputed that itching, redness, pain and swelling were all symptoms of inflammation. Again, I was unimpressed by his evidence on this topic, which was far less convincing than Dr Coles' evidence.

412. *Conclusions*. My conclusions are as follows. First, no clinical trial has been carried out which directly compares the side effects of higher and lower molecular weight copolymer-1. Thus reliable statistical evidence as to which, if either, has fewer side effects is not available. Secondly, the statistical analyses of the available clinical trial data are inconclusive. There is no clear statistical evidence either way, particularly bearing in mind the conflicting results of the two analyses and Dr Coles' evidence to the lack of biological credibility of both analyses. Thirdly, that just leaves Dr Coles' opinion as a clinician that there was no difference between the adverse event profiles. As he made clear in cross-examination, it was his view not merely that there was no evidence of difference, but that there was evidence of no difference. I consider that his opinion is one that merits respect for the reasons I have given above. Nevertheless, in the light of the statistical evidence, I am unable to accept it. In my judgment the proper conclusion to be drawn from the evidence as a whole is that it is inconclusive:

it is not possible to determine whether lower or higher molecular weight copolymer-1 causes fewer side effects or neither.

Insufficiency

The law

413. A patent is invalid "if the specification does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art" (section 72(1)(c) of the 1977 Act). I reviewed the law as to insufficiency in *Sandvik v Kennametal* at [106]-[124]. As I discussed there, it is possible to distinguish between three ways in which a patent may be invalid on the ground that the specification does not disclose the invention clearly enough and completely enough for it to be performed by the skilled person, although there is some overlap between them. First, where the skilled person is unable to carry out the claimed invention either at all or without undue burden and without needing inventive skill ("classical insufficiency"). Secondly, where the claim is ambiguous so that the skilled person cannot tell when he is within the claim or outside it. Thirdly, where the breadth of the claim exceeds the technical contribution to the art made by the invention. Neither side took issue with my analysis of the law in those paragraphs.

Classical insufficiency

414. As is common ground, the Patent directs the skilled reader at [0019]-[0020] to determine the average molecular weight and molecular weight distribution of copolymer-1 by SEC "on a calibrated gel filtration column (Superose® 12)" using a UV detector, but does not disclose any of the other conditions. In particular, it does not disclose either (i) what mobile phase should be used or (ii) how the column should be calibrated. Mylan contends that the Patent is insufficient as a result, partly because it imposes an undue burden on the skilled person and partly because different skilled persons would choose different conditions and thereby obtain different results. Thus this is partly an objection of classical insufficiency and partly an objection of ambiguity. For convenience I will consider it under the former heading.

415. As with the absence of any definition of "average molecular weight", I think that the skilled team would be very surprised that the inventors had failed to specify these matters, and rather cross at being asked to work them out for themselves. Again, however, the skilled team would not throw up their hands when confronted with this problem, but instead would see if they could work out what to do applying their common general knowledge.

416. Since the determination is by SEC, it is the common general knowledge of the SEC analyst which matters for this purpose. Mylan's witness on this aspect of the case was Dr Hunt, while the Defendants' witness was Prof Grant.

417. *Choice of mobile phase*. It was common ground between Dr Hunt and Prof Grant that the SEC analyst would expect to have to try a number of different mobile phases in order to select one that was appropriate. Dr Hunt's evidence, which I accept, is that the skilled person would start with eluents recommended in the Superose 12 data sheet. From those listed, he identified four as suitable, namely 70% formic acid at pH 1, 0.05M HCl at pH 1.4, 0.1M ammonium acetate at pH 5 and 6M Guanidine HCl at

pH 11.5. (As counsel for the Defendants pointed out, ammonium acetate might well be the first choice since it is the solvent mentioned in the Patent, albeit for preparative SEC, at [0018].) In addition, Dr Hunt accepted that 0.05M phosphate would be an option. Prof Grant agreed with these options, except for 6M Guanidine HCl at pH 11.5. His evidence, which I accept, was that the skilled person would be very hesitant about using such a basic eluent for a polypeptide.

