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Case No: HC12C03487

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

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

Date: 10/04/2014

Before:

MR JUSTICE BIRSS

- -

Between :

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

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- -

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

Hearing dates: 6th, 7th, 10th, 11th, 12th, 13th, 14th, 18th and 19th March 2014

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Judgment

Mr Justice Birss:

Contents	**Paragraph**

Introduction

1. Like all cancers, breast cancer is not a single disease. Much depends on the particular kind of cells which have become cancerous. The conventional therapeutic approaches were surgery, radiotherapy and chemotherapy or combinations of these various options. The agents used for chemotherapy were and are powerful drugs which are cytotoxic (i.e. cell killing). These drugs include Taxol (the trade name of paclitaxel), 5-flourouracil and many others. Generally these agents attack rapidly dividing cells. This will include cancer cells but will also include other rapidly dividing cells in the body. That is why hair loss can be a side effect of chemotherapy.

2. Some types of breast cancer can be treated with hormone therapy (such as Tamoxifen) but other types of breast cancer do not respond to hormone therapy. One class of breast cancers which was particularly difficult to treat was those in which the cells over-expressed a receptor known as HER2. The HER2 receptor (also known as the ErbB2 receptor) belongs to a class of receptors in the epidermal growth factor receptor (EGFR) family. 20% to 30% of breast cancers were classified as HER2 positive. They had a poor prognosis.

3. In general in pharmacology higher selectivity means that a drug can be given at an effective dose with fewer side effects. In other words the margin between safety and efficacy generally improves as selectivity increases. Thus an agent which could be targeted more closely to cancer cells in particular could be given at a higher dose in order to improve its efficacy, without compromising safety.

4. A major breakthrough in breast cancer therapy in recent years has been the availability of an agent known as Herceptin. Herceptin is the brand name of a monoclonal antibody called trastuzumab. This antibody targets the HER2 receptor. It was developed by Genentech and Roche.

5. Trastuzumab is different from conventional chemotherapeutic agents in a number of ways. Two important points stand out in the context of this case. First, it is highly targeted to a particular group of cancer cells, which in general terms means that the window between safety and efficacy is improved. Second, trastuzumab was at the time a new class of agent - a monoclonal antibody. Whereas conventional drug molecules are small, antibody molecules are large proteins. This difference has

consequences relating to the manufacture and formulation of the drug and may also affect the manner in which the drug behaves in the body.

6. Before Herceptin was approved in the USA and then later in Europe, those working in oncology had heard about it. The positive results of a Phase II clinical trial were published in March 1996 and in May 1998 the results of the Slamon trial were published at ASCO. In September 1998 Herceptin was approved by the FDA in the United States and in Europe it was approved in August 2000. Herceptin has been and remains a huge success. Worldwide sales from 1999 to 2013 totalled 49 billion Swiss Francs (£33 billion at present exchange rates) which includes European sales from 2010 to 2013 of 8 billion Swiss Francs (£5 billion).

7. Hospira sells generic medicines, particularly in the cancer field. It wishes to sell a generic form of trastuzumab in the UK. Hospira does not challenge the basic underlying patent held by Genentech on trastuzumab (EP 0 590 058). The supplementary protection certificate for that patent (SPC/GB04/015) expires on 28th July 2014. Hospira wishes to sell its generic trastuzumab product after that date. Genentech holds a number of patents of a later vintage which Hospira might infringe. Hospira contends that the patents are invalid and has brought this action to invalidate them. There is also a claim for a declaration of non-infringement in relation to one patent. When the case began there were three patents in suit but Genentech offered to surrender one of them a few months ago.

8. The two patents in suit are EP 1 210 115 entitled "Dosages for treatment with Anti-ErbB2 antibodies" and EP 1 308 455 entitled "A composition comprising anti-HER2 antibodies".

9. The application for the 115 patent was filed on 25th August 2000 claiming priority from two US applications, the first being filed on 27th August 1999. It was granted on 5th August 2009. The claims concern a dosing regimen for trastuzumab.

10. The application for the 455 patent was filed on 3rd May 1999 claiming priority from a US filing on 6th May 1998. It was granted on 22nd March 2006. The claims concern a composition of trastuzumab with less than certain thresholds of certain impurities.

11. Both patents were opposed in the EPO. In both cases the Opposition Division has held the patent is invalid. Both are presently under appeal before the Technical Board of Appeal. The parties did not know when the appeals are likely to be heard. Even if either appeal succeeds it may not bring the EPO proceedings to an end because in that event the Board may remit the case to the Opposition Division.

The issues

12. The 115 patent relates to the use of a particular dosing schedule of trastuzumab to treat breast cancer. The dosing schedule involves administering trastuzumab every three weeks whereas the existing schedule was weekly.

13. Hospira contends that the claims of the 115 patent are not entitled to the earliest claimed priority date. Genentech maintains the claim to priority but accepts that if priority is lost the patent is invalid. Hospira also contends that even if entitled to priority, the patent is invalid. The invention is said to be obvious over the state of the

art at the earliest priority date. The key item of prior art is the FDA label for Herceptin which was published when the product was approved by the FDA. Genentech accepts the FDA label is prior art but does not agree it makes the claimed dosing regimen obvious.

14. Hospira's primary case is that the invention is obvious but if the claims of the 115 patent do involve an inventive step then Hospira contends the patent is insufficient. Hospira argues essentially that if it was inventive to conduct a clinical trial over what was known from the prior art then the same logic will apply starting from the patent and the result must be insufficiency. Although it is true that the patent specification does contain more data than was in the state of the art, Hospira point out that the patent specification does not contain the result of a clinical trial of the claimed dosing regimen. Genentech does not agree with this either as a matter of reasoning or on the facts. It points out that the claimed dosing regimen is in fact safe and effective to treat the disease. Genentech also argues that, unlike the position over the prior art, a skilled person reading the patent in the light of their common general knowledge will have sufficient confidence to conduct a clinical trial.

15. Finally Hospira advanced a case based on added matter but by closing it became clear that the point does not need to be addressed.

16. The only relevant claim of the 115 patent is claim 1. In response to the way in which the arguments on priority developed, Genentech made an application to amend the claim to include a reference to "intravenously". By the closing this was the only claim to be focussed upon.

17. The 455 patent is concerned with purifying trastuzumab and claim 1 relates to a composition of trastuzumab with less than about 25% of certain acidic variants of the antibody. Hospira argues that claims 1, 2 and 4 lack novelty over a previous Genentech PCT application PCT/US96/12251 ("Andya") which was published as WO 97/04801 on 13th February 1997 and entitled "Stable Isotonic Lyophilised Protein Formulation". Andya describes stability tests on various trastuzumab formulations. Hospira contends Andya is an enabling disclosure of a composition of trastuzumab with 82% native protein and therefore no more than 18% acidic variants. Genentech does not agree. In addition to a point about exactly what is disclosed, the main debate over Andya concerns enablement. Hospira also contends that Andya makes all claims of 455 obvious.

18. Hospira also relies on slides presented at a conference called The Waterside Monoclonal Conference in April 1996 (Waterside). These slides present analytical data in the context of phase III trials of trastuzumab for breast cancer. Hospira contends that the invention in 455 is obvious starting from these slides or from the common general knowledge alone. Genentech denies this.

19. The argument over common general knowledge alone has two distinct strands. One adds little to the obviousness argument over Andya and Waterside. At this stage it is enough to note that the other argument involves considering what the levels of acidic variants were in the starting material used in the patent, which came from a Protein A affinity purification step.

20. Hospira advanced an insufficiency case on 455 but by closing it became clear that the point does not need to be addressed.

21. Hospira sought a declaration of non-infringement in relation to certain trastuzumab formulations which they propose to sell in the UK if they cannot invalidate any or all claims of the 455 patent. I made the order granting the declaration during the trial, with reasons to be given in this judgment.

The witnesses

22. Hospira's first witness relating to the 115 patent was Dr Robert Earhart. He has worked in academia and in industry as a physician and clinical pharmacologist since 1975. In 1995 he joined Rhone-Poulenc Rorer and was responsible for clinical trials on the chemotherapeutic agent docetaxel (Taxotere). His evidence was concerned with pharmacokinetics. His view was that if a clinician had asked him to consider a clinical trial of a three weekly dosing regimen of trastuzumab, then based on a consideration of the information in the FDA label, he would advise that there was no reason not to conduct such a trial on pharmacokinetic grounds.

23. Hospira's second witness relating to the 115 patent was Professor Robert Leonard. He 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. His opinion was that it would be obvious to a clinician at the relevant time to contemplate conducting a small clinical trial of a three week dosing regimen for trastuzumab and that the clinician would consult a pharmacokinetics expert about whether such a trial was worthwhile. If the response of the pharmacokinetics expert was the one advanced by Dr Earhart then the clinician would go ahead and conduct the trial.

24. Genentech's first witness on the 115 patent was Professor Peter Barrett-Lee. He qualified as a doctor in 1982 and is now 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. His opinion was that at the relevant time a trial of a three weekly dosing regimen for trastuzumab was not obvious. It would not occur to the skilled clinician to consider such a trial and if it did occur to him, he would dismiss the idea and he would not consult a pharmacokinetics expert about it. If the clinician did consult a pharmacokinetics expert and their response was the response Genentech contended would emerge from considering the prior art, then he would not conduct a trial of a three weekly dosing regimen. On the other hand if a skilled team was presented with the patent, then based on Prof Boddy's analysis of the pharmacokinetics using the data in the patent, Prof Barrett-Lee would carry out the clinical trial.

