Case No: HP-2013-000004

Neutral Citation Number: [2014] EWHC 3857 (Pat)

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice, Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 21/11/2014

Before :

MR JUSTICE BIRSS

- -

Between :

HOSPIRA UK LIMITED	**Claimant**
- and -	
GENENTECH INC.	**Defendant**

- -
- -

Richard Meade QC, **Tom Mitcheson QC** (instructed by **Taylor Wessing**) for the **Claimant**
Michael Tappin QC and **Mark Chacksfield** (instructed by **Marks & Clerk Solicitors**) for the **Defendant**

Hearing dates: 14th, 15th, 16th, 17th, 20th and 21st October 2014

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Judgment

Mr Justice Birss :

Introduction

1. This is another patent case between Hospira and Genentech about patents relating to the landmark breast cancer drug known as Herceptin. The active ingredient in Herceptin is trastuzumab. Trastuzumab targets the HER2 receptor. Over expression of this receptor had been associated with poor prognosis in breast cancer. This is the second Herceptin case I have decided in 2014. The first one was [2014] EWHC 1094 (Pat). The two cases are entirely distinct. This case relates to a priority date (14th March 1996) which is much earlier than any of the priority dates in issue in the earlier case.

2. The patents are EP (UK) 1 516 628 and EP (UK) 2 275 119. They are divisionals from the same parent, filed on 23rd July 1996. Their title is "Stable Isotonic lyophilized protein formulation". Priority is claimed from two applications but it is common ground that the correct priority date is 14th March 1996.

3. The patents are concerned with the lyophilised (i.e. freeze dried) formulation of antibodies. Two antibodies are referred to in the specification. One is trastuzumab. It is called huMAb4D5-8 in the specification. The other antibody in the patents is

rhuMabE25. The patents explain rhuMabE25 may have a role to play in treating allergy.

4. At the priority date phase III clinical trials of Herceptin were in the process of being set up. The phase II trials had been completed and results published in an abstract presented at the 1995 conference of the American Society for Clinical Oncology ("ASCO"). The abstract is Baselga et al "*Phase II study of recombinant anti-HER2 monoclonal antibody (rhuMAb HER2) in stage IV breast cancer*" Proc. of ASCO, 1995, 14, p.103, abstract no. 113. It was not until 1998 that the phase III results were announced and the drug was approved by the FDA. European approval came later.

5. Trastuzumab itself is protected by a different patent, EP (UK) 0 590 058 and supplementary protection certificate SPC/GB04/015. That SPC expired on 29th July 2014. Hospira wishes to sell generic trastuzumab now that the SPC has expired. Hospira needs a generic authorisation based on the existing marketing authorisation for Herceptin and argued that the regulatory framework applicable to such biosimilar products at least strongly encourages, if it does not actually require, the generic to use the same formulation as the originator's product. This action is to clear the way.

6. Trastuzumab and rhuMAb E25 are monoclonal antibodies. Monoclonal antibodies are large protein molecules. Although by 1996 the pharmaceutical industry had had a long history of formulating small molecule drugs, the formulation of therapeutic proteins in general and antibodies in particular was not so well established. This is an important factor in this case.

7. Formulation patents are one of the kinds of pharmaceutical patent sometimes called second-generation patents, because they do not relate to the drug itself. Such patents are sometimes criticised as an attempt by the pharmaceutical company to unduly prolong its monopoly, after the first generation patent for a drug itself has expired (so called evergreening). There were hints of that in Hospira's submissions. However there is no legal principle that formulation patents should be treated in any way differently from any other patent. The principles applicable are the same.

The issues

8. Genentech has applied to amend both patents and before this court does not seek to defend the validity of the relevant claims as granted. Thus for the purposes of this case I need only be concerned with the proposed amended claims. They are set out in annexes 1 and 2 for 628 and 119 respectively. Claims 1 to 7 of 628 are sought to be deleted and replaced by new claims 1 and 2. The remaining claims are to be renumbered. All granted claims of 119 are sought to be deleted and replaced by new claims 1 to 4. Genentech contends that each of the newly proposed claims (1 and 2 of 628 and 1 to 4 of 119) are independently valid.

9. It is convenient to use the 628 patent specification as the relevant specification both for the claims of 628 itself but also for 119. There are only irrelevant differences between the specification of the 119 patent and the 628 patent. The real difference is simply the claims. From now on unless the context otherwise requires I will refer to the specification of the 628 patent only.

10. The claims refer to three excipients in the formulation as well as trastuzumab. They are polysorbate 20, histidine and trehalose. A major issue in this case is about the status of these three excipients (if any) in the common general knowledge of the skilled person.

11. Hospira's primary case is that each of the newly proposed claims (1 and 2 of 628 and 1 to 4 of 119) is obvious over common general knowledge alone.

12. Hospira also relies on two items of prior art, Carter and Draber:

    i) "Carter" refers to two papers which it is agreed should be read together since they cross-refer. They are a 1994 paper "*Towards an immunotherapy for p185^{HER2} overexpressing tumors*" by Carter et al published in Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment and a PNAS paper published in 1992 called "*Humanization of an anti-p185^{HER2} antibody for human cancer therapy*" by Carter et al.

    ii) "Draber" is a 1995 paper "*Stability of monoclonal IgM antibodies freeze-dried in the presence of trehalose*", Journal of Immunological Methods 181 (1995) 37-43.

13. Hospira also contends that new claims 1 to 4 of the 119 patent are insufficient. This point is advanced as a squeeze relative to Hospira's primary case that those claims are obvious.

14. Finally Hospira contends that none of the amendments proposed should be allowed. This is on four grounds: extension of scope, a point on product by process claims, clarity and added matter.

15. Genentech denies the claims are obvious, denies the claims of 119 are insufficient and contends that the amendments are allowable. Genentech also advances an alternative amendment to deal with the point on extension of scope. This is to replace the word "comprising" in each claim with the words "consisting of". This amendment was properly foreshadowed with an application before trial.

16. If I find that all the claims proposed for 119 are not allowable as amendments or are invalid, then that patent must be revoked. However since Hospira does not challenge the validity of granted claims 8 to 11 of 628, it follows that if the attacked claims (newly proposed claims 1 and 2) are not allowable amendments and/or invalid then the consequence is that the 628 patent must be amended to delete granted claims 1 to 7, leaving behind claims 8 to 11 as granted. They would need to be renumbered.

The witnesses

17. Hospira relied on the evidence of Prof Gavin Halbert and Prof Robert Leonard.

18. Since 1992 Prof Halbert has been Director of the Cancer Research UK Formulation Unit at the Strathclyde Institute of Pharmacy and Biomedical Sciences at the university. Amongst other things, this role requires overall pharmaceutical and scientific management and active participation in the formulation of new cytotoxic

agents for clinical trials. He has maintained a teaching role at the university since 1984 covering, amongst other things, formulation and biopharmaceutics.

19. Genentech submitted that Prof Halbert had spent his entire career at the University of Strathclyde and had no experience in the pharmaceutical industry. Genentech also pointed out that Prof Halbert had not formulated any protein drugs by March 1996 and work he had mentioned in his report on an antibody (105AD7) was not formulation work because it had been formulated already before he was involved. Genentech pointed out that Prof Halbert had not produced a lyophilised formulation of a therapeutic protein for use in a clinical trial. It submitted he lacked the necessary experience to assist in this case. I reject Genentech's submission. Prof Halbert has a wealth of experience in formulation science, had relevant experience and understanding relating to lyophilisation, relating to proteins and working with industry. Overall he has ample experience to assist.

20. Genentech also criticised Prof Halbert's approach to the use of literature in his reports and evidence. I will return to that below in context.

21. Prof Leonard has been a practising clinician for over 40 years, with particular expertise in the treatment of breast cancer. Today he is Professor of Cancer Studies at Imperial College and a consultant (Honorary) Medical Oncologist, Imperial College NHS Trust.

22. Genentech submitted that Prof Leonard could not really remember what happened almost 20 years ago. The professor was entirely candid about his recollection and I will take his testimony on that into account.

23. Genentech relied on the evidence of Prof Tudor Arvinte and Prof Peter Barrett-Lee.

24. Prof Arvinte is the CEO and President of Therapeomic AG, a biotechnology consultancy dealing with characterisation and formulation of therapeutic proteins. He is Titular Professor of Biopharmaceutics at the School of Pharmacy at the University of Geneva. Following his PhD in 1985 Prof Arvinte worked in universities in Europe and the USA and in industry as a research scientist formulating proteins for human use. In 1989 Prof Arvinte joined Ciba-Geigy in Horsham, UK and worked on formulation of peptides and proteins there until 1994. In 1994 he was appointed Head of the Exploratory Formulation Development Laboratory at Ciba-Geigy (later Novartis) in Basel and remained there until 2002 when he founded Therapeomic AG.

25. Hospira criticised Prof Arvinte in a number of respects. The first related to an oddity in his report, that although he had chosen to screen trehalose (and histidine) as excipients in formulation studies at about the relevant time, as drafted Prof Arvinte's report did not make that clear. This was odd given the central role these excipients play in this case. The fact the information could be found by following up references which were given is not a sufficient explanation.

26. In cross-examination Prof Arvinte referred to research in the food industry about trehalose and concerns about patients with diabetes and cancer. Although his report addressed concerns about toxicology, these particular points were not made. If they had been then they could have been put to Prof Halbert but since they were not referred to, they were not put. They are not accepted by Hospira. I was not

convinced that either point was of sufficient weight to take into account over and above the professor's important, but more general, evidence about toxicology.

27. In cross-examination Prof Arvinte suggested for the first time that there was basis in the patent for saying that the trehalose formulations were better than the sucrose formulation. If that was important it should have been referred to in his report. Further cross-examination undermined the point in any event and I do not accept the professor's opinion on this.

28. Also in cross-examination Prof Arvinte referred to a "wow" moment when he first heard about Genentech's Herceptin formulation. Taking his testimony as a whole, I conclude that the "wow" moment was caused by surprise relating to the effort he assumed Genentech must have gone to obtain approval for a trehalose containing formulation and that Genentech must have found a major formulation benefit to justify that effort. However while I am sure Prof Arvinte was explaining his genuine reaction I will place no weight on it. There is no evidence that great effort to obtain approval was required. As to the benefits of a trehalose based formulation, the evidence consists of the contents of the patent. That can be assessed on its own merits. There is no other evidence of advantages relating to a trehalose formulation.

29. Further lesser criticisms of Prof Arvinte by Hospira were the following:

    i) The fact that Prof Arvinte's report downplayed the role of sucrose but in cross-examination he accepted it would be one of the first lyoprotectants to try.

    ii) A criticism relating to the professor's evidence on histidine but that was a very minor matter.

    iii) The suggestion that a double standard had been applied by Prof Arvinte to the prior art Draber as compared to the patent. The professor made his views about Draber very clear. There was no double standard.

30. A further point raised by Prof Arvinte related to the chemical difference between polysorbate 80 and polysorbate 20. Again this ought to have been foreshadowed if it was an important point. I was not persuaded it was significant.

31. Finally a point arose about whether 22 mg/ml could be rounded to 21 mg/ml. I was not convinced it could. It was a very minor point.

32. Although I have accepted a number of Hospira's points for what they are worth, I do not accept any of them either alone or together are matters of such significance that they undermine the reliance I might place on the evidence Prof Arvinte gave in his reports and in cross-examination on the fundamental issues. The professor is clearly an expert in protein formulation and in giving his evidence he was aiming to help me to understand the issues and his perspective on them.

33. Professor Peter Barrett-Lee is Medical Director & Consultant Clinical Oncologist of Velindre NHS Trust, and Professor of Oncology in the School of Medicine at Cardiff University. He has been a consultant oncologist at Velindre in 1994, specialising in breast and skin cancer and is the lead specialist in breast cancer and skin cancer at Velindre and Cardiff University.

34. Hospira submitted that Prof Barrett-Lee's evidence relating to the skilled clinician's reaction to the patent was inconsistent with his evidence about the same person's reaction to the Baselga paper. I will address that in context.

35. Each side criticised the experts called by their opponent to a greater or lesser extent. I am not satisfied any of these points are of sufficient weight to seriously undermine the evidence given. All four professors strove to give their evidence fairly. I am grateful to all four of them for their work on this case.

The skilled person

36. There was no real dispute about the identity of the person skilled in the art. The person will be a team working in the biotechnology industry. The members will include a formulation scientist and others with experience in analysis and manufacturing. The team will also include a clinician. This would be a clinical oncologist specialising in breast cancer.

The common general knowledge

37. In ***KCI Licensing v Smith & Nephew*** [2010] EWHC 1487 Arnold J pulled together the various authorities on common general knowledge in a passage at paragraphs 105-112. His summary of the law was approved by the Court of Appeal at [2010] EWCA Civ 1260. I will rely on that summary.