418. Dr Hunt suggested in his first report that it might not be possible to identify a mobile phase which avoided non-size interactions. In cross-examination, however, he substantially accepted that the skilled person would expect to be able to avoid or minimise such interactions by use of the standard techniques discussed in paragraph 63 above. In any event, there is no evidence that any of the likely choices of eluent do give rise to problematic interactions.

419. The only point pursued by Mylan in its closing submissions was that difference in pH between the various mobile phases would be expected to affect the molecular weight results. I do not accept that this renders the Patent insufficient for the following reasons. First, as I have already said, I do not think that the skilled person would have chosen a substantially basic eluent. Secondly, the reason why Dr Hunt suggested that pH would have this effect was that it would affect the conformation of a charged polymer, and it is common ground that copolymer-1 is amphoteric (i.e. it has both negatively and positively charged groups). As he accepted, however, copolymer-1 is a random coil in solution. As Prof Grant explained, it follows that its conformation would not be expected to change with pH. Thirdly, there is no evidence that this does in fact occur or, if so, as to the extent of the effect on the molecular weight results. Prof Grant fairly accepted that he could not say that different mobile phases would not have an effect on the results, but no specific figure for the magnitude of the effect was put to him in this regard.

420. *Calibration method*. As discussed above, the SEC analyst would be familiar with a number of different methods of calibrating SEC.

421. Dr Hunt's evidence was that the skilled person would begin by trying commercial narrow standards. This was because this would not take long - a day for each – and so he would favour giving them a go to see if he got lucky. The order he said he would try them in was denatured protein standards first, since these were recommended by Pharmacia in the Superose 12 datasheet, followed by PEOs, PEGs and dextrans.

422. Prof Grant's evidence was that the skilled person would recognise that narrow standards would be unlikely to give an accurate calibration because of the chemical differences between copolymer-1 and commercially available standards. Because of this, he would not start with them, but would go straight to universal calibration or self standards.

423. In cross-examination, Prof Grant accepted that denatured proteins would be an option. He thought that PEGs and PEOs were too different to cop-1 to give a proper calibration, but said that he would not have anything against anyone giving them a go to see if they worked. For his part, Dr Hunt accepted that these kinds of standard were not chemically similar to polypeptides.

424. In my judgment, the upshot is that, with the possible exception of denatured proteins, commercial narrow standards would be understood to be likely to give inaccurate results and would be viewed by the skilled person as a waste of time. It matters little, however. Even if the skilled person were to follow Dr Hunt's course, he would only spend a few days trying these standards. After that, he would be likely to move to universal calibration or self-standards.

425. Prof Grant's evidence was that universal calibration would be expected to work for copolymer-1, since it was known to work for many types of polymers, including most random coil polymers and copolymer-1 was a random coil in solution. I did not understand Dr Hunt to dispute this. Furthermore, as counsel for the Defendants pointed out, we now know that it does in fact work, because Natco uses it to determine the average molecular weight of Mylan's glatiramer acetate product. In cross-examination Prof Grant was asked why, if universal calibration would have been regarded as a suitable approach, Teva had not used it in the late 1980s and early 1990s. He said that he did not know. As counsel for the Defendants submitted, given the evidence that universal calibration (a) was common general knowledge, (b) would be expected to work and (c) would in fact work, it does not matter what the explanation is. (For all I know, it may have been that Teva did not possess an online viscometer.)

426. As discussed above, in principle there are two ways of calibrating using self-standards, namely using narrow and broad self-standards. So far as narrow self-standards are concerned, Dr Hunt made the point that fractionation is a time-consuming business. He estimated that this could take as long as 6 months. He accepted, however, that it was a routine technique which could be given to a technician to perform. He was not aware of anything about copolymer-1 which would make it difficult to fractionate. As for his estimate that it could take 6 months, this was based on 1 gram of each of 6-10 standards. In cross-examination, however, he accepted that only 5 fractions would be needed and that only 10 mg of material would be needed if light-scattering (SEC-MALLS, a commercially available technique) was used to measure the M_n and M_w of the fraction. Accordingly, I conclude that much less time would be required to calibrate an SEC column for copolymer-1 in this way.