25. Genentech's second witness relating to the 115 patent was Professor Alan Boddy. He obtained a PhD in pharmacokinetics in 1986 and today is Professor of Cancer Pharmacology and Team Leader of the Pharmacology group at the Northern Institute for Cancer Research at Newcastle University. His opinion was that based on the information made available to the public in the prior art, a pharmacokineticist would

not support a trial of three weekly dosing of trastuzumab. In relation to the issue of sufficiency, Prof Boddy's view was that the pharmacokinetic data in the patent coupled with the information publicly available at the time would lead a pharmacokineticist to support a three weekly dosing trial.

26. Hospira's expert witness on the 455 patent was Dr Uwe Gottschalk. He trained as a biochemist and has a PhD in Chemistry from the University of Münster. He worked at Bayer from 1991 to 2004 as a research and process development biochemist and from then until today Dr Gottschalk has worked at Sartorius Stedim Biotech which supplies process technology to the biopharmaceutical industry. He is currently Group Vice-President of Purification Technologies.

27. Dr Gottschalk's opinions supported Hospira's case that the 455 patent lacked novelty and did not involve an inventive step. He addressed the characteristics of various trastuzumab compositions and expressed the view that trastuzumab could be separated from the relevant acidic variants on an analytical scale and that purifying trastuzumab on a larger scale was obvious, albeit that the separation of the acidic variants from the native protein might involve sacrificing yield.

28. Hospira also served a witness statement from Rekha Patel, the Regulatory Affairs Product Manager for Global Biologics Development at the claimant. She verified the contents of Hospira's Statement of Case which dealt with Hospira's trastuzumab product and was relevant to the declaration of non-infringement. She was not cross-examined.

29. Genentech's witness on the 455 patent was Professor Nigel Titchener-Hooker. He graduated from UMIST in 1983 with a degree in chemical engineering and is now Professor of Biochemical Engineering and the Head of the UCL department of Biochemical Engineering. He is also the Director of the EPSRC Centre for Innovative Manufacturing in Emergent Macromolecular Therapies. Prof Titchener-Hooker addressed the scaling up of protein purification. He explained that separating trastuzumab from the acidic variants on a large scale was difficult and not obvious.

30. Genentech had served reports from a second expert in relation to the 455 patent, Professor Zhaohui Sunny Zhou, but during the trial decided not to call the Professor.

31. Each of the witnesses at trial were good witnesses who gave their evidence fairly, seeking to help the court. Neither side criticised the other's witnesses.

The 115 patent

The skilled person and the common general knowledge

32. It was common ground that the skilled addressee of the Patent would be a team and that the team would comprise a clinician, specifically an oncologist, and an expert in pharmacokinetics. At one stage there appeared to be a dispute about whether the skilled clinician would be a "pure" clinician with no research interest (Genentech) or a practising clinician who is part of a team investigating new dosing regimens (Hospira). I find that the relevant skilled clinician would not necessarily be someone already working in a team investigating new dosing regimens, but they would be a

clinician who was prepared to contemplate and propose new dosing regimens. There was clear evidence that clinicians in this field would regularly do this.

33. The common general knowledge can be divided between that possessed by the clinician and that possessed by the pharmacokinetics expert.

34. The important elements of the common general knowledge of the clinician member of the skilled team at the priority date are the following:

    i) Breast cancers could be classified in a number of ways, including by stage (early, late or locally advanced) and by receptor status (HER2-positive, oestrogen receptor (ER) positive etc.). Early stage breast cancer was regarded as operable (curable by surgery); late stage disease (metastatic disease) was regarded as incurable but was still treated; locally advanced disease was regarded as inoperable but could potentially be rendered operable by treatment. Clinical trials of new cancer agents would generally have been conducted in patients with metastatic disease who had not responded to other treatments for risk/benefit and ethical reasons, although positive results in such patients would be expected to lead to a greater response rate in other patient settings.

    ii) There were three established categories of non-surgical breast cancer therapy – endocrine (hormone) therapy, cytotoxic chemotherapy and radiotherapy – and antibody therapy had recently been introduced as a further category;

    iii) Paclitaxel and docetaxel were approved and established cytotoxic chemotherapy drugs that were administered every three weeks when used to treat metastatic breast cancer;

    iv) In September 1998 trastuzumab, alone or in combination with paclitaxel, was approved by the FDA (as Herceptin) for the treatment of metastatic breast cancer. The FDA label is a formal document which forms part of the approval process of any drug. The FDA label for Herceptin was part of the common general knowledge.

35. Another aspect of the common general knowledge of the skilled clinician related to convenience. The primary consideration of any therapy is safety and efficacy. However Prof Leonard's view was that, although it was a secondary consideration, nevertheless it was desirable to administer therapies in a manner as convenient as possible for the patient and medical staff and that increased convenience could be achieved by alternative routes of administration, less frequent dosing and co-administration. Prof Barrett-Lee's view expressed in his report was that this was very much a subsidiary matter. In cross-examination he accepted that it was a factor in all patients and that clinicians always have to take into account how drug treatments will be given and what impact this will have. He agreed it was a factor in wanting to modify a treatment. Papers looking carefully at quality of life and convenience in the context of cancer treatment were put to Prof Barrett-Lee. They spanned a period from 1983 to 1998.

36. I find that at the relevant date (1999) convenience was an important factor for cancer treatment in general and treatment of metastatic disease in particular. To the skilled

clinician in oncology it would be routine to think about improving quality of life by looking at how drugs were administered. Tests would then be carried out to ensure safety and efficacy.

37. The important elements of the common general knowledge of the pharmacokinetics expert member of the skilled team at the priority date are the following:

i) A drug effect arises from a pharmacodynamic interaction between a drug and its target within the body and generally depends on the concentration of the drug at the site of action.

ii) Pharmacokinetic methods model the effects of four general processes: adsorption, distribution, metabolism and excretion and allow the concentration of a drug at the site of action (or toxicity) to be modelled over time after a dose is administered.

iii) The rate of elimination of a drug from the body is commonly first-order (i.e. proportional to the first power of the concentration of the drug) but may also be zero-order (i.e. a constant/proportional to the zeroth power of concentration).

iv) Where the relevant elimination process may be saturated by a high concentration of drug the drug will exhibit dose-dependent pharmacokinetics (i.e. zero order above the saturation level, first order below it).

v) There are three categories of pharmacokinetic model: classical compartmental models, physiologically-based compartmental models and non-compartmental models.

vi) Regarding compartmental models:

a) In a one-compartment model the body is modelled as a single central compartment into which the drug distributes and the concentration of the drug at the site of action is assumed to be the concentration in this single compartment.

b) In a two-compartment model the drug is modelled as diffusing rapidly in the blood and highly perfused organs and that, at a slower rate, distributing to other tissues that are less well perfused.

vii) These models are theoretical and do not relate to actual compartments in the body. An important point is that the choice of model is determined by the data and not a physiological theory as to how the drug will behave in the body.

viii) In classical compartmental models the volumes of the compartments are apparent volumes derived from measurements of variation in drug concentration, whereas in physiologically-based models the compartment volumes are based on estimates of the real volumes in the human body that they represent.

ix) A commonly stated pharmacokinetic parameter for a drug is the serum half life. This is the time the serum concentration will drop by one half. In a one

compartment model there is a single half life whereas in a two compartment model there are two distinct half lives.

x) When a drug is administered repeatedly the concentration in the body approaches a steady state concentration.

xi) For drugs given by repeat dosing, an initial higher dose (loading dose) was a commonly used method to reach steady state concentrations more rapidly.

xii) Doses may be expressed in absolute dose levels (mg) or weight-adjusted dose levels (mg/kg). It is a standard assumption that the average patient weighs 70kg. Unless specific patient weight data is available, the weight-adjusted dose level is obtained by dividing the absolute dose level by 70kg.

38. One kind of dose dependent non-linearity arises when a compound exhibits Michaelis-Menten kinetics. In general terms Michaelis-Menten kinetics relate to a situation in which there may be a given quantity of an enzyme to act on a substrate. For example there could be an enzyme which catalyses the breakdown of a drug. The rate of the reaction will increase as the concentration of substrate (i.e. the drug) rises from zero but that increase will reach a maximum once the substrate is in large excess relative to the enzyme. At low substrate concentrations the elimination may be approximately first order but when the substrate is in large excess the elimination is zero order because the given quantity of enzyme is in effect working flat out.

39. When a drug is administered repeatedly the serum concentration rises to a peak sometime after dosing and falls to a trough just before the next dose is given. An assessment will be made of the target trough serum concentration which is needed for the drug to be efficacious. From the point of view of achieving efficacy the aim will be to have a dosing regimen which keeps the trough serum concentration above the target. Just as the trough is relevant for efficacy, the peak may be relevant to toxicity and the risk of side effects.

40. An issue between the parties was the extent to which the pharmacokinetics expert would take into account views they might have about the behaviour of antibodies in general: when the antibodies were in circulation in the body and when they were eliminated. Dr Earhart thought the expert would know about this and take it into account and Prof Boddy thought the expert would not. Although I preferred Dr Earhart's view on this point, I do not think it plays a major part in the issues I have to decide and I will assume the point in Genentech's favour.