The common general knowledge of the clinician

38. It was known that the HER2 receptor was overexpressed in certain breast cancer patients and that these types of cancer were particularly aggressive. This work had originated in the laboratory of Dennis Slamon in the 1980s and was high profile. I find that it was common general knowledge that the HER2 receptor was a significant potential target for future cancer therapies. Skilled clinicians would have been most interested to hear about drugs for that target being developed and would be interested in any information suggesting active steps had been taken towards developing a therapy for use in humans.

39. The issue was whether one or other of two further points were part of the clinician's common general knowledge. Hospira submitted that either or both of the following were common general knowledge. First: the results of the phase II study on trastuzumab which had been completed well before the priority date. They had been published in the Baselga abstract. Second: the existence of the phase III trial of trastuzumab for breast cancer. The phase III trial was launched in June 1995 on the back of the Baselga results (inter alia).

40. I am not satisfied that the Baslega abstract or its results formed part of the common general knowledge as a result of its presentation at ASCO in May 1995. I accept that ASCO is one the largest cancer conferences in the world. It is probably the most important. However there is no evidence that Baselga's presentation at ASCO made any impact at all. Prof Leonard did not attend ASCO 1995. Prof Barrett-Lee did not recall seeing it there.

41. Hospira pointed out that Baselga has much more clinical detail in it than the patent. It noted that Prof Barrett-Lee's opinion was that a skilled person would be very interested in the patent. So Hospira reasoned the skilled person would be very interested in Baselga. Prof Barrett-Lee did not accept this but in my judgment his evidence on this was not consistent. He was prepared to place more weight on very unspecific language in a patent specification than he was on clear clinical data in an abstract.

42. If the data in the patent is very interesting to a skilled reader then in my judgment Baselga would be at least as interesting. However just because a document forming part of the state of the art (made available to the public) would be very interesting is not enough to make it common general knowledge. It might simply not have come to anyone's attention. Hospira sought to answer this by contending that large numbers of clinical oncologists specialising in breast cancer must have been in the session when Baselga was presented and so it must have attracted their interest and so it must be common general knowledge. I reject this reasoning. It is too easy, with the hindsight knowledge today of the great success of Herceptin, to think that Baselga must have made an impact but there is simply no proper evidence that it did. I find it was not common general knowledge.

43. I turn to the existence of the phase III trial of trastuzumab for breast cancer. It is clear that there were numerous discussions about this with many clinical oncologists specialising in breast cancer in 1995 and before March 1996. Both Prof Leonard and Prof Barrett-Lee were well aware of the phase III trials existence. It is also clear that Genentech itself was publicising the existence of the Phase II results and the existence of the Phase III trials in its public filings before the New York stock exchange. The existence of the trial was clearly publicly known to at least one American breast cancer patients' pressure group before March 1996. That group were pressing for compassionate use of trastuzumab.

44. However Genentech correctly submits that for the fact, that trastuzumab was in phase III trials, to be common general knowledge the question is whether it was generally known to the bulk of those in the art. Genentech submitted it was not. Professors Barrett-Lee and Leonard were from only two of the six or seven centres which actually participated in the trial in the UK. Prof Barrett-Lee did not remember any public discussion of the trial. The details were confidential although the fact of the trial was not. Prof Leonard accepted in cross-examination that looking back nearly 20 years his memory was not sufficient to say if it was something known to the bulk of the relevant clinicians.

45. Hospira put a publication called SCRIP to Prof Barrett-Lee. It describes the trastuzumab trial. SCRIP is a pharmaceutical industry newssheet well known to lawyers and judges who work on pharmaceutical patent cases but Prof Barrett-Lee had not heard of it. As evidence in this case it has no value. Had Hospira approached the matter differently they might have been able to call evidence focussed on those actually working in industry about this point but no such evidence was produced.

46. The relevant evidence is that of Prof Barrett-Lee and Prof Leonard. Bearing that in mind I am not persuaded that the existence of the trastuzumab phase III trial was part of the common general knowledge in March 1996.

The common general knowledge of the formulator

47. It was common ground that formulating proteins was more difficult and complex than formulating small molecules. Prof Arvinte's unchallenged evidence was that the task was difficult and unpredictable, taking a great deal of work and often encountering dead ends. I accept that formulating proteins in general (and monoclonal antibodies in particular) was a challenge and was an essentially empirical exercise.

48. On the other hand one cannot take this general difficulty too far. Although, as Prof Arvinte explained, what I will call "big pharma" had not really focussed on biotechnology by 1996 and was still focussed on small molecule drugs, a significant specialist biotechnology industry existed and was developing rapidly. By March 1996 the formulator would know that protein products of the biotechnology industry had been successfully formulated for human use, starting with recombinant insulin from Eli Lilly approved by the FDA in 1982 and followed by products such as human growth hormone from Genentech approved by the FDA in 1985 and erythropoietin from Amgen approved by the FDA in 1989. By 1996 there were a number of recombinant therapeutic proteins available, including two monoclonal antibodies. The skilled team would also know that more monoclonal antibodies were under active consideration although that does not mean the formulations of those development products were themselves common general knowledge.

49. When it was put to Prof Halbert, he did not accept that the formulation exercise represented a "serious" challenge. Genentech submitted this did not reflect the thinking of the notional skilled formulator but rather reflected the fact that Prof Halbert had never in fact lyophilised a therapeutic protein for human use. I do not agree. The Professor had a wide experience in formulation and was able to address the common general knowledge of a skilled formulator tasked with considering a lyophilised protein.

50. I have accepted that the task was a challenge and essentially empirical but nevertheless by March 1996 it was a task which had been successfully undertaken by a number of groups and the skilled formulator would know that. I find that a skilled formulator approaching the overall task of formulating a monoclonal antibody for human use in March 1996 would not underestimate the potential risks and would recognise that the project might fail. However they would not give up even if the early results were negative. To the skilled formulator in 1996, such an exercise was well worth carrying out and was worth pursuing seriously.

51. A very different point is that the skilled formulator could not, in advance, say of any given putative formulation that it would work. So for example standing at the priority date and without conducting any formulation tests, the skilled person could not say that a lyophilised formulation made by lyophilising 25 mg/ml trastuzumab in 5mM histidine, pH 6.0, 60mM trehalose and 0.01% polysorbate 20 would be stable. It might or it might not.

52. The general approach was well established. That general approach was to conduct stability tests including accelerated aging studies, using various candidate excipients of different types, in various conditions. One of the conditions which would always be tested was pH. In other words the formulator would want to find out the pH or pH range which gave optimum stability.

53. The overall exercise is partly a form of screen. Candidate excipients and conditions are screened in successive rounds, looking for promising results to follow up. However this cannot be taken too far. The tests are time and resource consuming and require access to quantities of antibody. The exercise would not go on for ever.

54. Proteins are food and so swallowing a tablet into the stomach does not usually work as a way of administering a protein based medicine. When eaten, the protein is degraded by the gastro-intestinal (i.e. enteric) tract. Accordingly when they were to be administered to patients, proteins in general and monoclonal antibodies in particular were generally administered "parenterally", in other words not via the enteric system. A standard parenteral mode of administration is by injection (intravenous, subcutaneous or intramuscular). Injection requires the protein to be available in a liquid.

55. There were two general approaches to formulating proteins at the priority date: producing a liquid formulation and producing a dry lyophilised formulation. Both were common general knowledge. The liquid formulation could be injected directly. A lyophilised formulation would be reconstituted e.g. by dissolving it in sterile water for injection.

56. In lyophilisation an aqueous solution of the substance is cooled so that the water turns to ice. The frozen material is placed in a vacuum and the temperature is raised somewhat so that the ice is removed by sublimation (i.e. evaporating directly from solid to gas). After this primary drying process there may be a secondary drying step too to drive off as much water as possible. The dry solid left behind by lyophilisation is generally an amorphous material. It contains the drug and the solutes which were in solution. It is sometimes called a cake. Anything volatile would have been driven off. The excipients in this case are not volatile.

57. To be useful as a therapeutic agent, the formulated protein had to be stable over an extended period. That would normally be many months or more realistically one or two years. If a liquid formulation was sufficiently stable it would be used, if not a lyophilised formulation would be considered. As a generalisation, the dry lyophilised material was likely to be stable for a longer period than a liquid since chemical reactions (such as those causing degradation) tend to run faster in solution. On the other hand the lyophilisation process itself might degrade the protein.

58. Lyoprotectants are a class of excipients used in the context of lyophilisation. They are used to protect the substance to be lyophilised from the stresses associated with freeze-drying. A compound which only protects during the freezing process could be referred to as a cryoprotectant while some defined a lyoprotectant in contrast as something which helps during both freeze-drying and subsequent storage. However in my judgment the terminology in 1996 was not exact. In some contexts the term lyoprotectant was used in general terms although in other contexts a distinction could be drawn between cryoprotectants and lyoprotectants. One paper (Nema) refers to "lyo-cryo protective agents".

59. The typical classes of excipients that would be considered for inclusion in a lyophilised formulation included buffers, surfactants, lyoprotectants (by which I mean the general class), tonicity modifiers, anti-oxidants and bulking agents.

60. Buffers are used to keep the pH at a certain level. That is because the stability of many drugs is pH-dependent. Surfactants (also referred to as stabilisers) are used to minimise aggregation of proteins. I have described lyoprotectants already. Tonicity modifiers are used to adjust the tonicity (ionic strength) of a solution. Sometimes when a drug is to be injected, it is important that the liquid is isotonic with (has the same ionic strength as) the human bloodstream. Salts may be used as tonicity modifiers. The function of anti-oxidants is obvious from their name. Bulking agents are sometimes used to add mass to the lyophilised cake. Mannitol was a typical bulking agent. Some excipients may have multiple roles.

61. In addition to trastuzumab, the claims all refer to three further ingredients, histidine, polysorbate 20 and trehalose. Hospira contended each was an excipient which was common general knowledge within the relevant class. Genentech did not agree. I will consider each in turn.

62. Buffers which were common general knowledge included phosphate, citrate, succinate, acetate and other organic acids, bases such as imidazole, HEPES and TRIS and amino acids such as glycine. Hospira submitted that histidine, another amino acid, was a common general knowledge buffer as well. Histidine has a number of possible roles as an excipient. I find that it was part of the formulator's common general knowledge as a possible buffer for formulating recombinant proteins in general (and monoclonal antibodies in particular). Prof Arvinte accepted that. There were more common buffers than histidine, and the re-examination of Prof Arvinte highlighted this by reference to the Nema paper. Nema publishes the results of a review of excipients used in injectable products. Although it was post published, it is safe to infer that it reflects the position in March 1996. Histidine's status as part of the common general knowledge is also supported by the fact that it had been used in a lyophilised formulation of a therapeutic recombinant protein on sale at the priority date, as shown by a list produced by Prof Arvinte.

63. Common surfactants/stabilisers included polysorbate 80 and human serum albumin (HSA). By the priority date HSA was going out of favour. The polysorbate surfactants used by the skilled team were often referred to by their brand name Tween, (e.g. Tween 80). Hospira submitted that polysorbate 20 (Tween 20) was another common general knowledge surfactant. Hospira pointed out that thirteen of the thirty products on Prof Arvinte's list contained polysorbate of which three were polysorbate 20 and that Nema identifies both polysorbate 80 and polysorbate 20 as surfactants in use. Prof Halbert said he expected formulators to have Tween 20 in their laboratory. I find it was common general knowledge.

64. I turn to consider lyoprotectants. At the priority date a large number of agents had been used. Examples in common use were monosaccharides (dextrose, glucose, lactose), disaccharide (sucrose), polyhydric alcohols (inositol, mannitol, sorbitol), polyethylene glycols, polyvinylpyrrolidone and proteins (albumin and gelatine).

65. Some lyoprotectants are sugars. Chemically, some are reducing sugars and some are non-reducing sugars. Reducing sugars can react with proteins in a well known reaction called the Maillard reaction. It is common in cooking and leads to browning. Lactose is a reducing sugar. Sucrose is a non-reducing sugar although it can degrade and produce glucose – a reducing sugar. These facts were all basic chemistry and common general knowledge but whether this element of common general knowledge

would ever have been brought to bear in the context of their use as lyoprotectants is a matter I will return to below.

Common general knowledge of trehalose

66. This case is concerned with trehalose. Trehalose is a disaccharide. It consists of two glucose molecules joined in a particular way. It is a non-reducing sugar. It is present in the diet. It is quite plain that the existence of trehalose as a chemical substance, a disaccharide, was part of the common general knowledge of a formulator. Neither Prof Arvinte nor Prof Halbert gave evidence to the contrary.

67. The issue is the extent to which trehalose was part of the common general knowledge as a potential lyoprotectant for use with proteins. Prof Halbert maintained in his reports and in cross-examination that it was. He was taken to scientific papers which he had referred to in his report in cross-examination. It was put to him that they did not support his opinion. Despite the cross-examination, Prof Halbert firmly maintained his view that the potential of trehalose as a lyoprotectant for proteins was common general knowledge. Genentech criticised him for saying "it was out there" or "it was in the literature". I will return to that below.