427. As to broad standards, as discussed above, there are two ways in which the column could be calibrated by means of a single broad standard. Prof Grant's evidence was that the skilled person would have been more likely to use either universal calibration or a range of self-standards. In any event, the only real issue identified by Dr Hunt was, in the case of the linear method, whether the calibration curve of the standards was linear in the range of interest. There is no evidence that this is not the case here.

428. In its closing submissions Mylan placed considerable emphasis on the use of a range of broad self standards as discussed in paragraphs 161-162 above. I have concluded that this was a common general knowledge technique, but only for log normal distributions. The reason for this emphasis is that it appears from Teva's disclosure documents that Teva used a technique of this kind from 1987 to 1996, initially assigning the molecular weights of the peak by viscometry and later by MALLS. Furthermore, Mylan contends that the evidence shows that Teva did not achieve accurate results in this way. Prof Grant's evidence, however, was that he did not consider that what Teva did was representative of what the skilled person trying to

follow the Patent would do. Furthermore, he pointed out that the skilled person could check the accuracy of his results by absolute methods.

429. The conclusion which I draw from the evidence summarised above is that the skilled person would be able to calibrate his SEC column to measure the average molecular weight of copolymer-1 without undue burden and without inventive skill.

430. *Different results*. The conclusion I have just reached does not in itself provide an answer to Mylan's point that different skilled people could use different calibrations and get different results. Although Prof Grant was surprisingly resistant to the suggestion, it is clear from the evidence (e.g. the Shortt paper referred to above) that in practice different calibrations can lead to different results even though, in theory, any proper calibration should yield the same answer. The first question is how different. The second question is what the significance of this is.

431. So far as the first question is concerned, Mylan has not carried out an experiment to quantify the differences in average molecular weight which could be caused by different calibrations. Instead, Mylan relies on various pieces of documentary evidence from Teva, of which the most significant are as follows. First, the average molecular weights of two of the samples lying behind the Figures in the Patent were measured by Teva in July 1993 as being 7150 and 7250 Da respectively and in May 1994 as both being 7700 Da (it is not entirely clear which "average molecular weight" these are, but it appears that in fact they are M_p). Prof Grant regarded this as reflecting the normal variability of SEC of up to 10%.

432. Secondly, a report by Dr Dora Lis and Dr Alexander Gad on behalf of Teva in April 1998 sets out average molecular weights obtained used polypeptide standards they had prepared compared to those obtained with the previous broad standards used by Teva. The authors concluded:

> "The molecular weights obtained using the two calibration sets within the specification range differed by, typically, not more than 20% in the low molecular weight range and by not more than 12% in the RRT [relative retention time] specification range of the peak (average molecular weight)."

Again, Prof Grant's evidence was to the effect that the 12% figure for average molecular weight was broadly consistent with the reproducibility one would expect from SEC.

433. Turning to the second question, I have already found that the skilled person would know from his common general knowledge that SEC measurements of average molecular weight had a variability of about 5-10%, possibly slightly more. It is important to emphasise that this represents random error, not systematic error. Thus the skilled person would appreciate that a measured average molecular weight of within $\pm$5-10%, or possibly slightly more, of (say) 8 kDa could not be distinguished from a true average molecular weight of 8 kDa.

434. The evidence discussed above suggests that the reproducibility which the skilled person would obtain when measuring the average molecular weight of copolymer-1, even allowing for the effect of different calibrations, would be at the top end of the

range which the skilled person would expect from his common general knowledge, but would not significantly exceed that range.

435. In the circumstances, I do not consider that the claims are insufficient. Rather, they have a fuzzy boundary with respect to the average molecular weight criteria due to the inherent imprecision in the measurement technique specified. Perhaps slightly surprisingly, it has not been shown by Mylan that the inventors' failure to specify the calibration method to be used leads to significantly greater uncertainty in the average molecular weight than that which is inherent in the choice of measurement technique.