41. The skilled clinician would regard pharmacokinetics as a province of experts in that field but that does not mean they had no appreciation of general concepts. They would understand drug half lives and the idea of a trough serum concentration for a drug.

42. In reality the members of the skilled team would consult and work together however for the purposes of analysis it is useful to consider a slightly stilted choreography between the two members of team in order to illuminate and address the issues. That choreography is reflected in the sections on obviousness and sufficiency below.

The 115 patent specification

43. Claim 1 in the amended form sought by Genentech is to:

> Use of the anti-ErbB2 antibody huMab4D5-8
>
> in the manufacture of a medicament for use in a method for treating a human patient diagnosed with a breast cancer characterized by overexpression of ErbB2,
>
> said method comprising the steps of
>
> administering intravenously to the patient an initial dose of 8mg/kg of the anti-ErbB2 antibody; and
>
> administering intravenously to the patient a plurality of subsequent doses of the antibody in an amount that is 6 mg/kg, wherein the doses are separated in time from each other by three weeks.

The words underlined were sought to be added by amendment in the application notice dated 3rd March 2014.

44. The claim is in the familiar Swiss type form. Claim 4 is written in the "product for use" form but is otherwise in the same terms. I will focus on claim 1. The antibody referred to is trastuzumab. The disease is breast cancer characterised by overexpression of ErbB2 (i.e. HER2). The method involves an 8mg/kg loading dose and subsequent doses of 6mg/kg on a three weekly schedule. This regimen can be summarised as 8 + 6 q3w. For what it is worth there must be a plurality (i.e. at least two) subsequent doses. The dependent claims 2 and 3 (and correspondingly 5 and 6) combine the antibody treatment with a chemotherapeutic agent in general (claims 2/5) or with paclitaxel or docetaxel in particular (claims 3/6).

45. Despite the relatively narrow terms of claim 1, the specification of the 115 patent as a whole is written in broad terms. The first paragraph, entitled Field of the Invention, explains that the disorders the document relates to are those characterised by overexpression of ErbB2 or disorders expressing EGFR. This includes but is not limited to cancer. There is a reference to cancer but it is not limited to breast cancer. Any antibody which binds ErbB2 is covered. There is a general reference to front loading the dose of the antibody. The cancer treatment may involve combining the antibody with a chemotherapeutic agent such as paclitaxel or docetaxel or an anthracycline derivative. In the latter case there may also be treatment with a cardioprotectant. This reflects the fact that trastuzumab combined with anthracycline derivative chemotherapeutic agents had been linked to cardiotoxicity. The paragraph ends with a wide reference to "infrequent dosing" of the antibodies.

46. The remainder of the specification is also written in similarly wide terms. The Summary of the Invention section (paragraphs 13 to 33) starts with a reference to front loading in order to achieve early attainment of the target trough serum concentration, again written in broad terms. Very wide ranges for peak and trough serum concentration are given in paragraph 16. A range of periods for the first subsequent dose is mentioned in paragraph 16 from 4 weekly to "*most preferably one week or less*". Initial doses of 12mg/kg and 8mg/kg are mentioned with subsequent

maintenance doses of 6mg/kg three weekly but also (paragraph 20) 8mg/kg every week, or 2 or 3 weekly.

47. Paragraph 19 refers to "still another embodiment" as an 8mg/kg initial dose and a three weekly 6mg/kg maintenance dose. This corresponds to claim 1 albeit there is no reference in this paragraph to the disease to be treated.

48. Paragraph 25 includes a long list of cancers to be treated. They are characterised by overexpression of ErbB2. Breast cancer is the first in the list of over twenty cancers. Paragraph 26 refers to antibodies. Trastuzumab is not the only one mentioned. A combination with other chemotherapy drugs, including paclitaxel and docetaxel is mentioned in this Summary section.

49. The Detailed Description of the Preferred Embodiments section comes next along with the drawings. This section runs from paragraphs 34 to 177. Part V of this section is concerned with Treatment with Anti-ErbB2 Antibodies. Paragraph 168 in this part contains another reference to the 8 + 6 q3w dosing schedule, again without reference to a particular disease or antibody and again among a number of other dosing proposals.

50. From paragraph 177 onwards are six examples. Example 1 presents the results of a clinical trial of the 4 + 2 q1w dosing regimen of intravenous Herceptin in metastatic breast cancer patients in combination with chemotherapy consisting of either Taxol (paclitaxel) or a combination of anthracycline and cyclophosphamide. The results are positive for the combination with paclitaxel. The combination with anthracycline derivatives is contraindicated due to the cardiac side effects.

51. Example 2 presents pharmacokinetic and pharmacodynamic data following a 4 + 2 q1w dosing regimen by intravenous infusion. The disease treated is metastatic breast cancer (paragraph 197, referring back to the inclusion criteria for Example 1).

52. The results of Example 2 are presented in two sets. Table 2 gives the mean peak and trough serum concentrations for all patients over eight weeks. Figure 3 sets out the mean trough serum concentrations for the smaller number of patients who completed the study to week 36. The data shows that the first mean trough level (at week 1) is 25μg/ml and that the mean trough level rises to a plateau after about week 12 of about 70μg/ml.

53. Examples 3 and 4 relate to experiments performed on mice and were not focussed upon.

54. Example 5 sets out a series of proposed dosing regimens for delivery of Herceptin. The disease to be treated is metastatic breast cancer (paragraph 215, referring to the inclusion criteria of Example 1). Various dosing regimens are proposed. They include the 8 + 6 q3w regime (paragraph 217). The delivery is by intravenous (infusion or bolus) or subcutaneous bolus injection. Paragraph 217 predicts that the regimen will maintain a trough serum concentration averaged for the entire group of approximately 10-20μg/ml. Example 5 is entirely "prophetic", that is to say it would be understood to be making predictions rather than reporting the results of tests actually carried out.

55. Example 6 describes a proposed clinical trial in 12 metastatic breast cancer patients of a 8 + 6 q3w regime for Herceptin combined with three weekly paclitaxel. Para 227 states that a simulation of the proposed treatment suggests the trough serum concentration will be 17μg/ml. The example predicts that the treatment will be effective.

Claim construction

56. There was no dispute about the proper interpretation of the claims. I have summarised the construction at the start of the section on the 115 patent above.

57. Citing ***Regeneron v Genentech*** [2013] EWCA Civ 93 paragraph 56, Genentech submitted that the treatment of HER2 positive breast cancer was a "functional technical feature" of the claim. In other words the claim is to something which is indeed an effective treatment of the disease. Hospira agreed with this approach and I accept it.

58. It was also common ground that the word "for" in claims in this form and in the form used in claim 4 are exceptions to the general rule that "for" means "suitable for". In this sort of claim "for" means "suitable and intended for".

59. Nevertheless despite the fact these points are common ground it is worth dwelling briefly on their implications. The effect of these points is that such claims are generally regarded as novel over a mere proposal to administer the drug to patients in the manner claimed. That is because the mere proposal does not disclose that the treatment is indeed efficacious. If it was obvious that the treatment would be efficacious, or at least it was obvious to conduct a trial of the treatment which would involve treating patients, then the claim is likely to lack inventive step but that is another matter.

60. One might say therefore that the patent specification must contain the results of a clinical trial in order to prove efficacy, since the claims contain this element as a feature. But to require that at least in all circumstances may cause another problem. Finding new treatments for disease is highly desirable. Clinical trials are a necessary but very expensive and complex part of that process. The existence of a patent (or application) may facilitate investment in the clinical trial which might not otherwise take place but that means that the patent has to be applied for before the results are known. So a rule which demanded clinical results could cause real difficulties.

61. On the other hand, if all the patent contains is a mere proposal, then it has not made a contribution to the art in this example. One has now come full circle. A mere proposal is not a disclosure of the claim, properly construed. But the patentee can hardly argue, and the Court or Patent Office is unlikely to accept, that a mere prior proposal is not enough to invalidate the claim if all that is present in the specification of the patent is a mere proposal followed by a use claim.

62. Moreover it would be a recipe for abuse if all that was required in order to obtain a patent in this field was a proposal, without any basis, to use drug A to treat disease B.

63. Patent law seeks to address these factors balancing the requirements for sufficiency of disclosure against the rules of novelty and inventive step. But the conventional

sufficiency test of asking whether the claimed invention works, does not help. The treatment does work but what if the patent does not say so?

64. For these reasons the idea of "plausibility" as part of the law of sufficiency of disclosure has been developed both in the EPO (***T609/02 Salk Institute***) and the UK (***Regeneron***). The term "plausibility" has been coined to characterise what it is that a patent specification must provide in order to be sufficient, short of full clinical proof of efficacy.

Obviousness

65. 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.

66. 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."

67. 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 paragraph 117 - 186.

Obviousness – the FDA label

68. I have identified the skilled team and the common general knowledge above. The claim is clear and there is no need to devise a separate inventive concept.

69. The starting position is the FDA label. The label shows that Herceptin administered intravenously on a 4 + 2 q1w regimen has been approved as effective to treat metastatic breast cancer when combined with paclitaxel. The paclitaxel is administered on a three weekly schedule. The difference between the disclosure of the FDA label and the claim of the 115 patent is the dosing regimen. The FDA label does not disclose an 8 + 6 q3w dosing regimen nor does it disclose that such a dosing regimen will be effective to treat breast cancer.