68. Hospira submitted that the case put to Prof Halbert was different from what Prof Arvinte had said in his evidence. There is some force in that point. In his reports Prof Arvinte explained his clear view that trehalose was not a standard excipient and gave his opinion that it would not be obvious to include trehalose in a screen of excipients for use in a lyophilised formulation of trastuzumab, but his reports were striking in that they did not say trehalose was unknown as a lyoprotectant. His key point was that it had never been used in formulation for human use and never used in a parenteral formulation. It was expensive and its use would be a risk because of concerns about safety/toxicity and because it had no regulatory track record.

69. In cross–examination Prof Arvinte's evidence was clear. The professor was asked to leave toxicology to one side and the following exchange occurred:

> "25 Q. Let me ask you about the functional qualities of trehalose as
> 2 a lyoprotectant. Do you agree that if you were looking for a
> 3 non-reducing lyoprotectant at the priority date, the common
> 4 general knowledge perception would be that trehalose was just
> 5 as good as sucrose and potentially better?
> 6 A. Yes."
> [day 3 p409]

70. Mr Tappin submitted that this evidence should not be taken at face value. That was because it came after a long passage in cross-examination in which a number of documents were put to the Professor. Those documents included some which, in the way they were put, Genentech submitted had been presented unfairly and in a way which might mislead the witness into thinking that trehalose was a common general knowledge lyoprotectant at the priority date when in fact it was not. This included post published papers and an internal Genentech document which, at least in other respects, appeared to include references to the making of the invention in this case.

71. If I thought the answer given by Prof Arvinte did not represent his genuinely held view or was the result of having been misled in some way, I would not place weight on this evidence. But I reject Genentech's submission because the exchange quoted above merely reflects in summary form the view the professor had been expressing throughout his cross-examination about trehalose. Prof Arvinte gave clear evidence throughout that he thought it would not have been obvious to use trehalose in a protein formulation for therapeutic use (and so would not have been obvious to include in a screen). However his reason was not that the skilled person did not know of trehalose as a lyoprotectant. His reason was a concern about possible safety / toxicity and the lack of a regulatory track record for trehalose. I will consider that concern in the obviousness section below. On another occasion, entirely separate from the documents Mr Tappin submitted were not fairly put, the following passage in cross-examination occurred (at day 3 p370-371). It related to a paper (Ford and Dawson) in which trehalose was used in formulating materials used for biological standards.

> Q. Then it says: "Trehalose is currently the carbohydrate most
> 25 frequently used in the formulation of biological materials
> 2 requiring long-term stability for use as international
> 3 standards." Is that a fair statement?
> 4 A. Yes.
> 5 Q. Is that a fair statement that was part of the common general
> 6 knowledge?
> 7 A. Yes, I repeat all the time the same thing. It was part of
> 8 common general knowledge but was not used in humans. I mean,
> 9 at the same time, if you have picked up literature on toxicity
> 10 studies on trehalose, they were starting in the '80s from the
> 11 food industry.

72. This reflects the same point Prof Arvinte was accepting at p409 (above). I reject the idea that Prof Arvinte's evidence on trehalose did not represent his considered opinion.

73. In any event I do not accept that the cross-examination was improper or unfair. Prof Arvinte was clearly a highly intelligent and knowledgeable expert witness who understood the issues and the nature of the documents put to him. Both sides had referred to post-published papers and so putting such papers to the professor cannot be criticised. He knew when they were published. Whether the passage put in the Genentech internal document, a historical review, was or was not based on information acquired after the priority date was not clear. The re-examination dealt with that document.

74. An element in the debate about the status of trehalose as common general knowledge relates to the relevance of the literature. Genentech submitted that none of the documents relied on by Prof Halbert and put to Prof Arvinte was a "common general knowledge document". I agree. The field of formulating biopharmaceutical products in 1996 was at a relatively early stage of development. Papers and some review articles were being published. Very general textbooks made some high level reference to the issues. A specialist textbook by Banga (Therapeutic Peptides and Proteins, *Formulation, Processing and Delivery Systems*) was published very close to the priority date. I am not satisfied Banga was actually made available to the public

before March 1996 but I am satisfied it represents only information and ideas gathered from before that time.

75. The fact that none of the individual documents referred to by Prof Halbert or the further documents put to Prof Arvinte were themselves part of the common general knowledge is relevant but it is not determinative. There was no one document which everybody read. Nevertheless, for example, both experts in this case knew of trehalose, its history and the idea of using it as a lyoprotectant. I reject Genentech's criticism of Prof Halbert for saying it was "out there" or "in the literature".

76. I believe the argument about Prof Arvinte's answers in cross-examination involves a mischaracterisation of the role of the expert. The expert's role was not to look at all the evidence (including those documents) and make a judgment whether trehalose was common general knowledge. That is the role of the court. In part Genentech's submission about Prof Arvinte's answers in cross-examination is in effect that the documents put to him did not support the conclusion he expressed. Even assuming they did not, that is not the issue. The professor was not expressing a judgment on the state of the evidence, he was expressing his opinion, as an expert and someone who had worked in the field at the time, about the thinking of a skilled person at that time.

77. A point which sometimes arises in the context of arguments about common general knowledge is to take care about what fact is actually common general knowledge. Sometimes it is safe to say simply that X was common general knowledge. I have expressed myself that way above about polysorbate 20.

78. However on other occasions one needs to be more precise. The position of trehalose is one of those occasions. I have already found that the existence of trehalose as a chemical compound was common general knowledge. The question is whether the idea of using trehalose as a possible lyoprotectant for proteins was itself common general knowledge. As a topic of scientific interest, trehalose had been found in organisms which appeared to be able to survive freezing and/or desiccation. From there the art had moved on to consider and apply it in lyophilisation and also air drying. Its mode of action was the subject of debate and there were some who thought it was a cryoprotectant rather than a lyoprotectant while others thought the opposite. But the existence of that debate did not mean it was not used in the lyophilisation of proteins. I find that the common general knowledge of the skilled person included the idea of using trehalose as a possible lyoprotectant for proteins. There was ample evidence to that effect at trial.

79. In terms of its properties as a lyoprotectant, part of the common general knowledge relating to trehalose was that it was likely to be just as good as sucrose and potentially better. On the other hand, also part of the common general knowledge was that while trehalose had been used as a lyoprotectant for proteins, it had not been used as a lyoprotectant for a therapeutic agent. The proteins with which it had been used were not ones administered to humans as drugs. Thus the formulator knew that using it in a formulation of a therapeutic protein would require consideration of toxicology and would require the approval of the regulator. That might (or might not) involve further work on toxicity which could itself be substantial.

80. Although trehalose was in the human diet, necessarily trehalose had not formed part of a formulation administered by the parenteral route (thereby bypassing the stomach).

That was part of Prof Arvinte's concern about possible toxicity. The fact that something can be eaten safely does not mean it can be injected safely.

81. Genentech referred to the expression "good basis for further action", which was used in ***General Tire*** [1972] RPC 457. The argument was that given the possible toxicity and regulatory issue, trehalose could not be a "good basis for further action" and there was not common general knowledge. I do not accept that. Trehalose was known to have been used as a lyoprotectant for proteins. In that sense it was a good basis for further action. I will consider the impact of the toxicity/regulatory issues below in the obviousness section.

The patent specification

82. The point of the invention disclosed in the patent is to produce stable lyophilised protein formulations suitable for parenteral administration to humans. The document starts with a summary of the invention, written in much broader terms than merely by reference to trastuzumab.

83. The formulations produced are stable in the lyophilised state and can be reconstituted to produce a stable reconstituted formulation (paragraph 6). The reconstituted liquid formulations may have a higher protein concentration than the protein concentration in the pre-lyophilised material but that further aspect is not the subject of the claims with which this case is concerned.

84. After a section summarising the content of the figures there is a general section from paragraphs 20 to 88. Example 1 starts at paragraph 89. It contains a detailed set of tests on trastuzumab. The tests involve lyophilising various samples of trastuzumab formulated with different excipients and measuring the stability after lyophilisation and reconstitution. The tests include accelerated studies. So for example the levels of intact protein are measured in lyophilised samples kept for two weeks at 5°C or at 40°C (e.g. Table 2) and are measured over time in reconstituted samples kept at 5°C and 25°C (Tables 4, 5, 6 and 7). The tests all use polysorbate 20 as a surfactant but vary the pH, buffer, lyoprotectant and protein concentration. From the early screening studies which use a variety of lyoprotectants, the work focuses down on two lyoprotectants: trehalose and sucrose and two buffers: succinate and histidine.

85. The results show that stable lyophilised formulations of trastuzumab can be made. Four examples are the formulations of Tables 4, 5, 6 and 7. In terms of the composition of the liquid before it was lyophilised, they are:

    i) 25 mg/ml trastuzumab in 5mM sodium succinate, pH 5.0, 60mM trehalose, 0.01% polysorbate 20;

    ii) 25 mg/ml trastuzumab in 5mM histidine, pH 6.0, 60mM trehalose, 0.01% polysorbate 20;

    iii) 25 mg/ml trastuzumab in 5mM histidine, pH 6.0, 38.4mM mannitol, 20.4 mM sucrose, 0.01% polysorbate 20; and

    iv) 21 mg/ml trastuzumab in 10mM sodium succinate, pH 5.0, 250mM trehalose, 0.2% polysorbate 20.

86. The solution in sub-paragraph (ii) above is in Table 5 and is the one on which the relevant claims are now to be based. I will refer to it as the Table 5 Solution. There is no material difference between these four in terms of their stability. They are all stable.

87. After Example 1 there is a similar example dealing with tests on rhuMAb E25.

Claim construction

88. There was no dispute about the general approach to claim construction based on ***Kirin-Amgen*** [2005] RPC 9. There is a particular point about ***Kirin-Amgen*** and product by process claims but I will deal with that in context.

89. It was common ground, referring to ***Regeneron v Genentech*** [2013] EWCA Civ 93 paragraph 56, that the treatment of HER2 positive breast cancer was a "functional technical feature" of the claims sought in the 119 patent. In other words those claims are to something which is indeed an effective treatment of the disease.

90. The debates about extension of scope, product by process claims and added matter all include elements of claim construction and it is convenient to address those construction points in that context.

91. At this stage it is convenient to make some general observations about the interpretation of the claims.

92. Both proposed claims 1 and 2 of 628 are claims to a product. The product is a lyophilised formulation of trastuzumab. So it is in the dry state, ready to be reconstituted. The product has to comprise at least four ingredients: a lyoprotectant, buffer, surfactant and antibody. The lyoprotectant has to be trehalose, the buffer has to be histidine, the surfactant has to be polysorbate 20 and the antibody has to be trastuzumab (huMAb4D5-8). Other things can be present too since the claim uses the word "comprising".

93. The product claimed in claim 1 of 628 must also be obtainable by lyophilising the Table 5 Solution. The precise effect of this feature will be addressed below.

94. The product claimed in claim 2 of 628 must be one which satisfies a test relating to reconstitution. The test is: a sample of lyophilised material is taken which represents 450mg of trastuzumab. That sample is reconstituted by mixing it with 20ml of bacteriostatic water for injection (BWFI). The BWFI must have benzyl alcohol in it at either 0.9% or 1.1%. The result must be a solution with the concentrations and pH referred to in claim 2. The resulting solution must have 22 mg/ml trastuzumab, 52mM trehalose, 4mM histidine and 0.009% polysorbate 20.

95. Note that the test involves reconstituting the lyophilised product with 20ml of BWFI, it does not involve reconstituting the material to a volume of 20ml. The two are not the same because of the phenomenon of displacement volume. Reconstituting the material with 20ml BWFI will produce a final volume which is a bit more than 20ml. The impact of this issue will be addressed below.

96. Claim 2 does not claim a reconstituted material nor does it matter for the purposes of infringement whether the lyophilised material is intended for reconstitution in BWFI at all. That point is significant because reconstitution in BWFI is normally done in order to make a multi-use liquid sample. 450 mg represents about three doses of trastuzumab and making it up this way is a prelude to injecting one dose (about 150mg) first, keeping the made up material in a fridge for a while and using it for two more doses. The benzyl alcohol is a preservative. In the USA the FDA has approved multi-use trastuzumab whereas in Europe I understand trastuzumab is approved by the EMA as a single use vial of 150mg. For single use the relevant quantity of lyophilised material is reconstituted in sterile water for injection (WFI). This has no benzyl alcohol in it. It is not reconstituted in BWFI.

97. Claim 2 covers a sample of lyophilised trastuzumab regardless of whether it is intended for a single use or not, as long the material would satisfy the test if that test was performed on it.

98. Claims 1 and 2 of 628 are drafted in different ways and subject to a point about reconstitution volume that I will address below, they both cover a lyophilised material produced by lyophilising the Table 5 Solution. The wider scope of each claim may differ from the other.