Ambiguity

436. Mylan contends that the claimed inventions are insufficient since the references to "average molecular weight" and the molecular weight distribution features in the claims are ambiguous. For the reasons given above, I have concluded that these features of the claims are not ambiguous. It follows that the claimed inventions are not insufficient on this ground.

Excessive claim breadth

437. Finally, Mylan contends that the product claims are insufficient since they make no technical contribution to the art. Mylan relies in support of this contention on the same evidence as it relies upon in support of its case that product claims are obvious for want of technical contribution. In this context, Mylan particularly relies upon the evidence concerning the clinical trials. It is common ground that, for this purpose, it does not matter that this evidence post-dates the priority or application date of the Patent.

438. Counsel for the Defendants submitted that the product claims were "ordinary" product claims comparable to that under consideration in *Generics (UK) Ltd v H. Lundbeck A/S* [2009] UKHL 12, [2009] RPC 13 rather than a claim of the kind which was in issue in *Biogen Inc v Medeva plc* [1997] RPC 49. I do not accept this submission. As I endeavoured to explain in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1669 (Pat) at [473]-[475] and *Sandvik v Kennametal* at [124], in *Generics v Lundbeck* the House of Lords proceeded on the basis that the technical contribution made by the invention was the single product which was the subject of the claim. Accordingly, the breadth of the claim did not exceed the technical contribution, and it was neither here nor there that the specification only disclosed one way of making the product. In the present case, however, even claims 1-3 cover a range of products. Claims 4-6 and 11-12 are not simple product claims at all. Furthermore, the key characterising features of all these claims, the average molecular weight and molecular weight distribution features, depend at least to some extent upon the way in which the copolymer-1 is made.

439. Even so, it is debatable whether the claims are insufficient even if it is factually correct that copolymer-1 as claimed does not have a lower incidence of side effects than the higher molecular weight copolymer-1 used in Bornstein 1987 (and Bornstein 1991). In particular, the inventions disclosed in claims 1-3 are copolymer-1 fractions having the molecular weight features of those claims. There is no dispute that the skilled team would be able to make such fractions. Mylan's objection is not that the breadth of those claims exceeds the technical contribution to the art made by the

invention in the sense explained by Lord Hoffmann in *Biogen v Medeva*, namely that they cover ways of achieving the desired result which owe nothing to the Patent or any principle it discloses. Rather, Mylan's objection is that none of the claimed products have the advantage claimed for them in the specification. It seems to me that it is arguable that that is an objection not of insufficiency, but of inutility, which is not a ground of objection under section 72 of the 1977 Act.

440. It is not necessary to come to a conclusion on this point, however, since I have already concluded that Mylan has not proved that copolymer-1 as claimed does not have a lower incidence of side effects than the higher molecular weight copolymer-1 used in Bornstein 1987. It is true that I have not concluded that it does have a lower incidence, but the burden does not lie on the Defendants to establish this.

Added matter

The law

441. A patent is invalid if "the matter disclosed in the specification of the patent extends beyond that disclosed in the application for the patent, as filed" (section 72(1)(d) of the 1977 Act). The test for added matter was stated by Aldous J in *Bonzel v Intervention Ltd (No 3)* [1991] RPC 553 at 574 as follows:

> "The decision as to whether there was an extension of disclosure must be made on a comparison of the two documents read through the eyes of a skilled addressee. The task of the Court is threefold:
>
> (1) To ascertain through the eyes of the skilled addressee what is disclosed, both explicitly and implicitly in the application.
>
> (2) To do the same in respect of the patent [as proposed to be amended].
>
> (3) To compare the two disclosures and decide whether any subject matter relevant to the invention has been added whether by deletion or addition. The comparison is strict in the sense that subject matter will be added unless such matter is clearly and unambiguously disclosed in the application either explicitly or implicitly."