70. The FDA label also contains some pharmacokinetic data. It explains that the serum half life for trastuzumab is dose dependent (i.e. non-linear). The half life ranges from an average of 1.7 days at a 10mg weekly dose to 12 days at a 500mg weekly dose. The half life on the 4 + 2 q1w regimen is 5.8 days. On the 4 + 2 q1w schedule the serum concentrations reach a steady-state between weeks 16 and 32 with mean trough and peak concentrations of 79 μg/ml and 123 μg/ml.

71. Turning to the fourth ***Pozzoli*** question, I start by considering the reaction of the clinician member of the skilled team to the FDA label. Hospira argues that the clinician would consider that a three weekly dosing schedule for the Herceptin would provide benefits. The simple point is that paclitaxel is being administered three weekly and if the patient can be given the Herceptin on the same three weekly schedule the number of visits to the hospital will be reduced significantly. This would improve convenience from the point of view of the hospital but it would also improve the patient's quality of life.

72. Genentech argues that the clinician would not conceive of a three weekly dosing of Herceptin at all. The first question I have to decide is whether, without hindsight, it would even occur to a clinician to think about it.

73. Professor Barrett-Lee maintained that it would not even occur to a skilled person to conceive of a three weekly dosage of Herceptin. Essentially his reasons were because the focus at that time was entirely on the efficacy of Herceptin. It was a breakthrough drug and at that early stage in its development no one was thinking about such things. On the other hand Professor Leonard thought that a three week schedule would spontaneously occur to a skilled person because it arises from consideration of the FDA label and because improvements in dosing regimens are the kinds of things which clinicians such as the two experts before me propose to pharmaceutical companies in the course of pharmaceutical development and clinical work.

74. Prof Barrett-Lee also focussed on the half life data in the FDA label. The point is that the 5.8 days half life reported for the 4 + 2 q1w regimen supports weekly dosing and is too short to support a three weekly schedule.

75. There was some argument about evidence of what actually happened in practice at the relevant time. It is clear that neither Prof Barrett-Lee nor Prof Leonard actually proposed three weekly dosing although they were working with trastuzumab at the time. Hospira also argued that we did not know whether anyone had proposed three weekly dosing to Roche (since they are not a party to this case and have given no disclosure). Hospira also submitted that we did not know if any such proposal had been made to Genentech but I reject that latter point. If such a proposal had been made at the relevant time, it would have been something for Genentech to disclose and so its absence from the disclosure means one can say no such external proposal was made to Genentech.

76. Genentech also referred to two roughly contemporaneous publications: *Cobleigh et al.* (1999) Journal of Clinical Oncology, Vol.17(9): pg 2639-2648) and *Goldenberg et al* (1999) Clinical Therapeutics Vol 21(2): pg 309-318 which considered trastuzumab but did not suggest three weekly dosing.

77. A further point made by Genentech was that the clinician would or might think that Genentech must have chosen a one weekly regime for trastuzumab with good reason and so they must think a three weekly schedule was infeasible. I do not accept that this would have a major impact on the thinking of the skilled person because they would be aware that changes to dosing regimes were a routine aspect of the development of existing drug treatments.

78. Genentech pointed out that Prof Leonard had accepted it was very difficult for him to put himself back into the relevant position at the relevant date and to consider the matter without hindsight. The witness did accept these points but in my judgment they do not indicate his views were in fact tainted with hindsight.

79. Genentech also relied on two other contemporaneous publications (*Perez E*, The Oncologist 1998; 3:373-389 and *Seidman et al*, J Clin Oncol 1998; 15:3353-3361) which discussed a combination of trastuzumab and paclitaxel on a weekly schedule. Neither publication bears directly on the issue however since they were both focussed on paclitaxel rather than on trastuzumab. Also neither publication was common general knowledge. I do not accept that the idea of once weekly paclitaxel is one which would play a part in the thinking of the skilled clinician in this case.

80. I find that the idea of a three week schedule for Herceptin is something which would naturally occur to a skilled but uninventive clinician. The idea of three weekly dosing arises because the treatment is combined with paclitaxel which is itself three weekly. It would be entirely obvious that a three weekly schedule for Herceptin, if it is safe and efficacious, would deliver immediate and concrete convenience and quality of life benefits. On this point I prefer the opinion of Professor Leonard. I do not regard the secondary evidence as of sufficient cogency or weight to make any material difference to this aspect of the case either way.

81. It is important not to take this too far. A clinician thinking of a possible three weekly dosing schedule for Herceptin knows very well that it would not be approved for clinical use unless it could be demonstrated to be safe and efficacious. The clinician at this stage will not know whether a three weekly dosing schedule for Herceptin would indeed be safe and efficacious but I am satisfied it would occur to skilled clinicians to think about it.

82. The next question is whether even if it occurred to a skilled clinician they would instantly dismiss it and not take the idea any further. I do not accept that. The reason advanced why it might be immediately dismissed by a clinician without discussing the matter with a pharmacokinetics expert was the 5.8 day half-life. Prof Barrett-Lee said that he (and everybody else) was surprised three weekly dosing was proposed by Dr Leyland-Jones after the priority date and the surprise was for that reason. I do not accept that this reflects the approach of a notional skilled person. The notional skilled person will read the FDA label as a whole. That contains a clear disclosure that the half-life of trastuzumab is dose dependent and that at a higher 500mg dose, the half life is 12 days. To the extent that a skilled clinician was prepared to consider the question of half life at all before consulting a pharmacokinetics expert, they would see that the possible longer half life at higher doses meant that one could not simply consider the matter based on the 5.8 day half life. Having thought of three weekly dosing as something desirable, the skilled clinician would either consult the pharmacokinetics expert without considering half life at all or, if they considered half lives at all before doing so, would not focus only on the 5.8 day half life. Three weekly dosing would not be dismissed out of hand. The fact that the clinician would not know at this stage whether such a dosing schedule was safe and efficacious was not a reason to dismiss it from consideration.

83. The skilled clinician would consult a pharmacokinetics expert. The question would be whether a small clinical trial of a three weekly dosing schedule of trastuzumab was warranted.

Pharmacokinetics:

84. I now turn to consider the reaction of the pharmacokinetics expert in the skilled team to the FDA label. The context in which the pharmacokinetics expert will look at the FDA label is that the team is considering whether to test three weekly dosing of Herceptin in a small clinical trial.

85. The possible trial would be one with a small number of patients (about 12) with HER2 positive metastatic disease. Given that trastuzumab was an approved treatment the two arms of the study would consist of patients on a weekly dose in accordance with the FDA label tested against patients on a three weekly dose. Both groups of patients would also receive three weekly paclitaxel.

86. The FDA label contains a section dealing with pharmacokinetics. Its purpose is to support the approved dosing regimen but the data is not only focussed on a 4 + 2 q1w regimen. In addition to the dose dependent half life and serum levels mentioned already the label also gives volume of distribution data (44ml/kg).

87. It was common ground that the pharmacokinetics expert looking at the FDA label would find and consider two further papers which contain information relevant to trastuzumab pharmacokinetics. They are *Baselga et al.* J Clin Oncology, Vol 14, No 3 (March), 1996: pp 737-744) and *Pegram et al.* J Clin Oncology, Vol 16, No 8 (August) 1009: pp2659-2671. In other words Baselga and Pegram are part of the common general knowledge in the sense that they are things which the skilled person would find and consider.

88. From these papers the skilled person would see that the target trough serum concentrations used by Genentech for trastuzumab were 10 μg/ml (Baselga) or 10 - 20 μg/ml (Pegram). This is a key piece of information to use to assess whether a proposed dosing regimen would be effective. It was common ground that 20 μg/ml would be used as the target by a skilled person albeit, as Hospira emphasised, this is a cautious approach given the references to 10 μg/ml.

89. Another point which I find the skilled pharmacokinetics expert would derive from Baselga is that Genentech had used a one-compartment model to estimate serum levels over time.

90. Armed with this information two things would be clear to the skilled pharmacokinetics expert looking at the FDA label. First trastuzumab had been safely administered to patients at higher doses than those used on the 4 + 2 q1w schedule. A weekly 500mg dose had been safely administered. That equates to just over 7mg/kg making common assumptions. Moreover the 500mg dose was associated with a half-life of twelve days.

91. Dr Earhart showed that the information available allowed the skilled pharmacokinetics expert to estimate the serum level at three weeks (21 days) after a

single dose of 500mg trastuzumab based on a 12 day half life. He showed the result in figure 1 to his report:

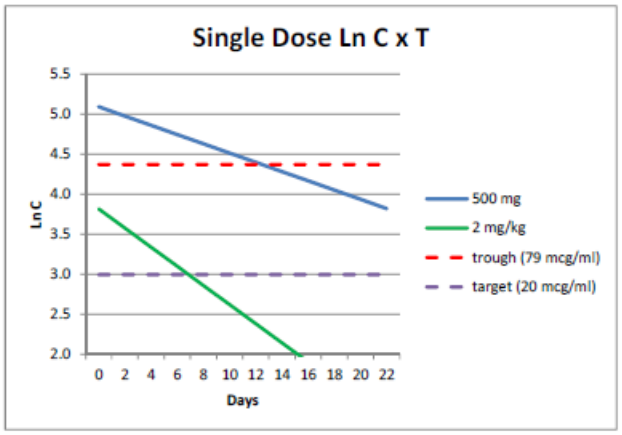

Figure 1

92. The upper sloping line (blue in colour) represents the serum concentration after a 500mg dose with a 12 day half life while the lower sloping line (green) represents the serum concentration after a single 2mg dose with a 5.8 day half life. The upper (red) dashed line represents the 79 µg/ml trough serum concentration reported in the FDA label as achieved by the approved regimen and the lower (purple) dashed line represents the 20 µg/ml target trough serum concentration the skilled person would derive from the common general knowledge.