99. Proposed claims 1 to 4 of 119 are based on the same ideas as claims 1 and 2. The differences are that claims 1 and 2 of 119 are Swiss style pharmaceutical use claims while claims 3 and 4 are "product for use in a method for treatment" claims allowed instead of the Swiss style claims by EPC 2000. In all four cases the therapeutic indication is the same. It is the treatment of breast cancer characterised by the overexpression of the HER2 receptor.

100. In effect the four claims of 119 can be seen as follows:

i) Proposed claim 1 of 119 is a claim to the use of the lyophilised material defined in claim 1 of 628, in the preparation of a medicament for the therapeutic indication.

ii) Proposed claim 2 of 119 is a claim to the use of the lyophilised material defined in claim 2 of 628, in the preparation of a medicament for the therapeutic indication.

iii) Proposed claim 3 of 119 is a claim to the lyophilised material defined in claim 1 of 628 for use in a method for the therapeutic indication.

iv) Proposed claim 4 of 119 is a claim to the lyophilised material defined in claim 2 of 628 for use in a method for the therapeutic indication.

101. Thus all the claims of 119 amount to is to add to the claims of 628 a reference to the therapeutic indication in the various permutations.

102. In the claims of 119 the therapeutic indication is a functional technical feature. The claims are not construed merely as something suitable for the use, but intended for that use (see my earlier judgment between these parties ***Hospira v Genentech*** [2014] EWHC 1094 paragraph 58).

103. Claims 1 and 3 of 119 present no difficulty as compared to claim 1 of 628 but there is a point arising from this in relation to claims 2 and 4 of 119 as compared to claim 2 of 628. Given that these claims relate to a material intended for a particular therapeutic indication, the skilled reader would be forgiven for thinking that they related to a material intended for use when reconstituted using BWFI. I will not decide the point since I believe it does not arise for decision.

104. Finally, although none of the claims use words like "stable", the skilled reader would understand that what is claimed is a stable lyophilised formulation, suitable for parenteral administration to humans.

Extension of Scope

105. Section 76(3)(b) of the Patents Act 1977 prohibits any amendment to a patent (in other words any amendment post-grant) which extends the protection conferred by the patent. In the EPC the relevant provisions are Art 123(3) and 138(1)(d) EPC.

106. This rarely comes up at trial in the UK, no doubt because the law is clear and usually easy to apply. The correct approach is to compare the scope of the claims as granted with the scope of the claims as proposed to be amended. In both cases the scope is that of the claims properly construed in accordance with the Protocol. If the proposed amended claim covers something that would not have been covered by the granted claims then the prohibition is engaged.

107. Usually to make the argument good the person challenging the amendment needs to identify a concrete thing which did not fall within the scope as granted but which would fall within the scope after amendment if the amendment was allowed. If such a thing cannot be identified in concrete terms, that is usually an indication that there is no extension. Because the prohibition is absolute, the thing need not be commercially realistic.

108. The purpose of the prohibition is the protection of the public. Once a patent has been granted, the public can rely on its scope and know that it will not get any wider by amendment. There is no corresponding prohibition pre-grant. The law of added matter is different. It applies both pre- and post-grant.

109. Both new claims sought in 628 can be seen as amendments starting from claim 1 of 628 as granted. As granted claim 1 of 628 is for:

> A formulation comprising a lyophilized mixture of a lyoprotectant and an antibody, <u>wherein the molar ratio of lyoprotectant: antibody is 200-600 moles lyoprotectant : 1 mole antibody</u>, wherein the lyoprotectant is trehalose or sucrose and wherein the antibody is a monoclonal antibody.
>
> (my emphasis)

110. The critical aspect of the amendments is that the words underlined above are to be deleted. Hospira says that the true reason they are being removed is because they add matter. I do not have to decide that question.

111. Since what seems to be a clear limitation in the claim is being deleted, any tribunal will be *en garde* in relation to extension of scope. I am surprised that the UKIPO made no comment about the proposed amendments on this ground at all. The letter of 27th August 2014 from the UKIPO, which stated that the Comptroller had no comments to make and did not wish to be represented, only refers to clarity, added matter and support. I can only conclude that the UKIPO did not consider the issue at all.

112. Genentech submits that no extension will occur because as amended, although they do not say so in terms, the claims are in practice limited to a molar ratio of 360:1. That is the result of being a product obtainable by lyophilising a liquid with 25mg/ml trastuzumab and 60mM trehalose. There is no dispute that if one lyophilised a solution consisting of 25mg/ml trastuzumab and 60mM trehalose, the molar ratio in the lyophilised material would be 360:1.

113. Hospira takes two points. The first is best addressed in the context of the product by process question although it is an extension of scope argument. I will address it in that context. Hospira's second point is that the claim covers a formulation with more than one protein and/or more than one lyoprotectant and that while the 360:1 ratio is true if the starting solution has only 25mg/ml trastuzumab and 60mM trehalose, it is not true if the starting solution also has another antibody and/or another lyoprotectant.

114. Genentech's answer is that as a matter of construction even if a second antibody or second lyoprotectant (or I think both) were present, the ratio of lyoprotectant (being trehalose) to antibody (being trastuzumab) would still remain at 360:1 and so no broadening has taken place. As a fall back Genentech seeks to amend the claims to replace "comprising" with "consisting of". That would exclude the possibility of a second lyoprotectant or second antibody and solve the problem.

115. I start with claim construction. The patent clearly contemplates the possibility of a formulation comprising two antibodies together. That is expressly stated in paragraph 73. Moreover there is no reason why the skilled reader would exclude the possibility of using two lyoprotectants (at least trehalose and sucrose) in one formulation. So as a matter of construction the claims cover lyophilised material with more antibodies than trastuzumab and/or more lyoprotectants than trehalose.

116. It would be clear to the skilled reader that what counts in terms of ratio of lyoprotectant to antibody is the total amount of lyoprotectant to all the antibodies. Accordingly Genentech's approach to construction, in which a ratio can be determined by looking only at the relative amounts of trastuzumab and trehalose in a composition which includes other antibodies and/or other lyoprotectants is wrong.

117. The conclusion on construction does not depend on what follows but can be understood in the following way. In over simplistic mechanistic terms the job of the lyoprotectant is to surround and penetrate each antibody molecule and thereby protect it. The lyoprotectant consists of relatively small molecules whereas the antibodies are relatively large. One mole of either represents the same number of molecules (Avogadro's number). So a ratio of 600 moles lyoprotectant to 1 mole antibody allows each antibody molecule to be protected by 600 molecules of lyoprotectant. A lyoprotectant which is protecting one antibody may well not be able to protect another (although no doubt it is never quite this simple). I should emphasise again that this is

simplistic. The key thing is that a skilled reader would not think the claim could be read whereby particular lyoprotectants or particular antibodies in a mixture can be singled out for the purposes of determining the ratio.

118. Hospira proposed the following formulation with two antibodies:

Ingredient	**Concentration (pre-lyophilised)**	**Concentration (reconstituted with 20 ml)**
Trastuzumab 450mg	25 mg/ml	22 mg/ml
Anti-VEGF monoclonal antibody (IgG) 450mg	25 mg/ml	22 mg/ml
Trehalose	60 mM	52.8 mM
Histidine pH 6.0	5 mM	4.4 mM
polysorbate 20	0.01%	0.009%
Molar ratio of lyoprotectant : antibody	180 : 1	

119. This formulation would fall within claims 1 and 2 of the 628 patent as proposed to be amended. Assuming it was sold for use in treating breast cancer it would also infringe all the claims sought for the 119 patent.

120. The question is whether it would have fallen within the granted claims. Genentech said it fell within the claims because the ratio of trehalose to trastuzumab was 360:1. For the reasons I have already given above, that is not the correct way to interpret claim 1 of 628 as granted. (The same logic applies to 119.) The relevant molar ratio of lyoprotectant to antibody is 180:1, taking into account both antibodies. Thus this formulation would not fall within the scope of protection of either patent as granted.

121. Accordingly the amendments would lead to an extension of the scope of protection and I will not allow them as proposed.

122. Genentech's fall back position is to replace "comprising" with "consisting of". It cures this defect. The effect of the change is as follows. The word "comprising" allowed for other ingredients to be present. The term "consisting of" in these claims has the effect of limiting the composition to the particular ingredients referred to and no others.

123. With that change, the example formulation proposed by Hospira would not infringe the amended claims. There are two antibodies present and so the formulation is outside all the claims irrespective of the effect of the product by process language.

124. The amendments proposed with the words "consisting of" do not contravene s76(3)(b) (EPC Art 123(3)).

Product by process claims

125. Product by process claims are tricky. Before coming to the House of Lords in ***Kirin Amgen*** there are some background matters to deal with.

126. One of the key problems which a system of patents for inventions has to handle is how to legislate for future inventive (non-obvious) developments. By definition they are often hard to foresee. One way this is done is to give inventors more or less complete freedom in the drafting of their patent applications. They can define the invention in a claim in any way and using any language they like so long as the definition is clear to a person skilled in the art and the invention satisfies various other criteria.

127. Most inventions are either products or processes and it has proved possible for the law to define acts of infringement by reference to these different kinds of inventions. Section 60 of the Patents Act 1977 does just this. It is based on the Community Patent Convention (CPC) rather than the EPC. The way s60(1) is drafted one might assume that an invention must be either a product or a process. There is no such rule. By and large the system works but there can be difficulties. A well known example is a new pharmaceutical use of an old drug which gives rise to Swiss style claims. Infringement of these claims is often argued only under s60(2) (infringement by supplying means essential) which avoids the problem of deciding whether it is a product or a process.

128. Another kind of claim which straddles the boundary between products and processes is a product by process claim. As a matter of language there are two kinds: (1) a product "obtained by" a process, and (2) a product "obtainable by" a process. At least at first sight they are different.

129. At first sight the scope of a claim to a product "obtained by" a process would be only to products which had actually been made by the process. There might be problems of proof in an infringement case or for novelty but conceptually there is no difficulty. If no products had ever been made that way in the past, then the claim would be novel. The fact that such products are physically entirely identical to products made in the past would not alter the fact that no product made by that process had been made available to the public before. They would only be infringed by products actually made by the relevant process. This was the view taken of product by process claims in the Court of Appeal in ***Kirin Amgen*** ([2002] EWCA Civ 1096, [2003] RPC 3).

130. There can be clarity problems, particularly if the process conditions are not specified carefully, but in the past there was good reason to have such claims. Before s60(1)(c) was enacted (based on the CPC and Art 64(2) EPC) it was not clear that a process claim was infringed by selling a product of the process. Even today there may still be a motive for seeking such a claim because the inventor wishes to catch a product made by a process but not directly so (but query if that leads into problems of the "tin whistle on a ship" variety). On the other hand some "obtained by" claims may well be regarded as abusive in simply being an attempt to re-patent an old thing by reference to a spurious change in process conditions.

131. Turning to "obtainable by" claims, they are no panacea and present their own conceptual difficulties. The point of such a claim is to cover a product which was not made by the defined process but could have been. One might ask how a product which was in fact made one way could ever have been made a different way. What the process language in these kinds of claims is really intended to be referring to is a particular characteristic or characteristics of the product. So in the ***Johnson Matthey*** case cited in argument (T956/04) the patentee wanted to define the product (a

catalyst) by reference to the size distribution of crystallites. The information in the patent would allow them to specify actual values for other characteristics (such as preferred amounts of cobalt) but the only way to define the product by reference to the characteristic of crystallite size distribution was by reference to the process conditions which produced that particular distribution.

132. In other words what the patentee was trying to do was claim a product irrespective of how it was made but with a particular characteristic which is the same characteristic which results from using a given process. If it is clear what the characteristic is and is true that in fact process conditions can be specified which do produce the given characteristic then one can see why this makes sense. Claim 1 in ***Johnson Matthey*** used the "obtainable by" language.

133. So "obtainable by" claims create an additional potential problem of clarity over and above the "obtained by" claims. Unless the claim specifies the characteristic being referred to, how is the skilled reader to know which characteristic is being referred to?

134. The view taken by the EPO in the 1980s (see e.g. ***IFF / Claim Categories*** T150/82 and later cases T248/85 and T219/83) was firmly against the idea that an old thing could be patented using product by process language. The EPO held that defining a product by the process by which it was made could not confer novelty on a product which was known *per se*. The product itself had to be novel. In effect in these cases the EPO was deciding to treat "obtained by" claims and "obtainable by" claims in the same way, at least for its purposes, i.e. for validity. Regardless of the claim wording, all claims were treated as if they meant "obtainable by". If the process conferred a particular characteristic on the product then one could take that characteristic into account. But if not, then the process feature made no difference and the product was not different from the prior art. The product would lack novelty.

135. The EPO's approach to overt product by process claims today is settled. They will be permitted (and only permitted) if there is no other way of defining the product open to the patentee. This is a decision based on policy. Such claims present clarity problems and are best avoided but if there is no alternative way of defining the characteristic in question, then they will be permitted.