442. More recently, Jacob LJ stated the law in *Vector Corp v Glatt Air Techniques Ltd* [2007] EWCA Civ 805, [2008] RPC 10 as follows:

> "4. In *Richardson-Vicks' Patent* [1995] RPC 568 at 576 I summarised the rule in a single sentence:
>
> > 'I think the test of added matter is whether a skilled man would, upon looking at the amended specification, learn anything about the invention which he could not learn from the unamended specification.'
>
> I went on to quote Aldous J in *Bonzel*. His formulation is helpful and has stood the test of time.

5. The reason for the rule was explained by the Enlarged Board of Appeal of the EPO in G1/93 *ADVANCED SEMICONDUCTOR PRODUCTS/Limiting feature* [1995] EPOR 97 at [Reasons 9]:

> 'With regard to Article 123(2) EPC, the underlying idea is clearly that an applicant shall not be allowed to improve his position by adding subject-matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying upon the content of the original application.'

6. Mr Richard Arnold QC provided a clear articulation as to how the legal security of third parties would be affected if this were not the rule:

> 'The applicant or patentee could gain an unwarranted advantage in two ways if subject-matter could be added: first, he could circumvent the "first-to-file" rule, namely that the first person to apply to patent an invention is entitled to the resulting patent; and secondly, he could gain a different monopoly to that which the originally filed subject-matter justified.'

7. Kitchin J has recently helpfully elaborated upon the *Bonzel* formulation in *European Central Bank v Document Security Systems* [2007] EWHC 600 (Pat), 26th March 2007:

> '[97] A number of points emerge from this formulation which have a particular bearing on the present case and merit a little elaboration. First, it requires the court to construe both the original application and specification to determine what they disclose. For this purpose the claims form part of the disclosure (s.130(3) of the Act), though clearly not everything which falls within the scope of the claims is necessarily disclosed.
>
> [98] Second, it is the court which must carry out the exercise and it must do so through the eyes of the skilled addressee. Such a person will approach the documents with the benefit of the common general knowledge.
>
> [99] Third, the two disclosures must be compared to see whether any subject matter relevant to the invention has been added. This comparison is a strict one. Subject matter will be added unless it is clearly and unambiguously disclosed in the application as filed.
>
> [100] Fourth, it is appropriate to consider what has been disclosed both expressly and implicitly. Thus the addition of a reference to that which the skilled person would take for granted does not matter: *DSM NV's Patent* [2001] RPC 25 at [195]-[202].

> On the other hand, it is to be emphasised that this is not an obviousness test. A patentee is not permitted to add matter by amendment which would have been obvious to the skilled person from the application.

[101] Fifth, the issue is whether subject matter relevant to the invention has been added. In case G1/93, *Advanced Semiconductor Products*, the Enlarged Board of Appeal of the EPO stated (at paragraph [9] of its reasons) that the idea underlying Art. 123(2) is that that an applicant should not be allowed to improve his position by adding subject matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application. At paragraph [16] it explained that whether an added feature which limits the scope of protection is contrary to Art. 123(2) must be determined from all the circumstances. If it provides a technical contribution to the subject matter of the claimed invention then it would give an unwarranted advantage to the patentee. If, on the other hand, the feature merely excludes protection for part of the subject matter of the claimed invention as covered by the application as filed, the adding of such a feature cannot reasonably be considered to give any unwarranted advantage to the applicant. Nor does it adversely affect the interests of third parties.

[102] Sixth, it is important to avoid hindsight. Care must be taken to consider the disclosure of the application through the eyes of a skilled person who has not seen the amended specification and consequently does not know what he is looking for. This is particularly important where the subject matter is said to be implicitly disclosed in the original specification.'

…

9. A particular, and sometimes subtle, form of extended subject matter (what our Act calls 'additional matter') is what goes by the jargon term 'intermediate generalisation'. Pumfrey J described this in *Palmaz's European Patents* [1999] RPC 47, 71 as follows:

> 'If the specification discloses distinct sub-classes of the overall inventive concept, then it should be possible to amend down to one or other of those sub-classes, whether or not they are presented as inventively distinct in the specification before amendment. The difficulty comes when it is sought to take features which are only disclosed in a particular context and which are not disclosed as having any inventive significance and introduce them into the claim deprived of that context. This is a process sometimes called "intermediate generalisation".'"