93. There is no doubt about the mathematics. Based on this calculation the trough serum concentration would be 48 µg/ml on day 21. In other words after three weeks, at the time the next dose would be due on a three weekly schedule, a 500mg dose of trastuzumab would produce more than double the target trough serum concentration. This 500mg dose would be higher than the approved regimen but was itself known to be safe based on the data in the FDA label. Dr Earhart modelled multiple three weekly dosing of 500mg trastuzumab using a one compartment model. The trough serum concentration after 12 weeks is roughly the same as the one achieved on the existing 4 + 2 q1w regimen.

94. At this point it is pertinent to note that it was common ground that the skilled team based on the FDA label and common general knowledge would be prepared to administer a dose of up to 8mg/kg on safety grounds bearing in mind 500mg equates to 7.1 mg/kg.

95. Thus Dr Earhart would advise the clinician that there was no reason not to try three weekly dosing using these sorts of higher doses.

96. Prof Boddy did not agree with this approach and Genentech submitted it did not represent the approach of the skilled person. A key point made by Genentech is that it involves combining linear and non-linear pharmacokinetics at the same time: non-linear because it relies on the higher dose dependent 12 day half life at 500mg but linear because it then applies that 12 day half life across the whole 21 day period. As Genentech point out, “dose dependent” really means “concentration dependent” and so the skilled person would understand that in a non-linear situation the half life itself

will reduce as the concentration drops. In other words in Figure 1 both sloping lines should in fact curve downwards as the concentration drops.

97. A figure of up to 20% error in relation to half lives was repeated in the cross-examination in various contexts. Genentech submitted that Dr Earhart had accepted that there were multiple sources of uncertainty. He did so. There clearly were multiple sources of uncertainty. Genentech also submitted that Dr Earhart accepted there were multiple sources of 20% errors, in other words that Dr Earhart accepted a cumulative error of at least two 20%s (i.e. in effect 40% or more). It was never put in terms to Dr Earhart that there were cumulative 20% errors and that is not how I understood his evidence. In my judgment Dr Earhart accepted that the half life estimates might be out by up to 20% but that was his overall estimate taking into account the various uncertainties. However I do not place much weight on the estimated numerical magnitudes of this error. The important point is that there were multiple sources of uncertainty and that the possible effects of these uncertainties were themselves of uncertain magnitude.

98. Another point which arose related to the way in which the half lives quoted in the FDA label had been derived. Dr Earhart accepted that he did not know but his evidence, which I accept, was that this did not materially affect his conclusions.

99. There are many uncertainties around this kind of modelling in pharmacokinetics. It is nothing more than a model based on a very small amount of data. But Dr Earhart's clear view was that it was sufficient for him to be able to advise the clinician in the team that there was no reason on pharmacokinetic grounds why a trial of three weekly dosing of a dose such as 500mg administered three weekly should not be tried. The expectation would be that the target serum trough concentration would be exceeded probably by a substantial margin and so one would be entitled to expect that the drug would be efficacious. On the other hand considering safety, the serum levels achieved from dosing at 500mg (or up to 8mg/kg) would not be expected to raise any safety concerns over and above what one would normally expect because the FDA label shows that 500mg was a dose which had safely been administered to patients already.

100. In other words trastuzumab was a drug which was well tolerated at the somewhat higher serum levels which would be required in order to allow three-weekly dosing using this simple model.

101. Another criticism was that Dr Earhart's approach uses a one compartment pharmacokinetic model. I do not think there is anything in this criticism for three reasons. First it is clear that in general pharmacokinetics experts are quite prepared to use a simple one compartment model to make assessments of this kind. Second the only model which could be used based on the FDA label was a one compartment model. Indeed it is clear from the information in the FDA label that a one compartment model was used. Third Baselga indicates that Genentech had used a one compartment model for trastuzumab. Accordingly a skilled person would have confidence that a one compartment model was sufficient in order to draw conclusions in relation to the pharmacokinetics of trastuzumab.

102. A further point was that Dr Earhart's simple one compartment model makes predictions which are inconsistent with the FDA label. The point is that it predicts a time to steady state which is shorter than that noted in the FDA label. Genentech

contended that the point was compounded by the fact that Dr Earhart's approach uses parameters derived from modelling (such as half life) and was inconsistent with actual measured data (time to steady state). Like the other points, Dr Earhart accepted the point for what it was but did not accept it would change his overall opinion. On the specific question of the time to steady state he thought that the team would not be unduly concerned about that. He said the real focus would be on trough serum concentration, particularly at the early stages.

103. It was suggested that Dr Earhart's approach overestimates the trough serum concentration to an unspecified and unknowable extent, particularly at the early stages, and so one simply cannot know whether the first trough will be below the 20 μg/ml target. Dr Earhart accepted that there were grounds for thinking that the result was an overestimate at this stage but he also thought were other grounds for thinking it could be an underestimate. He maintained that his approach was a worst case scenario and taking Genentech's points into account he still maintained that he would give a positive response to the clinician.

104. Dr Earhart also pointed out that if the skilled person was concerned about the risk of a lower concentration at the outset, front loading the dose was a routine expedient.

105. A point I have not mentioned so far is the exact dose that would be used on a three weekly study. That takes me to another aspect of Dr Earhart's reasoning. After satisfying himself that three weekly dosing of a 500mg dose would maintain sufficient trough serum concentrations, Dr Earhart sought to consider what the lowest dose below 500mg would be which could be administered to give a 20 μg/ml trough concentration at the end of three weeks. Based on some interpolation of half life figures and other estimates Dr Earhart produced a result of 4.5 mg/kg as a dose which he would advise would be likely to keep the serum trough concentration above 20 μg/ml. For safety he set the lower limit as 5mg/kg.

106. This aspect of Dr Earhart's reasoning was subjected to a sustained attack by Genentech. In the end I was not convinced that the reasoning to support the derivation of the 4.5 mg/kg lower limit was robust but I do not believe it matters for the following reasons.

107. Although the claim specifies 8 mg/kg for the initial dose and 6 mg/kg for the three weekly maintenance dose, there was no evidence that those particular numbers would be inventive once a skilled team had decided to conduct a trial of three weekly dosing based on the data in the FDA label. In other words there is no evidence before me to support the idea that selecting figures of 8 mg/kg for the initial dose and 6 mg/kg for the three weekly dose would be inventive once a pharmacokinetics expert had carried out the first part of Dr Earhart's reasoning. On the basis of that reasoning, a number of combinations of doses are all equally obvious, including the combination of an 8 mg/kg initial dose and 6 mg/kg maintenance dose.

108. Moreover the point is only concerned with seeing what dose below 500mg (7.1 mg/kg) might be feasible. Even of the whole of it was rejected, the pharmacokinetics expert would still be prepared to support 500mg three weekly and it would have been wholly obvious to try to use somewhat lower doses on the three weekly schedule if the schedule was efficacious.

109. Apart from anything else there is no basis in the specification of the 115 patent to support the idea that it would be inventive to select that particular three weekly dosing regime from the other three weekly dosing regimes which it discloses.

110. It is clear that Prof Boddy would not have taken the approach taken by Dr Earhart and based on the FDA label he would not have supported a three weekly clinical trial. Essentially his reason is simple: the available data means that the position is too uncertain.

111. In the end it seems to me that it is important to be clear about the nature of the exercise being carried out. The proposal is to consider running a small trial of a new dosing schedule for an existing drug. The skilled team is being asked to make what Dr Earhart called a go/no go decision. Such decisions are made by real teams. Both Dr Earhart and Prof Boddy had experience of making go/no go decisions about clinical trials but Dr Earhart had more of that experience than Prof Boddy.

112. Dr Earhart's approach seeks to estimate what will happen using the information to hand from the FDA label. Weighing up and balancing the risks and uncertainties associated with such an estimate is the task of the pharmacokinetics expert. It is not simply a matter of mathematics. In carrying out the task they bring their experience to bear.

113. I found Dr Earhart's approach to be compelling and I find that it reflects what a skilled pharmacokinetics expert would do. Therefore I am satisfied that a pharmacokinetics expert would advise the clinician that there was no reason on pharmacokinetic grounds not to conduct a study of three weekly dosing. Choosing 8 mg/kg for the initial dose and 6 mg/kg for the three weekly maintenance dose would be obvious.

The reaction of the clinician

114. The next issue is to consider the reaction of the clinician to the pharmacokinetics expert's response. It was common ground that the clinician would not simply delegate the decision to a pharmacokinetics expert. The clinician would expect the pharmacokinetics to explain their reasoning and justify their conclusions.