136. But despite their apparently esoteric nature (even by the standards of patents) product by process language is actually quite common and hardly remarked upon. Claim 1 of 628 as granted is a product claim which uses process language in an unexceptional way. The opening words are "*A formulation comprising a lyophilised mixture of...*". This is a claim to a product defined by reference to the process by which it has been made. Claims drafted this way are granted routinely and rarely raise any issue. No-one calls these claims product by process claims and the EPO does not apply its case law to this language. That is why I referred to "overt" product by process claims in the previous paragraph.

137. Does claim 1 mean the claimed formulation actually has to have been lyophilised or would it cover an air dried material with the right characteristics? If the latter, one might ask what characteristics are produced by lyophilisation and which ones are relevant.

138. In ***Kirin-Amgen*** the House of Lords had to consider the novelty of an overt product by process claim. This is dealt with in the speech of Lord Hoffmann at paragraphs 86 to 101. A number of points arise. Lord Hoffmann dealt with the history of product by process claims and noted that the advantage they had before the 1977 Act was removed by s60(1)(c) (paragraphs 88-89). He noted that the idea that a process could confer novelty on a known product was not particularly logical since the history by which it was made is not an attribute which it carries around and makes it new (paragraph 88). He dealt with the EPO's practice starting from the 1980s, referring to the ***IFF/claim Categories*** T150/82 decision and the EPO's practice (paragraphs 90-91). He was puzzled by an earlier decision of the EPO relating to the patent in suit which appeared to be based on inconsistent findings of fact as to whether the process of making recombinant erythropoietin (rEPO) did or did not necessarily give rise to differences with known urinary erythropoietin (uEPO) (paragraphs 92-95) and noted that the trial judge (Neuberger J as he then was) had found as a fact that there was no necessary distinction between rEPO and uEPO (paragraph 96).

139. In ***Kirin-Amgen*** the Court of Appeal had held that the product by process claim (claim 26) was novel because of the novel process feature. The Court of Appeal had refused to follow the EPO's practice about permitting such claims only in certain circumstances because that was a rule of practice of no concern to national courts. Lord Hoffmann (with whom the other lords agreed) did not agree with the Court of Appeal's reasoning (paragraphs 98-101). He held that a difference in the method of manufacturing did not make a product new and that was so as a matter of law. On that basis the claim could only be novel if the process definition gave the product a new characteristic of some kind. On the finding of fact in ***Kirin-Amgen***, therefore claim 26 lacked novelty since the process did not necessarily do so. The decision of the Court of Appeal was wrong. The UK should follow the approach of the EPO.

140. Therefore the ratio of the decision in ***Kirin-Amgen*** is that an identical product made by a new process does not count as new. In that respect the UK now follows the EPO. Lord Hoffmann did not agree with the Court of Appeal's decision but the focus of his disagreement was not about the EPO's rule of practice, the issue was that there was a point of law underpinning that practice. Lord Hoffmann was concerned to align the UK law of novelty with the law applied in the EPO. Beyond a need for a claim to be novel, he was not commenting on whether the EPO's practice was sound or not and did not comment on the Court of Appeal's refusal to follow it as a rule of practice only, subject to applying the correct law of novelty.

141. On 13th December 2007, after ***Kirin-Amgen*** was decided, section 75 was amended to insert new sub-section (5) which requires that in considering whether or not to allow an amendment, the court or Comptroller shall have regard to any relevant principles applied under the EPC. The point of this change was to sweep away various discretionary factors which used to be applied in the UK when considering amendments (see Floyd J as he then was in ***Zipher v Markem*** [2008] EWHC 1379).

142. Thus despite the judgment of the Court of Appeal in ***Kirin-Amgen*** and the scope of the decision of the House of Lords in the same case, it seems to me that s75(5) of the 1977 Act means that the court should follow the principles applied by the EPO in the context of considering whether to permit an amendment to create an overt product by process claim. Both sides submitted that I should although they disagreed about its impact.

143. However a question not focussed upon by Lord Hoffmann in ***Kirin-Amgen*** is whether the rule that the process feature is irrelevant for novelty is a rule of the law of novelty or a rule of mandatory claim interpretation. To be novel, a claim to erythropoietin made by the expression of a gene in a host cell had to be different from known urinary erythropoietin. But assuming the claim was novel, was it infringed by erythropoietin which had not been made by the expression of a gene in a host cell?

144. Now the House of Lords also decided that the defendant's rEPO did not infringe the patent because it was not the product of the expression of a gene in a host cell (see paragraphs 13 onwards, ending at paragraph 85 which finds no infringement of any claim). Thus Lord Hoffmann was applying the process feature as a relevant limitation which was not satisfied for the purposes of (non-)infringement but ignoring it for the purposes of novelty. That can only be on the basis that the product by process rule is a rule of novelty law, not claim construction.

145. The result is that a product not made by the claimed process has been found not to infringe because it was not made by the claimed process while another product not made by the process has been found to render the claim lacking novelty despite the fact it was not made by the process. This is a little paradoxical but it shows the difficulties one can get into with product by process claims. A further puzzle is the following. What if, in ***Kirin-Amgen***, the prior art uEPO had not been disclosed so as to be relevant for novelty but was something which was obvious? Presumably it would make the claim obvious for the same reason?

146. On the other hand treating the point as a rule of novelty works in the EPO since the EPO is only concerned with validity. The EPO does not have to grapple with the meaning of these claims from the point of view of infringement. It is not obvious that an inventor who drafted his or her claim in the form of a product "obtained by" a process ever intended to cover other things or would be understood to be using language to mean that. The test for novelty is one thing but to ignore the clear words of the claim may result in it covering things which owe nothing to the inventor's technical contribution and risk insufficiency. It is hard to see how one can apply one of the key principles of construction emphasised by ***Kirin-Amgen*** itself, that the reader considers what the draftsman was using language to mean, in any other way.

147. I derive the following principles from this consideration of the EPO and UK authorities:

    i) A new process which produces a product identical to an old product cannot confer novelty on that product. To be novel a product obtained or obtainable by a process has to have some novel attribute conferred on it by the process as compared to the known product.

    ii) This rule is a rule of the law of novelty. It is not a principle of claim construction. Although in effect the rule treats "obtained by" language as "obtainable by" language, nevertheless as a matter of claim construction a claim to a product "obtained by" a process means what it says. That will be the relevant scope of the claim as far as infringement and sufficiency are concerned.

iii) Although normally a patent is drafted by the inventor "in words of his own choosing", the EPO will not permit overt product by process language unless there is no other alternative available. By no other alternative, they mean no other way of defining a particular characteristic of the product in question.

Claim 1 of 628 as a product by process claim

148. The claim is to a "lyophilised mixture". As a matter of language and applying the principles I have just discussed, that is limited to something which has actually been made by lyophilisation. It does not say "obtainable by" lyophilisation, it is a claim to a product "obtained by" lyophilisation. Air dried material which had never been lyophilised might anticipate the claim (but none is suggested to) but it could never infringe.

149. The second clause in the claim requires that formulation must be "obtainable by" lyophilising a Table 5 Solution.

150. A critical aspect of Genentech's case is the submission that the claim covers lyophilised formulations made from liquid in which the concentrations of the four ingredients were not the ones stated in the claims. On this basis the claims cover formulations made by lyophilising a liquid which contained, for example, trastuzumab at a concentration of 100mg/ml. The limit imposed by the "obtainable by" clause is said to be that the lyophilised formulation must contain the four ingredients in the same relative molar ratios as they appear in the Table 5 Solution before it is lyophilised. (Strictly it is the molar ratio after lyophilisation of that solution but since the ingredients are not volatile, there is no difference.)

151. In other words not all formulations made from a liquid with 100mg/ml trastuzumab would fall within the claim but some will. The ones which fall within the claim are the ones in which the other ingredients are at the right level to give a final formulation with the same molar ratios as would have been obtained by lyophilising the Table 5 Solution. So crudely if the protein concentration in the liquid before lyophilisation is four times the one in the claim (100mg/ml = 4 x 25 mg/ml) the other four concentrations need to be quadrupled as well.

152. So Genentech's case is that the characteristic of the lyophilised formulation which the process language defines is the molar ratio of the four ingredients in the lyophilised material.

153. Hospira does not accept Genentech's submission on construction. It contends that the skilled reader would have no way of knowing what characteristic is to be the one governed by the process language and as a result the "obtainable by" language imposes no limitation at all. I am troubled by Genentech's submission but I am not convinced Hospira is correct that this language imposes no limits.

154. It does not make sense to say that a material with a molar ratio different from that produced by lyophilising the defined ingredients falls within the claim. Such a material is not obtainable by the process. It seems to me that the right construction must be that for a material to be "obtainable by" lyophilising the Table 5 Solution it must have every single characteristic which is the inevitable consequence of that process. There is no basis on which to select which characteristics are relevant and

which are not. It must have the same molar ratio but it must also be the same in every other way. If something does not have all those attributes then it is not obtainable by the process. Even if only one attribute is missing, then it is not obtainable. If the process inevitably produced amorphous material then the material must be amorphous. The claim does not put limits on the nature of the lyophilisation process to be used beyond the starting material. That may well make it hard to find the limits of the claim. No doubt lyophilised material has a low water content (being dry) but there is no indication what levels are obtainable by this process and what are not. Perhaps the water content will vary between wide limits as a result. However it does not mean that limits do not exist. The same goes for the amorphous nature of the dry material. Perhaps the material obtainable by the process is inevitably entirely amorphous or perhaps it could be partly amorphous and partly crystalline. The evidence does not address any of this.

155. The problem is caused by the way the claim is drafted in using "obtainable by" language but not specifying what characteristic the process feature is supposed to define. Nevertheless Hospira's submission that the result is that the process feature imposes no limit at all goes too far.

156. I turn to consider and try to apply the EPO's practice of permitting overt product by process claims only if there is no alternative. Genentech contends it is clear that the EPO's approach is satisfied because there is no alternative to the product by process claim. No other potentially valid claim presents itself (save for proposed claim 2, which I can ignore for now at least on the basis that it will only matter if in the end claims 1 and 2 are both otherwise valid, in which case I may need to return to this). The granted claims can be assumed to be invalid and no other option has been identified.

157. I confess that trying to apply the EPO's stated approach is not easy but my tentative conclusion is that Genentech's submission is wrong. The EPO's practice is not that product by process claims are a sort of last resort when all else fails in the sense that every other claim is invalid. That sort of approach would be unprincipled. On that basis they would be available in all cases. Since the EPO's practice runs counter to the idea that a patentee is entitled to use words of his own choosing in describing his invention, it must be based on some principle. The principle underlying the EPO's practice is shown by the ***Johnson Matthey*** case. It is a principle of clarity (Art 84 EPC, s14 of the 1977 Act) and amounts to a trade off between clarity and fairness, tolerating an increased lack of clarity in that limited class of cases. If a patentee can identify a characteristic or parameter disclosed in the patent for which no other definition is available in the specification other than an "obtainable by" process definition, then a product by process claim may be allowed as a way of claiming that attribute. It is impossible to apply that approach properly without knowing what characteristic the process feature is to be used to define. That would be best stated in the claim expressly but it may be clear from the specification.

158. Proposed claim 1 of 628 does not expressly state which characteristic is referred to. The skilled reader could draw up a list of characteristics but they would not know which one was intended either from the claim or from the specification as a whole. The only realistic conclusion is that every conceivable characteristic is caught by the definition. Maybe in some cases that would not cause a difficulty but here to say that every feature is relevant leaves the reader with the impossible task of having to create

for themselves a list of relevant attributes. The fact the skilled reader would include molar ratio on the list does not help.

159. Not without some hesitation, it seems to me that a principled application of the EPO's stated approach must lead to refusal of this amendment. My hesitation derives from the fact that I suspect in practice the EPO has permitted product by process claims in the past even when they do not expressly recite the attribute(s) to which the language applies. However since the reader of claim 1 of 628 cannot identify all the attributes to which the language applies, I do not see how I can permit a claim in that form. The fact the skilled reader of the 628 patent can identify one attribute is not sufficient since the reader would understand that there would in all likelihood be further attributes to which the product by process language also applies but that would be an indefinite class of attributes. Accordingly I will not permit the amendments to allow proposed claim 1 of 628 nor proposed claims 1 and 3 of 119. It makes no difference whether these claims use the words "consisting of" rather than "comprising".

160. As mentioned above, Hospira took a further extension of scope (s76(3)(b)/ Art 123(3) EPC) point on the basis that if, as it contends, the process language imparts no limitation at all, then there is a clear extension of scope. On Hospira's premise, the conclusion follows. However I have rejected the premise.

Clarity

161. It was common ground that claim amendments must satisfy the requirement for clarity. Although s76 does not mention clarity, claims are required to be clear and concise by s14 of the 1977 Act (based on Art 84 EPC). Moreover in the EPO (relevant as a result of s75(5)), lack of clarity is a ground for refusing an amendment.