Claims 2, 3, 5 and 6

443. In the present case Mylan raises three added matter objections. The first is that there is no disclosure in the application for the Patent (WO 95/31990, "the Application") of a copolymer-1 fraction wherein (i) said fraction contains less than 5% of species having a molecular weight over 40 kDa and over 75% of said fraction is within a molecular weight range from 2 to 20 kDa (i.e. a copolymer-1 fraction according to claim 1) and (ii) said copolymer-1 has an average molecular weight of 4 to 8 kDa (i.e. as claimed in claim 2) or 6.25 to 8.4 kDa (i.e. as claimed in claim 3). The same objection applies to claims 5 and 6.

444. The Application summarises the invention at page 2 lines 10-24 as follows:

> "The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).
>
> The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.
>
> In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.
>
> Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1."

445. At page 2 line 33 – page 3 line 14 the Application discloses the following:

> "The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.
>
> The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.
>
> In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa."

446. Counsel for Mylan submitted that what the second passage I have quoted did not do was to disclose any direct and unambiguous link between any particular average

molecular weight range and any of the previously stated options for molecular weight distribution. This was consistent with the claims of the application, which treated the average molecular weights (claims 5-6 and 10-11) as independent from the molecular weight distribution features (claims 1-4 and 7-8). Thus it was not possible to derive the combination claimed in claims 2 and 3 directly and unambiguously from the Application.

447. Counsel for the Defendants submitted that these were not independent disclosures of different inventions. Rather, they were additional features of the beneficial copolymer-1 fraction which had been discovered. That was made clear by the words "In addition". That being the case, it was perfectly legitimate for Yeda to have framed claims that combined the average molecular weight features with the molecular weight distribution features. There was no added matter.

448. In my judgment claims 2 and 3 do not add subject matter to the Application. The form of the claims in the Application does not matter. What matters is whether the Application discloses that the inventive copolymer-1 may have both the molecular weight distribution features of claim 1 as granted and the average molecular weight ranges of claims 2 and 3. In my view that is disclosed for the reasons given by counsel for the Defendants.

Claim 4

449. The disclosure in the Application is of compositions of cop-1 with "over 75%" of its molar fraction between 2 and 20 kDa, but claim 4 refers to a fraction having "75%" in that range. Mylan contends that this constitutes added matter. As I have concluded above, however, in the light of the rest of the disclosure of the Patent, the skilled reader would understand that the word "over" had been erroneously omitted from claim 4. Accordingly, there is no added matter.

450. As a precaution, the Defendants made a conditional application to amend claim 4 to insert the word "over". This application was not opposed by Mylan. In the event, it is unnecessary.

Claims 7-10

451. Mylan's third point is that there is no disclosure in the Application of the combination of the process steps set out in claims 7-10 being used to make copolymer-1 having over 75% of its molar fraction between 2 and 20 kDa.

452. As set out above, the Application discloses at page 3 lines 5-7 that it relates to copolymer-1 having over 75% of its molar fraction in the range from 2 to 20 kDa.

453. At page 3 line 31 – page 4 line 5 the Application states:

> "The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with

> subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain [sic] the correct species directly upon removing the protection."

454. Example 4 of the Application describes the process that is subsequently claimed in claims 7-10.

455. Counsel for Mylan accepted that Example 4 disclosed the relevant process features, but pointed out that it said nothing about the molecular weight distribution of the resulting product (as opposed to its "molecular weight" i.e. average molecular weight). In particular, it did not say that the product had over 75% of its molar fraction within 2 to 20 kDa. Accordingly, he submitted that this combination could not be derived directly and unambiguously from the Application.