115. At this point Genentech submitted that Prof Leonard had not really questioned Dr Earhart's analysis. I do not think that is a fair characterisation of Prof Leonard's position. The point which struck him about Dr Earhart's model was that it was closer to what the FDA label says than Prof Boddy's work which was advanced in the context of sufficiency and will be considered below. I think the fact that Dr Earhart's work is based on the data in the FDA label is something the clinician would and would be entitled to regard as reassuring albeit he or she would also be conscious of the inconsistencies with the label.

116. Prof Barrett-Lee considered Prof Boddy's criticisms and would not have accepted Dr Earhart's approach as a basis on which to move forward and conduct a trial. However as I have explained already, I do not accept that the points raised by Prof Boddy (addressed above) would lead the pharmacokinetics expert to give different advice from that espoused by Dr Earhart.

117. Having thought of the idea of three weekly dosing and approached a pharmacokinetics expert, the clinician would receive the expert's conclusion that there was no reason on pharmacokinetic grounds not to conduct the trial which would be supported by the detailed analysis described by Dr Earhart. The clinician would understand Dr Earhart's reasoning in general terms and would see that it supported three weekly dosing using doses in the relevant range. They would understand that nothing like an unequivocal assurance of success was being given but would have confidence in the reasoning given that the FDA had approved a label which indicated that there was a longer half life at higher doses and that a dose in the range contemplated could safely be administered. I find that the clinician in the team would go ahead and conduct the trial. They would treat a small number of metastatic breast cancer patients with a three weekly dosing regimen of trastuzumab. It would not be inventive to select 8 mg/kg as an initial dose and 6 mg/kg as a maintenance dose.

Obviousness - conclusion

118. I find that claim 1 of the 115 patent would be obvious to the skilled team having regard to the FDA label in the light of the common general knowledge.

Sufficiency

119. Hospira do not challenge the sufficiency of claim 1 of the 115 patent if that claim is obvious. Their case is that if claim 1 is not obvious then the claim is insufficient. Given that I have found claim 1 to be obvious, this alternative argument does not arise. However in deference to the arguments before me I will consider it on the hypothesis that claim 1 is not obvious and involves an inventive step.

120. The law relevant to sufficiency was addressed by the Court of Appeal in ***Regeneron v Genentech*** [2013] RPC 28 at paragraphs 95-103. The scope of the monopoly, as defined in the claims, must correspond to the technical contribution the patentee has made to the art. It must therefore be possible to make a reasonable prediction that the invention will work with substantially everything falling within the scope of the claim. Putting this another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. Therefore although proof that a medicine works for a particular therapeutic purpose is not required, the patent specification must show that the product has an effect on a disease process so as to make the claimed therapeutic effect plausible. The effect must be plausible to a person (or team) skilled in the art reading the patent with their common general knowledge.

121. A question for another day is the extent to which the standard for plausibility differs from the standard for obviousness. Given the way in which the case has been argued and the findings I have made, I do not have to address that question. On the facts of this case the key practical question is the same in both contexts – whether the skilled team would conduct a clinical trial.

122. Genentech's case on sufficiency is that the skilled clinician presented with the 115 patent would consult the pharmacokinetics expert as regards whether the claimed regimen would be likely to have therapeutic efficacy. Genentech also noted that it was common ground the skilled team would have the FDA label and Baselga and Pegram in this context. The pharmacokinetics expert would carry out an analysis of

the kind explained in Prof Boddy's reports. As a result they would have sufficient faith in the results to conduct a clinical trial of an 8 + 6 q3w regimen. Thus the data in the patent plausibly supports the claimed therapeutic use.

123. To consider this matter I need to look at Prof Boddy's modelling in more detail. The Professor starts by recognising that the patent does not contain any pharmacokinetic data from trials using the claimed regimen itself. However Example 2 contains pharmacokinetic data from a 4 + 2 q1w study which a skilled person would realise could be used to potentially simulate the claimed regimen. There was one study but there are two sources of data in Example 2: Table 2 and Figure 3. There was also data available from the FDA label, which was part of the common general knowledge.

124. Next Prof Boddy explained that the pharmacokinetics expert would interrogate the data in the patent and the FDA label to see what they revealed about the pharmacokinetics of Herceptin and the viability of the claimed regimen. The pharmacokinetics expert would know they could see if a one compartment or two compartment model could be fitted to the data and would also consider whether to use the Table 2 and Figure 3 data separately or together. Prof Boddy explored the various combinations of one and two compartment models with separate or combined data.

125. In order to model the pharmacokinetics Prof Boddy needed a time for the infusion of the drug. That comes from the FDA label, which indicates that the infusion starts at 90 minutes and if the first dose is well tolerated, moves to 30 min infusions. In order to perform the one compartment model two parameters (volume of distribution and elimination rate constant) need to be taken or derived from the FDA label.

126. A one compartment model can be fitted satisfactorily to the data in Table 2 albeit that the fit was not particularly good. A half life of 6.2 days is predicted. (It may be noted that this is close to the half life given for the 4 + 2 q1w regime in the FDA label.) A one compartment model can also be fitted to a combination of data from table 2 and Figure 3. The fit is not good although the parameters of the model are estimated with reasonable precision. The estimated half life is 11.2 or 12.1 days depending on whether the model uses a 90 min or 30 min infusion time.

127. A two compartment model can be applied using data in Table 2. The fit is greatly improved as compared to the one compartment model. The elimination half life (the relevant one in a two compartment model) is predicted to be 30.3 or 30.7 days.

128. Finally Prof Boddy applied a two compartment analysis using the combination of Table 2 and Figure 3 data. With a 90 min infusion the fit is good and the coefficients of variation for the inter-compartmental rate constants are acceptable. However with the 30 minute infusion time the coefficients of variation are not acceptable. This may be because the model is struggling to match data from two different patient populations (in Table 2 and Fig 3). The value for the elimination half life for this two compartment model with 90 min infusion is 32 days. No reliable estimate of the elimination half life for the two compartment model with 30 min infusion can be given.

129. Using the pharmacokinetic parameters estimated from the two compartment model run with the combination of Table 2 and Fig 3 with a 90 min infusion time Prof Boddy modelled the 8 + 6 q3w regimen. At steady state the regimen produces trough

concentrations of 48 μg/ml and peaks of 193 μg/ml. His view was the skilled pharmacokinetics expert would regard this simulation as a reasonable prediction.

130. Prof Boddy derived a minimum target trough serum concentration of 10-20 μg/ml from various paragraphs in the patent and noted that the trough serum concentration predicted by his model is about 25 μg/ml after the first dose and rises to about 48 μg/ml at steady state. At this stage in the analysis Prof Boddy noted that Example 6 of the patent reports that a simulation of the claimed regimen predicted that the trough serum concentrations would be 17 μg/ml albeit it is not clear how the patentee arrived at that prediction.

131. Prof Boddy's conclusion about efficacy is that a pharmacokinetics expert could not give the clinician an unequivocal assurance that the claimed regimen would give the same response rate as the standard weekly regimen but the pharmacokinetics expert's opinion would be that there was sufficient reason to believe the claimed regimen would be effective for a clinician in good faith to enrol patients on a trial.

132. The Professor also made clear that the pharmacokinetics expert would consider the possible toxicity risk, given that higher doses are used in the claimed regimen than in the standard weekly regimen. He pointed out that the pharmacokinetics expert would learn from the FDA label that weekly doses of 500mg had been administered with no experience of acute side effects.

133. Thus overall Prof Boddy explained his opinion that the skilled pharmacokinetics expert would advise the clinician that there was a credible basis for the 8 + 6 q3w regimen. Genentech submitted that the clinician would commence a clinical trial of the claimed regimen on this basis and thereby achieve the effect of successfully treating HER2+ breast cancer with this regimen. The patent is sufficient because a person skilled in the art reading the specification in the light of the common general knowledge would carry out the clinical trial. Thus the test for plausibility is satisfied.

134. Hospira put to Prof Boddy that the modelling on which he relies makes predictions which are inconsistent with the FDA label. The two major points are these. First the elimination half life derived and used by Prof Boddy is about 30 days, which is much longer than any of the half lives reported in the label. Second Prof Boddy used an entirely linear approach, whereas the FDA label states that the half life is dose dependent. It was clear from the cross-examination that Prof Boddy was very close to saying that the FDA label was wrong. His view was that there was an unsolved problem with the data in the FDA label and Baselga and that he had effectively solved it.

135. In relation to the inconsistency with data in the FDA label, Genentech emphasised that the purpose of the FDA label was to support the approved regimen and not to provide a full or detailed explanation of the pharmacokinetics of the drug. This is correct but the fact remains that the FDA label is clearly something which is regarded with respect by the members of the skilled team. Inconsistencies with the FDA label are significant.

136. Genentech also emphasised that whereas the inconsistency here relates to model derived parameters (half life), the inconsistency between the FDA label and Dr Earhart's model related to observed data (time to steady state).

137. Genentech submitted that Dr Earhart accepted that Prof Boddy's model was a suitable one to apply to the data in the patent. That is correct but Dr Earhart also felt that his model was reliable. In a passage of cross-examination relied on by Genentech (at T1/144-145) in which Dr Earhart accepted Prof Boddy's approach, he (Dr Earhart) repeatedly made this clear. Dr Earhart never accepted that on the hypothesis that his own approach was invalid, nevertheless Prof Boddy's approach was valid.