162. The particular issue relates to proposed claim 2 of 628 (and equally to claims 2 and 4 of 119). The difficulty is as follows. If, using exact numbers for the antibody concentration, one took a lyophilised product made by lyophilising the Table 5 Solution and reconstituted 450mg trastuzumab with 20ml BWFI (with either amount of benzyl alcohol) then a result would be obtained which is not the one referred to in claim 2 of 628. There are different ways of looking at the problem but the best approach still produces a difference in the trehalose concentration. Prof Halbert dealt with this in his evidence.

163. The problem is in part caused by the effect of displacement volume. When something is dissolved in liquid, the volume of the solution is a little larger than the volume of the liquid was before anything was dissolved in it. The solute displaces some fluid and the increase is called the displacement volume. This is well known.

164. The skilled person would not be able to quantify in advance what the effect of displacement volume would be. So the skilled person would perform the test and measure the result.

165. The result for the Table 5 Solution, based on the data in the patent, and the numbers in claim 2 are:

	Actual Result (using exact numbers)	**Claim 2**

Trastuzumab	22 mg/ml	22 mg/ml
Trehalose	***53mM***	***52mM***
Histidine	4mM	4mM
Polysorbate 20	0.009%	0.009%

166. In answer Prof Arvinte addressed the effect of rounding. He approached the matter by considering the 22mg/ml concentration of trastuzumab. Numerically 22mg/ml can be regarded as a range of 21.5 to 22.5 based on normal rounding conventions. Taking that small range of concentrations into account along with the calculated reconstitution volume using the data in the patent, the concentrations of the other three ingredients in the reconstituted fluid will be as shown below:

	Results (without units)			**Claim 2**
	Lower bound	**Middle value**	**Upper bound**	
Trehalose	52	53	54	52 mg/ml
Histidine	4	4	5	4 mM
Polysorbate 20	0.009	0.009	0.009	0.009 %

167. The lower bound figures are the same as the claim. There is no dispute about the maths and the calculations. The question is whether this means the amendment satisfies the requirements for clarity. Prof Halbert accepted that the skilled person would see there was no inconsistency once rounding was taken into account. I accept that and so I reject the allegation of lack of clarity.

Added matter

168. No amendment to a patent or a patent application is permitted if it adds matter as compared to that disclosed in the original application (s76 of the 1977 Act, Art 123(2) EPC). The basic approach to be followed is that explained by Aldous J as he then was in ***Bonzel v Intervention*** [1991] RPC 553. Added matter was considered by the Court of Appeal in ***Vector v Glatt*** [2007] EWCA Civ 805 and by Kitchin J (as he then was) in ***European Central Bank v DSS*** [2007] EWHC 600 (Pat).

169. Hospira contends that claims 1 and 2 of 628 (and all the proposed claims of 119) involve added matter. Four distinct points arise and it is convenient to address them separately although Hospira submits that they are all symptoms of the same problem. The problem is that the application contained two disclosures: a very broad disclosure and a very narrow disclosure (Example 1). The broad disclosure was the one on which the granted claims were based but those broad claims cannot now be maintained. The added matter arises because the patentee is seeking to generalise out from the narrow disclosure in Example 1 to an extent which cannot be justified. The generalisation attempted by the amendments is intermediate in nature, broader than the narrow disclosure of Example 1 but not as broad as the originally granted claims. Hospira submits this is added matter because there is no teaching to that effect in the application. It submits that this is an impermissible intermediate generalisation (***Palmaz*** [1999] RPC 47 and ***Vector v Glatt*** [2007] EWCA Civ 805).

170. Genentech does not agree with this. It contends that the proposed amended claims are soundly based on the application as filed and do not add matter. It relies on the line of authority starting with ***AC Edwards v Acme*** [1992] RPC 131 and including ***Texas***

Iron Works [2007] RPC 207 and ***AP Racing v Alcon*** [2014] EWCA Civ 40. Genentech submits that while it is true that the claim covers a wider range of materials than are disclosed in Example 1, the amendment does not mean that the patent discloses new information. Thus the amendment is allowable.

171. It is not always easy to see which cases fall on the ***AC Edwards*** side of the line and which fall on the ***Palmaz*** side. I made that mistake in ***AP Racing v Alcon***.

172. The task of applying the law in this area is made more difficult by the fact that the EPO does not approach added matter this way at all. It is notable that neither side has cited an EPO decision supporting the ***AC Edwards*** principle. In ***AP Racing*** Floyd LJ referred in paragraph 32 to a decision in the EPO (***T065/03***) in which a broader term used in a claim was found to add matter. That was because the Board held that the effect of the broader language (combustion engine when only a diesel engine was disclosed) was to teach that the invention was suitable for any type of engine, a teaching absent from the application and therefore new matter.

173. ***AC Edwards v Acme***, ***Texas Iron Works*** and ***AP Racing*** are each concerned with mechanical inventions in which a word or phrase has been used to identify or describe a structure in the application ("*spring means"* for a coil spring and cotter arrangement in ***AC Edwards***, "*liner hanger unit"* for an arrangement of slips and cones in ***Texas Iron Works***, and "*asymmetric peripheral stiffening band*" for a hockey stick shaped peripheral stiffening band in ***AP Racing***). In each of those cases the inevitable effect of using this new descriptive language is that the claim will not be limited to the particular arrangement described in the application. The claim will have a broader scope. But in each case the court found that no other construction or thing was disclosed by the patent in which this language appeared in the claim.

174. I can see that this result follows in cases about descriptive language like this. Plainly the law cannot be that any change in descriptive language will never add matter but these cases show that some kinds of change in descriptions do not. Of course there is no reason to limit this principle to mechanical inventions, it just comes up naturally in those cases. I have more difficulty applying that principle to a case in which the skilled reader knows that the art is empirical, that the disclosure is a form of recipe, and that the point of the exercise is to produce a material which has certain properties, determined by carrying out tests on the material produced (e.g. stability).

Protein concentration

175. The first topic relates to the protein concentration in the pre-lyophilised liquid. It is clear as a matter of construction that proposed claim 1 of 628 does not contain any requirement relating to the absolute level of this protein concentration. Any lyophilised formulation is covered as long as it is "obtainable by" etc.. If the starting liquid has four times the protein concentration in the Table 5 Solution (100mg/ml) then as long as the ratio is maintained the lyophilised material will satisfy the claim.

176. I start with the disclosure of the application.

177. The whole teaching of the application (and the patent) is directed to stable formulations which can be successfully reconstituted. The application is concerned with a recipe for making stable proteins.

178. Hospira put to Prof Arvinte that the data in Example 1 (which is the same in both the application and the patent) indicated that stability depended on protein concentration. He agreed. Genentech's answer to this was that the questioning had not taken into account the molar ratio of the excipients. It is true that the questions did not do so but I do not accept that this undermines the significance of the Professor's evidence. Prof Arvinte understood the questions he was asked and accepted that the skilled reader would understand from the example that stability is sensitive to protein concentration. There was no re-examination on the point. If I thought the cross-examination was unfair I would not put weight on this answer but in my judgment the questioning was entirely fair.

179. Furthermore, in the course of discussing paragraph 97 of the patent on this topic, which used a protein concentration of 25 mg/mL Prof Arvinte also said the following:

> "A. …as a general formulation knowledge is that if something is stable at high concentrations it will also be stable at lower concentrations.
> Q. Right, but if you go higher you could have difficulty?
> A Yes.
> Q If you went up to 35 who knows what will happen
> A Yes" (T3 455 ln9-15)

180. English was not the professor's mother tongue but I understood this evidence to be referring to the common general knowledge of the skilled person. The point is that in general if something is stable at a certain protein concentration one does not know what will happen at even higher concentrations. I accept that this forms part of the common general knowledge. Indeed it makes sense.

181. Bearing in mind this element of the common general knowledge, it seems to me the court is in a position to understand this aspect of the disclosure of the application having adopted the mantle of the skilled reader even if the point had not been put to Prof Arvinte. Example 1 Table 2 used protein concentrations of 5.0 and 21 mg/ml. Later tests in the example used a concentration of 25mg/ml. I find that the skilled reader would understand that the document was teaching that a parameter which had an effect on stability was protein concentration.

182. The molar ratio of lyoprotectant:antibody in the Table 5 Solution in Example 1 is 360:1. The key point is that the skilled reader would understand this to be a disclosure that 360:1 provided stability when the protein concentration was 25mg/ml. It is not a disclosure that 360:1 provides stability at any protein concentration. At best stability might be expected at a concentration of less than 25mg/ml but it would certainly not be expected at a concentration well above that figure.

183. In other parts of the application a wide range of molar ratios of lyoprotectant:antibody are referred to and the reader might well assume that stability might be possible at a wide range of molar ratios. However that is not the same as a teaching that molar ratio is independent of protein concentration. For the sake of a concrete example (the numbers are made up), at a molar ratio of 200:1, a formulation might be stable but only at a lower protein concentration. Conversely at a concentration of 100 mg/ml perhaps the molar ratio has to be 600:1. The only relevant concrete teaching in the application is that a stable protein formulation could be made by lyophilising a liquid

consisting of the Table 5 Solution. In addition to its named ingredients, that solution has at least two potentially relevant attributes: molar ratio and protein concentration.

184. I turn to consider the proposed amended claim 1 of 628. There is no doubt that the claim is not limited to formulations made from a particular defined protein concentration. It undoubtedly covers more than Example 1/Table 5. The issue is what, if anything, it discloses. Does it just cover more (***AC Edwards***) or does it disclose something new?

185. In my judgment the skilled person would understand proposed claim 1 to be a definition of a stable protein formulation. To put things another way, the skilled reader of the amended patent would understand, as a matter of disclosure, that the product of proposed claim 1 of 628 is stable. That definition has the effect (inter alia) of limiting the molar ratio but does not include protein concentration. For this purpose I can assume Genentech's approach to the claim and consider the language as a limitation to the molar ratio only.

186. While the claim is a distinct part of a patent as compared to the description, nevertheless the claim is part of the disclosure and can be read as such by a skilled reader. Genentech does not seek to make amendments to any consistory clauses with this application but the allowability of the amendment cannot depend on that. In other words in substance the amendment must be just as good or bad if Genentech made corresponding amendments or insertions into the "Summary of invention" section of the description.

187. Starting from the 628 patent in its amended form including proposed claim 1, no doubt the first thing a skilled person seeking to put it into practice would do would be to consider repeating the lyophilisation of the Table 5 Solution. But I believe they would understand claim 1 to teach them that they would produce a stable formulation by lyophilising a solution with a higher protein concentration provided only that the lyophilised material was obtainable by the lyophilisation of the Table 5 solution, in other words provided that the Table 5 molar ratio was maintained. Taking that approach is something taught in the document as amended. It is new information. I find the amendment adds matter.

188. The same result follows for claim 2 of 628. Although again this claim appears to have a protein concentration in it, in fact the claim properly understood is not limited to any particular protein concentration. The effect is only to limit the molar ratios of the four ingredients. The skilled reader would understand that this claim too is teaching that stable trastuzumab formulations can be made with any protein concentration. The only thing which matters is the outcome of the test. That is new information in the same way.

189. This problem relates to all the claims proposed for both 628 and 119.

190. Mr Tappin submitted that this point was taken late and that had Genentech known about it earlier, Genentech might have wished to perform experiments to deal with it. I permitted the objection to be taken. The point on experiments is not relevant. The issue is concerned with the construction and disclosure of the patent itself. That is not affected by the outcome of experiments. For the purpose of this analysis one can assume that the new teaching is true. Its correctness is not in issue. The problem is

that it is not a teaching which is clearly or unambiguously derivable expressly or by necessary implication from the application.

Lyophilisation conditions

191. Hospira made the same point concerning the lyophilisation conditions. It submitted that the amended claims teach the skilled reader that a stable protein will be produced regardless of lyophilisation conditions. I do not accept this submission. The skilled reader would understand proposed claim 1 (and claim 2) as a teaching that lyophilisation conditions were not critical. However that is not new information. Such a disclosure is also present in the application as filed. It is at p6 ln18-34 of the PCT (paragraph 75 as granted) which is a general disclosure that different conditions may be used. Also relevant is the passage at p27 ln13-18 of the PCT (paragraph 113 as granted) which describes lyophilising trastuzumab in a single step process, different from the particular conditions used in the rest of Example 1.

192. Thus I reject this added matter point.

Benzyl alcohol and multi use

193. Hospira submitted that the introduction of the phrase "20ml BWFI (0.9% or 1.1% benzyl alcohol)" into claim 2 of 628 (and claims 2 and 4 of 119) was added matter. That was because Genentech had not stated in clear terms where the basis for the amendment was which would justify the inclusion of these words. A development of the same point was that the inclusion of this language was another impermissible intermediate generalisation because the references to reconstitution with BWFI were always and would be understood always to relate to a multi-use formulation. However as proposed to be claimed this has been stripped from its proper context since the claim is not limited to multi-use formulations.