456. Counsel for the Defendants pointed out that the last sentence of the passage in the Application quoted in paragraph 437 above disclosed that copolymer-1 "with the required molecular weight profile" could be made by the "further method" referred to. He submitted that the skilled reader would appreciate that the "further method" was that described in more detail in Example 4, and accordingly that that method would enable one to prepare copolymer-1 *inter alia* having over 75% of its molar fraction within 2 to 20 kDa.

457. In my judgment there is no added matter for the reasons given by counsel for the Defendants.

Declaration of non-infringement

458. Mylan seeks a declaration that the importation, keeping, offering for disposal, disposal or use of its proposed generic glatiramer acetate product would not constitute an infringement of any valid claim of the Patent. The product and the process by which it is to be manufactured are described in a confidential product and process description ("PPD"). Mylan contends that the proposed acts would not infringe for three reasons.

Not copolymer-1

459. Mylan contends that its product is not copolymer-1 as claimed in the Patent since the ratio of alanine: glutamic acid: lysine: tyrosine is not "approximately 6:2:5:1". The specification for the amino acid content of the product is as follows:

Amino acid	Molar fraction
Alanine	0.385 – 0.471
Glutamic acid	0.127 – 0.155
Lysine	0.303 – 0.371
Tyrosine	0.080 – 0.106

460. Counsel for the Defendants pointed out that the molar fractions must add up to one, yet the specification covered combinations which added up to both less than and more than one. Counsel for Mylan acknowledged that this was so as a matter of arithmetic,

but explained that no declaration was being sought in relation to products which could not actually be made.

461. In addition to the specification, the PPD contains analyses of three batches of active ingredient and three batches of formulated product, referred to by Prof Sampson as GMA2 to GMA7 respectively. The molar fractions expressed as percentages of the amino acids in these batches are as follows:

	Exactly 6:2:5:1	GMA 2	GMA 3	GMA 4	GMA 5	GMA 6	GMA 7
Alanine	42.9	42.7	43.2	44.0	46.2	46.3	46.4
Glutamic acid	14.3	14.4	14.8	14.2	13.7	14.6	14.4
Lysine	35.7	33.6	32.8	32.7	31.1	30.4	30.5
Tyrosine	7.1	9.2	9.2	9.2	9.0	8.8	8.8

462. In the light of my construction of "approximately 6:2:5:1", each of these batches falls within the claim. No reason has been identified by Mylan as to why a different conclusion should be reached in respect of other batches falling within the specification which it is possible to make.

Not a fraction

463. Mylan contends that its product is not a copolymer-1 fraction since it is not made by a process which involves separation. Since I have concluded that the claims are not limited to products made by separation, it does not matter even if Mylan is factually correct that its production is not made by such a process. The Defendants contend that this is not factually correct, however. In case I am wrong on construction, I shall make the necessary findings of fact.

464. The PPD shows that the process involves passing the product through a diafiltration unit. The PPD does not describe the diafiltration unit in any detail, but it does state that its purpose is "to remove piperidine". Prof Grant's evidence was that diafiltration was a form of separation. Prof Hunter agreed with this. Further, he accepted that diafiltration would remove all molecules smaller than the molecular weight cut-off point of the membrane and that the finest membrane available from the leading supplier, Millipore, would remove polypeptides having about 12 amino acid residues or less. Accordingly, even if the claims were construed as being limited to copolymer-1 made by a process which involves separation, I conclude that they would be infringed.

Not predetermined by small scale reaction

465. It is common ground that the process described in the PPD does not involve determining the time and temperature required for the cleavage step by means of a small scale reaction for each batch. As I have construed claim 7, this does not prevent the process from infringing.

Summary of conclusions

466. For the reasons given above I conclude that:

i) none of claims 2-3 and 5-12 is entitled to priority from the Priority Document;

ii) none of the claimed inventions is obvious in the light of Teitelbaum 1971, Bornstein 1987 or Johnson 1994;

iii) the product claims are not obvious as being an arbitrary selection;

iv) the Patent is not insufficient in any of the ways alleged;

v) none of the claims is invalid for added matter; and

vi) Mylan's proposed glatiramer acetate product would infringe the Patent.