138. Hospira submitted that although Prof Boddy's analysis could be performed by a skilled pharmacokinetics expert, if that skilled pharmacokinetics expert would not do what Dr Earhart did based on the FDA label, they would not do what Prof Boddy did based on the patent. Hospira also submitted that even if Prof Boddy's analysis was performed, it would not give sufficient confidence to the skilled team to perform the clinical trial. Again this submission is premised on the assumption that the patent was not obvious. The major reasons Hospira relied on were the following:

    i) Prof Boddy had used a two compartment model whereas it would be clear from the common general knowledge Baslega paper and the way the data was reported in the FDA label that a one compartment model had been applied by Genentech.

    ii) Prof Boddy's two compartment model using the 30 min infusion did not make reliable predictions yet a 30 min infusion is likely to be understood to be the way Herceptin was actually administered based on the FDA label. His predictions were based on the model using the 90 min infusion.

    iii) Prof Boddy's first trough was 25 μg/ml, not far above the 20 μg/ml lower limit, and he did not know the distribution of people around this.

    iv) The simulated steady state trough concentration of 17 μg/ml reported in Example 6 differed significantly from his analysis. Hospira asked rhetorically why the ordinary skilled person would reject a specific concentration based on an analysis by the patentee which if correct is rather a low trough serum concentration albeit above 10 μg/ml and prefer an analysis based on a different model from that of the FDA/Baselga and which gave an unaccountably high half life?

139. The two questions I have to decide are whether Prof Boddy's analysis would be performed at all and if it would be, whether it would give sufficient confidence to the skilled team to support a clinical trial.

140. Clearly Professor Boddy's analysis is one which could be performed by a skilled pharmacokinetics expert but that does not mean it is one which would in fact be undertaken. Both approaches (of Dr Earhart and Prof Boddy) start with incomplete data and both lead to inconsistencies with the FDA label. I recognise that the approaches differ in detail, that much less data is available in the prior art than is available from the patent and that the inconsistencies are not the same. However I am not persuaded that the differences between the approaches are sufficiently significant to allow one to say that if one approach would not be taken, the other would be. In my judgment the essential similarity between the approaches themselves and the similarities between the character of the problems and inconsistencies they give rise to mean that they stand or fall together.

141. The skilled team considering the prior art in the context of inventive step is the same team as the skilled team who would read the patent in the context of sufficiency. The difference is the context in which they are operating. I find that if Dr Earhart's approach would not be undertaken starting from the prior art then neither would Prof Boddy's approach be taken starting from the patent.

142. Moreover it seems to me that even if a skilled pharmacokinetics expert did set out to undertake Prof Boddy's analysis, the problems and inconsistencies it raises are sufficiently significant to mean that a skilled team which was not prepared to go ahead and carry out the clinical trial based on Dr Earhart's analysis of the pharmacokinetics would not be prepared to do so based on Prof Boddy's analysis.

143. In other words in my judgment, if the claim did involve an inventive step (which I have held it does not) then I find that the skilled team would not conduct a clinical trial of the claimed three weekly dosing regimen based on the information in the patent read in the light of the common general knowledge. Accordingly on that hypothesis the patent would not render the claimed effect plausible and the patent would be invalid for insufficiency.

Priority

144. The law of priority was summarised by Kitchin LJ in ***MedImmune Ltd v Novartis Pharmaceuticals UK Ltd*** [2012] EWCA Civ 1234, as follows:

> 151. Section 5(2)(a) of the Patents Act 1977 provides that an invention is entitled to priority if it is supported by matter disclosed in the priority document. By section 130(7) of the Act, section 5 is to be interpreted as having the same effect as the corresponding provisions of Article 87(1) of the European Patent Convention. Article 87(1) says that priority may be derived from an earlier application in respect of the "same invention".
>
> 152. The requirement that the earlier application must be in respect of the same invention was explained by the enlarged Board of Appeal of the EPO in G02/98 Same Invention, [2001] OJ EPO 413; [2002] EPOR 167:
>
> > "The requirement for claiming priority of 'the same invention', referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole."
>
> 153. The approach to be adopted was elaborated by this court in Unilin Beheer v Berry Floor [2004] EWCA (Civ) 1021; [2005] FSR 6 at [48]:
>
> > "48. …….The approach is not formulaic: priority is a question about technical disclosure, explicit or implicit. Is there enough

> in the priority document to give the skilled man essentially the same information as forms the subject of the claim and enables him to work the invention in accordance with that claim.

154. In Abbott Laboratories Ltd v Evysio Medical Devices plc [2008] EWHC 800 (Pat), I added this:

> "228. So the important thing is not the consistory clause or the claims of the priority document but whether the disclosure as a whole is enabling and effectively gives the skilled person what is in the claim whose priority is in question. I would add that it must "give" it directly and unambiguously. It is not sufficient that it may be an obvious development of what is disclosed. "

145. The parties also referred to the recent Court of Appeal decision on priority in ***Hospira UK Ltd v Novartis AG*** [2013] EWCA Civ 1663.

146. I also bear in mind that the international patent system permits priority documents to be filed without claims. That is not a licence to relax the requirements for disclosure described in ***MedImmune*** but it is worth recalling when reading the document. In a specification filed without claims the various features found in the claim of the granted patent are unlikely to be written out together in a neat paragraph.

147. Genentech submitted that the requirement for plausibility which is part of the law of sufficiency was not relevant in the context of priority and referred to a EPO decision T903/05 ***Gemvax*** in which the Technical Board of Appeal rejected the suggestion that to be entitled to priority it was necessary for the priority document to contain data which made it plausible that the claimed invention worked (paragraph 11). Hospira did not agree and submitted that in a case like this one, plausibility was as much part of the test for priority as it was part of the test for sufficiency. The investigation of whether an invention is plausible is part of the requirement for enablement. Hospira argued that enablement was not challenged in ***Gemvax***.

148. Although Hospira are right that enablement was not challenged in ***Gemvax***, the Board regarded plausibility as a separate requirement distinct from enablement. Genentech is right that the Board of Appeal held that plausibility was not a requirement for priority in any event.

149. Although I am reluctant to do so I disagree with the statement in ***Gemvax***. The requirement for priority is that the earlier application must be in respect of the same invention as the patent. The establishment of priority includes a requirement for an enabling disclosure (***Biogen v Medeva*** [1997] RPC at 48-49). In order to make an enabling disclosure of an invention it must be possible to make a reasonable prediction that the invention will work (***Regeneron*** paragraph 100). In the context of an invention which includes the achievement of a therapeutic effect as one of its features, absolute proof is not required but the patentee must show that the therapeutic effect is plausible (***Regeneron*** paragraph 103). It seems to me that this logic applies just as much to priority as it does to sufficiency of disclosure (see also ***Biogen*** on the relationship between priority and sufficiency). The alternative would be a recipe for abuse. A patentee could file a speculative priority application and obtain an earlier

priority date, thereby stealing a march on the competition. I find that in law the test for priority includes the requirement for plausibility in a case like this one.

150. I have found that the patent (if not obvious) would not satisfy the test of plausibility. This finding applies to the priority document as well. If anything there is less in the priority document than in the patent. The major difference is that Example 6 of the patent is not present in the priority document. It would be odd if its absence helped the patentee, since the Example is a proposal to conduct a clinical trial of the 8 + 6 q3w regimen.

151. A separate question for priority is whether the requirements for disclosure are satisfied. That is a question of construction of the priority document.

152. The priority document US 151018 P is very much the same as the specification of the 115 patent save for two major points: the absence of Example 6 and the absence anywhere of the words now making up claim 1 written out together in one place.

153. To support claim 1 Genentech relies on aspects of both the general parts of the priority document and elements of the specific examples.

154. In my judgment reliance on the examples is misplaced. All of them relate and would be understood to relate to HER2+ metastatic breast cancer whereas the claim relates to HER2+ breast cancer in general. The successful clinical results reported in Example 1 are treating metastatic disease and the trials proposed in Example 5 are to be in patients with metastatic disease. The specification at p43 ln 3-6 explains that the appropriate dose of the anti-ErbB2 antibody will depend on the severity and course of the disease. The skilled reader would understand that in the context of breast cancer this distinguishes between different stages of the disease, e.g. early or metastatic. The dose would have to be matched to the stage of the disease. This is clear as a matter of construction but was confirmed by Prof Barrett-Lee in cross-examination. In re-examination Prof Barrett-Lee explained that it would be expected that trastuzumab would be useful to treat breast cancer generally based on the metastatic data. I accept that but I also accept Hospira's submission that that does not assist with the question of what is disclosed by the priority document. The skilled reader would understand that the dosing described in the examples was addressed to metastatic disease and was not being disclosed as a dosing regimen for other stages of breast cancer. At best it would be obvious but the fact something might be obvious is not sufficient to found priority.

155. A further problem with relying on Example 5 is that the example is expressed as a proposal to carry out a test and does not assert that the regimens referred to will work. The passage at p58 ln9 makes clear that Example 5 is to test the dosing regimens. Thus I do not accept that passages in Example 5 can support claim 1.