194. Genentech relied on the passage at p23 ln7-12 of the application as follows:

> "The lyophilized protein was then reconstituted with either 4 or 20 mL BWFI (0.9 or 1.1% benzyl alcohol) to yield concentrated protein solutions:
>
> (a) 4mL: 102 mg/mL [trastuzumab], 245 mM trehalose, 21 mM sodium succinate pH 5.0 or 21 mM histidine pH 6.0, 0.04% [polysorbate 20];
>
> (b) 20mL: 22 mg/mL [trastuzumab], 52 mM trehalose, 4 mM sodium succinate pH 5.0 or 4 mM histidine pH 6.0, 0.009% [polysorbate 20]."

195. Genentech submitted this would be understood as a disclosure of either 4 ml or 20 ml BWFI with, in each case, either 0.9 or 1.1% benzyl alcohol and applicable to either (a) or (b). Claim 2 would be (b) (with histidine). Hospira submitted that read in the context of the previous table (Table 3) this passage did not have the broad meaning Genentech contended for but was a summary of the earlier work which only mentions certain sub-combinations and not the one now referred to in claim 2. I do not agree.

In my judgment read in context this passage provides a basis for claim 2 as proposed and thus the claim does not add matter in that respect.

196. A different issue was that in fact the application discloses that products reconstituted with 0.9% benzyl alcohol did not work (p27 ln8 of the application, accepted by Prof Arvinte). Thus the claim amounts to added matter for that reason. Genentech's response is that the language is part of a test for determining the molar ratio of the excipients and not a promise that material reconstituted with BWFI would be stable. I think that is right, since the claim is not limited to multi use products.

Consisting of

197. A point was taken on the effect of the change from "comprising" to "consisting of". I do not believe this point adds anything to the other added matter issues.

Obviousness

198. The structured approach to the assessment of obviousness was set out by the Court of Appeal ***Pozzoli v BDMO*** [2007] EWCA Civ 588. I will take that approach.

199. In ***Conor v Angiotech*** [2008] UKHL 49, [2008] RPC 28 the House of Lords considered the issue of obviousness. There Lord Hoffmann (with whom the others of their Lordships agreed) approved the following statement of Kitchin J made in ***Generics v Lundbeck*** [2007] RPC 32:

> "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."

200. In ***Medimmune v Novartis*** [2012] EWCA Civ 1234 the Court of Appeal emphasised that the nature of the court's task was ultimately to answer a single question of fact; see Kitchin LJ paragraph 93 and Lewison LJ paragraphs 117 - 186.

201. I have identified the person skilled in the art and the common general knowledge above. The inventive concept is a stable lyophilised formulation of trastuzumab, suitable for parenteral administration to humans, with the features claimed in the various claims. I now need to consider the differences between the invention and the various items of prior art and consider if the invention involves an inventive step.

Obviousness over common general knowledge alone

202. Since I have rejected Hospira's case that the existence of trastuzumab was part of the common general knowledge, the argument over common general knowledge alone cannot succeed.

Obviousness over Carter (1992 and 1994)

203. Carter teaches that trastuzumab, an anti-HER2 antibody, is in phase II clinical trials for breast cancer.

204. The difference between the disclosure of Carter and the claims of 628 is that Carter discloses a PBS (phosphate buffered saline) formulation of trastuzumab (i.e. a liquid) whereas the claim claims a lyophilised formulation with the relevant characteristics. Whatever the wider ambit of the claim, for this purpose the claims can be taken to cover the result of lyophilising a solution consisting of the Table 5 Solution. The claims of 119 also include the therapeutic indication for breast cancer.

205. Genentech submitted that there was a hole in Hospira's case, in that Hospira had not proved that Carter alone was sufficient motivation to the team to formulate trastuzumab or persevere with the project sufficiently to reach the claimed formulation for use in breast cancer. That was because Hospira's evidence on motivation assumed starting points at Baselga or the knowledge of the phase III studies.

206. I do not accept that. In my judgment knowledge that an anti-HER2 antibody is in phase II studies for breast cancer would be of real interest to the skilled person. They would know of the earlier Slamon work. It would be a sufficient motivation for a skilled team to set about formulating trastuzumab with a desire to produce a working therapeutic formulation. It would be entirely obvious to set about doing so. Whether that project would succeed depends on the details of the project, which I will consider below.

207. This also means that starting from Carter, the inventive step argument is the same for the claims of 628 as for the claims of 119.

208. Genentech submitted that since the evidence was that a skilled team would use a liquid formulation if they could, in the absence of evidence that a liquid formulation did not work, there would be no motivation to consider lyophilisation. Genentech argued that Hospira had assumed but not proved that a liquid formulation was not good enough. I do not accept this submission. In my judgment the court is entitled to infer from the circumstances of this case generally and also from paragraph 91 of the patent, that formulations of trastuzumab in the liquid state degrade sufficiently to mean that from the point of view of producing a therapeutic agent with sufficient stability to be useful, an alternative to a liquid formulation is needed. On that basis the skilled team would investigate lyophilisation. It was common general knowledge.

209. Hospira submitted that the invention was obvious over Carter. The skilled team would conduct a wholly conventional screening exercise of excipients with trastuzumab. This would involve lyophilising samples using different excipients in various concentrations. The object of the exercise would be to produce a suitable stable formulation. Taking this approach was routine. All three of the excipients in the claim were part of the common general knowledge. They were obvious candidates to include. No inventive step is involved in screening any of them either alone or in combination. The particular concentrations and/or molar ratios are not suggested to be the product of inventive effort. There is nothing else in any of the claims and so they all lack inventive step. Hospira's case is a powerful one. To examine it I need to consider the issues in more detail.

210. The approach which the skilled team would use to investigate lyophilising trastuzumab was well known. The screening methods described in Example 1 of the patent are not themselves inventive. Moreover the sorts of results reported – in which some combinations of excipients and conditions are promising and others are not, is what a skilled team would expect. They would not know in advance which would be which but that is a different matter.

211. The team would consider the issue of pH and would find, without any inventive activity, that trastuzumab was most stable at pH 5.0 to 6.0. A buffer system would be chosen which was appropriate for that pH range. I find that histidine was an obvious candidate. Other obvious buffers were phosphate and succinate. There was an argument about whether histidine was obvious because, unlike phosphate, it did not risk a pH shift on freezing. That may be right but in my judgment the position is simpler than that. Histidine was part of the relevant common general knowledge as a buffer for this pH range. The fact that phosphate and/or succinate were obvious too, does not make histidine inventive. A formulator deciding to test histidine was doing nothing more than exercising their common general knowledge in a non-inventive way.

212. The team would also consider a surfactant. Tween 20 (polysorbate 20) was an obvious candidate. In cross-examination Prof Arvinte raised a point that polysorbate 80 might have an advantage over polysorbate 20. I have already explained that I was not persuaded by this point. There was nothing inventive about choosing to use polysorbate 20 as a surfactant in a formulation of a lyophilised therapeutic protein in 1996.

213. The team would also consider a lyoprotectant. The issue is whether the team would also include trehalose in the screening tests.

214. Genentech submitted that the skilled team, without an inventive step, would not include trehalose in the screening tests. Analytically this can be divided into four main reasons, although they interact. The first was that trehalose was not part of the common general knowledge as a possible lyoprotectant but I have rejected that submission. The second, third and fourth points have not yet been addressed. The second is that toxicity of a trehalose based formulation was unknown and regulatory approval would be needed. The third reason is that trehalose would never be in a first screen of no more than four excipients, nor in a second screen of a similar number. At best trehalose would only be tested after the failure of a second screen (if at all). If the skilled team achieved success, it would stop testing lyoprotectants and so might never reach trehalose. If the project had not achieved success at the second screen then to pursue it further would involve the kind of persistence indicative of an invention rather than obvious development. Fourth Genentech argued that an undue focus on lyoprotectants generally or trehalose in particular is tainted with "enormous" hindsight. Even if a formulator looked at trehalose, the likelihood is that they would try it with phosphate or one of the common buffers, with albumin or polysorbate 80, possibly with some other salts. The point about stopping after success also applies to the other excipients as well as trehalose. On what basis, asked the patentee, would they end up with the three excipients claimed in combination?

215. Prof Arvinte supported Genentech's second point. His primary reason why trehalose was not obvious was because of a concern about toxicity and the ability to obtain

regulatory approval for a therapeutic formulation including trehalose. Prof Halbert thought that testing trehalose in the screen was obvious.

216. I reject this second point. In my judgment Prof Arvinte's wholly sincere opinion about the possible toxicity of trehalose and ability to obtain regulatory approval would not have the impact on the thinking of the notional skilled formulator that it has on Prof Arvinte. On technical grounds, trehalose was not simply one of the lyoprotectants worth considering, it was a very promising lyoprotectant, well worth testing. As regards toxicity, one could speculate that there might be an effect of trehalose when given parenterally but I am not satisfied there was any concrete reason to be concerned by that route of administration. In terms of interactions with other components, it is the case that any new combination of compounds might give rise to a toxic reaction in humans. That is one reason why clinical trials are carried out. There was no particular reason to be concerned about trehalose. I conclude that concerns about toxicity would not put off the skilled team from testing trehalose.

217. The team would know that since it had not been the subject of regulatory approval then if trehalose turned out to be effective, the matter would need to be considered with the regulator but that would not put them off including it in screening tests. They would not approach the regulator before doing the tests. The team would know that regulatory approval would be needed if it turned out that trehalose was the excipient they wanted to use. That does not make testing trehalose inventive. In fact when Genentech approached the FDA, there was no serious regulatory hurdle to overcome. The tests Genentech carried out involved treating mice for a fortnight.

218. I turn to the third and fourth arguments. It is convenient to consider them together.

219. Prof Arvinte defined "standard excipients" as ones actually used in approved protein formulation for human use. In his view these are what the skilled person would test. It is undeniable that trehalose would not fall within that definition. So approached that way, trehalose would never be tested. Against that Prof Halbert thought it was obvious to test trehalose. He was asked about the timing of the exercise and explained that (obviously) it depends on the resources available. He thought testing three or four excipients in a round of screening was reasonable.

220. Genentech submitted that the obvious lyoprotectants to use in a first screen were mannitol, glycine and possibly sucrose. I agree that mannitol and glycine would be in a first screen of lyoprotectants. In my judgment sucrose would also be included in a first round. Would trehalose be included in either a first or second round (assuming this tiered approach)? I think it would. I look at the question the other way round. Testing four lyoprotectants in two tiers (i.e. eight in total) is not inventive even if the first tier gives promising results. If a skilled person was to draw up a list of eight lyoprotectants to test on a protein in 1996 then in my judgment trehalose would be on that list. The fact it was not within Prof Arvinte's "standard excipients" does not make it inventive. It was part of the common general knowledge (with the qualifications already discussed). It was likely to be just as good as sucrose and potentially better.

221. Hospira referred to the fact that trehalose was a non-reducing disaccharide (like sucrose) and that this was relevant to obviousness. I do not regard that as a strong point. I believe the skilled formulator would have been aware of the Maillard reaction

but I am not persuaded it would have played any part in their thinking in terms of selecting lyoprotectants. There was clear evidence that reducing sugars were used (and tested) as lyoprotectants too.

222. The results in the patent report stable formulations using sucrose and trehalose. So one might say that since sucrose works and would be in a first tier screen, the skilled team would stop before they tested trehalose in a second tier. I do not accept that. On the basis of the data in the patent neither sucrose nor trehalose work in all circumstances. They are both part of different stable formulations. In any case the skilled team working without invention would wish, if possible, to go forward with more than one putative stable formulation so as to have a back up.

223. It is correct to keep in mind that the claim requires a particular combination of excipients. In addition to the status of trehalose as a lyoprotectant, Genentech submitted that at best histidine and polysorbate 20 might be included as second tier choices for the buffer system and surfactant. In other words again only if a first screen of some more obvious excipients did not work.

224. This is another way of putting Genentech's argument that if the skilled team achieved success they would stop and the answer is the same as before. Considered in terms of tiers I find that histidine and polysorbate 20 might well be in the first tier but they would certainly be in a second tier. They would not come lower down the list. No inventive step is involved in testing second tier ingredients even if promising results are obtained in the first tier screen.

225. The person skilled in the art is not a real person. The skilled person never sees what is inventive and never misses what is obvious. They represent part of the application of a legal standard to patents. It may be that some real skilled teams would find a working formulation which did not involve testing any of these ingredients. That does not alter the fact that all three ingredients are obvious agents to test.

226. In my judgment all of the differences between the claim and Carter are the result of nothing more than the application of routine screening techniques to common general knowledge excipients by a skilled team motivated in the way I have described already. There is no suggestion that any invention could be found to exist in the ratios or concentrations in the claim if the skilled team employed the relevant excipients. Accordingly there is a strong case that the claimed subject matter involves no inventive step over Carter. However before finally concluding on the point I will consider some other factors.

227. Hospira submitted, based on Prof Halbert's evidence, that the claimed formulation was one of the formulations that the skilled person could have derived by routine means. Genentech emphasised by reference to case law in the EPO (citing the Case Law of the EPO (7^{th} Ed 2013 at I.D.5)) and cases in this jurisdiction that the question is whether the skilled person would have arrived at the claimed invention, not whether they could have. Genentech argued that Hospira's submission was the highest that Hospira's case could be put and since it was put on the basis of the word "could", that was not enough to establish a lack of inventive step. This argument raises a number of points.

228. First, while the submission is an accurate way of stating part of Hospira's case, it is not the whole of the obviousness case. That case includes other elements, in particular the precise status of trehalose, histidine and polysorbate 20 in the common general knowledge of the skilled team.

229. Second, the law of obviousness cannot be accurately summarised simply by stating that the question is whether the skilled person would have arrived at the claimed invention, not whether they could have. The issue is multifactorial and based closely on the particular circumstances.

230. Third, the word "would" is not always straightforward. Sometimes asking simply if a skilled person "would" do something risks placing too much weight on what are really minor or irrelevant factors like cost, instead of focussing on the technical issues. Moreover, the well known 9 ½ inch plate is not something a skilled person *would* make. It is more accurate to say that it is not patentable because the skilled person could make it without any inventive step.

231. In other cases the difference between could and would is important. If the outcome rides on the result of a single experiment, the fact the skilled person could carry it out does not usually mean the invention is obvious. One often needs to ask if they would carry out the test in the expectation of a positive result.

232. This dependence on the facts is the reason why the passage from Kitchin J's judgment in ***Generics v Lundbeck***, approved in the House of Lords in ***Angiotech***, is significant and why the Court of Appeal in ***Medimmune*** emphasised that there is a single statutory test, repeating at paragraph 95 Lord Walker's concern (in ***HGS v Lilly***) about the utility of elaborate judicial exposition.

233. Fourth, real skilled teams faced with trying to formulate lyophilised trastuzumab would do many different things. They would have their own personal experience and idiosyncrasies and their own resource limitations. I am quite sure if one compared a number of real skilled teams side by side, they would test different combinations of excipients in a first and second screen. Some teams who found unpromising results in the first and second tier screen would continue past a second tier screen, others might not. Some real teams might never test polysorbate 20 or histidine at all. For all we know polysorbate 80 is just as good as polysorbate 20. Thus a real team which started with polysorbate 80 might never see a need to test another surfactant. Equally for all we know polysorbate 80 does not work with trastuzumab (in which case I am quite sure nearly every team would at least try polysorbate 20 when they encountered such problems). The only evidence before the court about what works and what does not is the data in the patent. Given the empirical nature of this field, the outcome of experiments which have not been carried out cannot be predicted.

234. My conclusions on the could/would argument are as follows. It is not true to say that a real team *would* arrive at a formulation consisting of polysorbate 20, histidine and trehalose. It would be idle to pretend otherwise and Hospira do not do so. But what Hospira's submission is getting at is that the claimed result can be reached by the application of nothing other than routine approaches applied to excipients which were part of their common general knowledge. In my judgment on the facts of this case that is correct.

235. I will deal with a number of further other points which arose in argument.

236. First, the debate about arbitrary selection. A question was whether the claims represented a selection (inventive or not) over the prior art and whether the claim was arbitrary. It is not correct to characterise the claim as an arbitrary selection. Clearly a lyophilised product made by lyophilising the Table 5 Solution is stable and in that very important respect is therefore better than the prior art liquid formulation of trastuzumab. It is also better than many lyophilised formulations too. However it is not better than lyophilising the Table 6 Solution. That solution, which contains sucrose and mannitol is another one which I find can be reached by the application of nothing other than routine approaches applied to excipients which were part of the common general knowledge. I make the same findings about the Table 4 and Table 7 solutions too (both with succinate and a different pH, one with a higher trehalose concentration). None of these solutions are arbitrary. However just because the invention produces a benefit as compared to the prior art does not mean it necessarily involves an inventive step. If a benefit is the product of the application of obvious steps to the common general knowledge starting from a public document (Carter) then it does not help.

237. Another way of looking at this arbitrary selection point is the following. In my judgment in this case the skilled team who arrived at the Table 5 Solution would be pleased they had produced a stable lyophilised formulation, and no doubt proud of their work, but not surprised. It is not a surprise that a stable lyophilised formulation of trastuzumab can be made. Nor would the identity of the ingredients be a surprise. Although none of the excipients are the most commonly used, they are all part of the common general knowledge.

238. Second, the research programme. At times it seemed to be suggested that even though the work was routine, it would take a "research programme" to reach the claim. The expression is a patent lawyers' cliché for work which represents an undue burden and so would lead to insufficiency if it was necessary to practice the invention and would demonstrate inventiveness if necessary to reach the claim from the prior art. If the notional skilled team would only get as far as screening trehalose, histidine and polysorbate 20 after a degree of persistence through unpromising results which did not represent the product of the true motivation of this skilled team in this case, then there might well be something in that point. But I do not accept that on the facts.

239. Third, ***Technograph***. Genentech submitted that Hospira's case was an extreme version of the hindsight ridden step by step approach deprecated in that well known decision of the Court of Appeal. I do not accept that. Hospira referred to what I said in ***Molynlycke v. Brightwake*** [2011] EWHC 376 at paragraphs 309-311. Since that judgment was overturned on appeal albeit, as Hospira submitted, not on this point ([2012] EWCA Civ 602) I have given the issue further thought.

240. The particular point made in ***Technograph*** was that it was wrong to find an invention was obvious if it was only arrived at after a series of steps which involve the cumulative application of hindsight. In some circumstances success at each step in a chain is a necessary predicate for the next one and it is only the hindsight knowledge of the invention as the target which could motivate a skilled person to take each step without knowledge about the next one. In a situation like that, ***Technograph*** is important.

241. But other cases, of which I believe this is an example, have other factors. Factors which characterise this case are:

i) Although a number of choices have to be made, the existence of these choices is not tainted with hindsight.

ii) Although the point cannot be taken too far since the ingredients interact and have to work in combination, nevertheless a number of the choices here fall to be made in parallel not in series.

iii) This is a highly empirical field and is one in which the skilled team will, without hindsight, want to test a range of ingredients.

iv) The tests themselves are run in parallel. The skilled team does not test one combination at a time. It tests a number together.

242. The warning to guard against hindsight is always vital and I have kept it in mind. However I do not believe the particular point made in ***Technograph*** is of significant importance to a case like this.

243. I conclude that none of the claims involve an inventive step over Carter.

Inventive step over Draber

244. On my findings, this does not arise. I will say that given the plain inadequacy of the science reported in Draber, I doubt that a skilled formulator who had never heard of trehalose as a lyoprotectant would put any weight on Draber.

Insufficiency

245. On my findings, this does not arise.

Conclusion

246. The amendments proposed would extend the scope of protection but that can be cured. The EPO applying its approach to product by process claims would not allow claim 1 of 628 and claims 1 and 3 of 119 as amendments and so neither will I. Claim 2 of 628 and claims 2 and 4 of 119 do not lack clarity. All the amendments would introduce added matter. All the claims in issue lack inventive step.

247. EP (UK) 2 275 119 will be revoked. EP (UK) 1 516 628 will be amended to delete claims 1 to 6, leaving claims 7 to 11 which will have to be renumbered.

248. I find for Hospira.

Annex 1 – claims of 628 as proposed to be amended

1. A formulation comprising a lyophilized mixture of a lyoprotectant, a buffer, a surfactant and an antibody, ~~wherein the molar ratio of lyoprotectant : antibody is 200-600 moles lyoprotectant : 1 mole antibody,~~ wherein the lyoprotectant is trehalose ~~or sucrose~~ wherein the buffer is histidine, wherein the surfactant is polysorbate 20 and wherein the antibody is ~~a monoclonal antibody~~ huMAb4D5-8, obtainable by lyophilizing a solution containing 25 mg/ml huMAb4D5-8, 5mM histidine pH 6.0, 60 mM trehalose and 0.01% polysorbate 20.

2. A formulation comprising a lyophilized mixture of a lyoprotectant. a buffer, a surfactant and an antibody, wherein the lyoprotectant is trehalose, wherein the buffer is histidine, wherein the surfactant is polysorbate 20 and wherein the antibody is huMAb4D5-8, such that an amount of said lyophilized mixture containing 450 mg of said antibody can be reconstituted with 20 ml of BWFI (0.9 or 1.1% benzyl alcohol) to yield a concentrated protein solution containing 22 mg/ml of said antibody, 52 mM trehalose, 4 mM histidine, pH 6.0, 0.009% polysorbate 20.

Existing claims 2 - 7 are to be deleted.

~~8~~3. A method for preparing a formulation, the method comprising the steps of:

(a) lyophilising a mixture of a lyoprotectant and an antibody, wherein the molar ratio of lyoprotectant : antibody is 200-600 moles lyoprotectant : 1 mole antibody, wherein the lyoprotectant is trehalose or sucrose and wherein the antibody is a monoclonal antibody; and

(b) reconstituting the lyophilised mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable and has an antibody concentration of at least 50 mg/mL, wherein the antibody concentration in the reconstituted formulation is about 2-40 times greater than the antibody concentration in the mixture before lyophilisation.

~~9~~4. A method according to claim ~~8~~3, wherein the antibody is an anti-HER2 antibody or an anti-lgE antibody.

~~10~~5. A method according to claim ~~8~~3 or ~~9~~4 wherein the formulation comprises a buffer.

~~11~~6. A method according to claim ~~10~~5, wherein the buffer is a histidine or succinate buffer.

Annex 2 – claims of 119 as proposed to be amended

1. Use of a lyophilized formulation comprising a monoclonal antibody, a buffer, a surfactant and a lyoprotectant~~, wherein the molar ratio of lyoprotectant : antibody is 200-600 moles lyoprotectant : 1 mole antibody~~, wherein the lyoprotectant is trehalose, wherein the buffer is histidine, wherein the surfactant is polysorbate 20, and wherein the monoclonal antibody is huMAb4D5-8 ~~an anti HER2 antibody~~, obtainable by lyophilizing a solution containing 25 mg/ml huMAb4D5-8, 5mM histidine pH 6.0, 60 mM trehalose and 0.01% polysorbate 20, in

the preparation of a medicament for the treatment of ~~a~~ breast cancer characterised by overexpression of the HER2 receptor.

2. Use of a formulation comprising a lyophilized mixture of a lyoprotectant. a buffer, a surfactant and a monoclonal antibody, wherein the lyoprotectant is trehalose, wherein the buffer is histidine, wherein the surfactant is polysorbate 20 and wherein the monoclonal antibody is huMAb4D5-8, such that an amount of said lyophilized mixture containing 450 mg of said antibody can be reconstituted with 20 ml of BWFI (0.9 or 1.1% benzyl alcohol) to yield a concentrated protein solution containing 22 mg/ml of said antibody, 52 mM trehalose, 4 mM histidine, pH 6.0, 0.009% polysorbate 20, in the preparation of a medicament for the treatment of breast cancer characterised by overexpression of the HER2 receptor.

~~2~~3. A lyophilized formulation comprising a monoclonal antibody, a buffer, a surfactant and a lyoprotectant~~, wherein the molar ratio of lyoprotectant : antibody is 200 600 moles lyoprotectant : 1 mole antibody~~, wherein the lyoprotectant is trehalose, wherein the buffer is histidine, wherein the surfactant is polysorbate 20, and wherein the monoclonal antibody is huMAb4D5-8 ~~an anti HER2 antibody~~, obtainable by lyophilizing a solution containing 25 mg/ml huMAb4D5-8, 5mM histidine pH 6.0, 60 mM trehalose and 0.01% polysorbate 20, for use in a method for the treatment of ~~a~~ breast cancer characterised by overexpression of the HER2 receptor, wherein the formulation is reconstituted with a diluent prior to administration to a patient in need thereof.

4. A formulation comprising a lyophilized mixture of a lyoprotectant. a buffer, a surfactant and a monoclonal antibody, wherein the lyoprotectant is trehalose, wherein the buffer is histidine, wherein the surfactant is polysorbate 20 and wherein the monoclonal antibody is huMAb4D5-8, such that an amount of said lyophilized mixture containing 450 mg of said antibody can be reconstituted with 20 ml of BWFI (0.9 or 1.1% benzyl alcohol) to yield a concentrated protein solution containing 22 mg/ml of said antibody, 52 mM trehalose, 4 mM histidine, pH 6.0, 0.009% polysorbate 20, for use in a method for the treatment of breast cancer characterised by overexpression of the HER2 receptor, wherein the formulation is reconstituted with a diluent prior to administration to a patient in need thereof.