156. In order to support the claim, the focus must be on the general parts of the priority document. Genentech's best case is based on the Summary of the Invention section. This is a lengthy section with 19 paragraphs and a lot of general wording. It starts at p5 ln7 with a general paragraph about the invention. This paragraph is not limited to trastuzumab, not limited to breast cancer, not limited to particular doses and refers to a range of dosing schedules from four weeks or less to "most preferably" one week or less. Embodiments of the invention start at p6 ln14. The first embodiment described

involves a high initial dose and a weekly dose of 2 mg/kg. The mode of administration is described as intravenous or subcutaneous by infusion or bolus. Further embodiments are set out and at p6 ln 25 the document discloses an 8 + 6 q3w dosing regimen for an anti-HER2 antibody. The relevant sentence does not include an express reference to intravenous administration, however I accept Genentech's submission that in context the reader would understand that the earlier reference to modes of administration also related to this embodiment. The fact that the skilled person would know that intravenous dosing might require different amounts to achieve the same effect from subcutaneous dosing does not matter. The passage discloses both. However the relevant sentence does not include an express reference to trastuzumab nor to breast cancer. I will return to that below.

157. Later in the same section after the list of embodiments is finished the disclosure describes diseases to be treated and at line 28 states that the invention is particularly suitable for the treatment of HER2+ breast or ovarian cancer. Unlike Example 5, this passage is a statement that the treatments are effective to treat breast cancer. Whether the assertion is plausible is a different question, at this stage the important point is that the statement is made.

158. Finally at the end of the Summary of the Invention section the patent refers to the identity of the antibody to be used, and identifies Herceptin.

159. Genentech emphasised that the document has to be read as a whole and submitted that the requirement for disclosure is satisfied.

160. Hospira submitted that the claimed features are not disclosed in the combination claimed. None of the passages in the specification satisfy the strict test that priority requires. They are either too general or too specific and the claim is not entitled to priority.

161. The issue turns on the passage at p6 ln 25, read in the context of the document as a whole. The embodiment described is a dosing regimen (8 + 6q3w). It is clear that read in context the disease to be treated by the dosing regimen in this passage would be understood to be a HER2+ disease. The issue is whether the document as a whole discloses that the dosing regimen treats breast cancer with trastuzumab. I think Genentech are right. The context of the document as a whole is concerned with using antiHER2 antibodies to treat HER2+ diseases. The skilled reader would see that the Statement of Invention section is divided into thematic parts. There is a part dealing with dosing regimens in which the intravenous 8 + 6q3w embodiment is described. There is a part related to diseases in which the treatment of HER2+ breast or ovarian cancer is described and there is a part relating to antiHER2 antibodies in which Herceptin is described. The skilled reader would understand that the preferable antibody to use for all the dosing regimens was trastuzumab and that one of the preferred diseases which it is said will be treated effectively is HER2+ breast cancer.

162. The priority document discloses a number of trastuzumab dosing regimens to treat breast cancer. They include a number of three weekly regimens including the one now claimed. I find that what I will call the pure disclosure requirement for priority is satisfied in any event albeit that the overall requirement for an enabling disclosure which includes plausibility would not be satisfied if the claim was inventive.

The 455 patent

The skilled team

163. The 455 patent is concerned with the purification of trastuzumab for therapeutic use. Since trastuzumab is a protein, the skilled team would include those skilled in the purification of proteins. It would include a bio-process engineer, that is to say a person concerned with larger scale production, and it would include an analytical protein chemist. In practice a team of this kind would receive input from others such as clinician, regulatory experts and perhaps also quality assurance personnel.

Common general knowledge

164. Proteins were known to undergo post-translational modifications. It was also known that native (i.e. unmodified) protein could be degraded by the deamidation of certain residues in the protein chain, such as asparagine. When asparagine degrades in this way the result is a conversion to aspartate. Aspartate has an acidic character as compared to asparagine.

165. Degradation of the native protein has effects which vary in nature and severity depending on where the degradation occurs. Changes in the Complementary Determining Region (CDR) of an antibody can vary the manner in which it binds to a target and may lead to loss of specificity and or avidity. A change in the constant region of the antibody may affect the immune response since the constant region is responsible for interacting with other components of the immune system.

166. Part of the common general knowledge includes knowledge of protein purification techniques. These techniques include the use of chromatography columns. There are different kinds of column and they separate the material in different ways. An ion exchange column exploits charge while size-exclusion chromatography exploits the size of the molecule. Often a purification scheme will employ a number of columns. Each column in such a scheme will be different. This way different differences between the constituents can be exploited to separate them.

167. Commonly when using an ion exchange column the material to be separated is loaded onto the column. The molecules such as proteins bind to the column, the binding being governed by the charge of the protein molecule and the functional groups present on the material in the column. The buffer fluid used in the column will have given properties such as conductivity and pH. These properties are then changed over time. So for example the salt concentration of the buffer may be raised while the pH remains constant. As the properties of the buffer change the interaction between a given molecular species and the column changes. At a given conductivity, a given molecule may no longer stay bound to the column but will come off (“elute”) whereas another different molecule will remain bound to the column. Hopefully different molecular species will elute at different conductivities of buffer and so will flow out of the column at different times. The amount of protein coming off the column is monitored by UV absorbance at a given wavelength. The material which is desired will come off at a particular stage in the process. That material is collected while the rest of what comes off the column is discarded. Thus the purity of the desired material has increased.

168. In all protein purification there is a trade off between purity and yield. Dr Gottschalk explained this with some schematic diagrams in his report. If two proteins X and Y can be separated entirely by a given chromatographic technique then one can recover the desired protein X entirely free of the other protein Y. One can achieve high purity at high yield. In some circumstances it may not be possible to entirely separate the two peaks representing X and Y coming off the column but that does not mean a high purity sample of X cannot be made. If the X and Y peaks overlap then one can obtain a highly pure sample of protein X by only taking a part of the peak which represents X and discarding the part of the X peak which overlaps with the Y peak. Pure X can be obtained but this is at the expense of yield because some of the X material is lost in the section of the X peak overlapping with the Y peak. In this situation the skilled person can choose between high purity and low yield or lower purity (a mixture of X and Y) with higher yield. This technique is called peak cutting. By judicious use of peak cutting one may still obtain a purer sample of X than one started with even if the X peak entirely overlaps with the Y peak, as long as the two are not coincident. The only circumstance in which this peak cutting technique does not work is if the two peaks are exactly and completely superimposed on one another. The actual numerical values of the trade off in a given case will depend on all the circumstances but these principles are basic knowledge to anyone involved with protein purification.

169. In general terms it is harder to separate similar proteins than it is to separate dissimilar proteins. When one has a native protein such as trastuzumab and a variant in which a single amino acid has been deamidated, this means that there are two species which are essentially identical save for the difference caused by the change to a single amino acid. The skilled team would know that these two species would be likely to differ in their charge and therefore in theory be potentially separable by ion exchange chromatography but the skilled team would also know that the difference in charge was very small and thus separation could be difficult.

170. An aspect of the common general knowledge relating to protein purification is the matter of scale. The scale of production depends on the ultimate use of the protein. Lab scale processes were used for initial work for pre-clinical studies. Proteins for therapeutic use were produced on either the IND scale (for early clinical studies) or the BLA scale (for later clinical studies and commercial manufacture). IND processes for the production of monoclonal antibodies for therapeutic use would typically involve bioreactors of about 1000L, chromatography columns of about 1-2L and would yield protein in the high 10s of grams to about 500 grams. BLA processes were larger still and would produce protein in the kilogram range. In practice proteins for therapeutic use were generally made on at least the IND scale.

171. It was common ground that as the scale of the chromatography process increased, the resolution decreased. This was for a number of reasons but the details do not matter.

172. In production the bioprocess engineer will be provided with a purity profile to be achieved. The bioprocess engineer will not have a significant role to play in setting the profile but will ensure the production process achieves the target.

The 455 patent specification

173. The patent relates to protein purification and explains that large-scale, economic purification of proteins is increasingly an important problem for the biotechnology

industry. The focus of the patent is on the purification of trastuzumab. The Summary of the Invention section describes a method of using a cation exchange column to purify trastuzumab. The method uses a special reverse wash step which it states is contrary to usual chromatography practice.

174. Trastuzumab is a recombinant antibody which one would expect would be made in recombinant cell culture. The patent is unspecific about the precise cell culture needed to make the recombinant antibody. Paragraph 103 refers to CHO cells. These are Chinese Hamster Ovary cells and were then a standard kind of cell to use to make recombinant proteins.

175. The patent describes the deamidation of trastuzumab. There is an asparagine at position 30 in the CDR regions of the molecule. This can be referred to as Asn 30. Thus a composition of trastuzumab can contain variants of the trastuzumab molecule in which the asparagine(s) have deamidated to aspartate. These are called acidic variants of trastuzumab.

176. The patent explains (paragraph 12) that the reserve wash step is a "*novel approach to ion exchange chromatography* [and] *is particularly useful in situations where a product molecule must be separated from a very closely related contaminant molecule at full manufacturing scale, where both purity and high recovery of polypeptide product are desired*" and "*accordingly*" the invention provides a composition comprising a mixture of anti-HER2 antibody defined in claim 1. Claim 1 defines a composition of trastuzumab with less than 25% acidic variants. The patent explains that such a composition may be made using the special reverse wash ion exchange method. Nevertheless claim 1 is not limited to compositions made by that method.

177. The detailed parts of the disclosure in the patent and the only example relate to the special ion exchange method. The single example describes taking trastuzumab made in recombinant cell culture through various steps. The material derived from the cell culture fluid is subject to a Protein A affinity chromatography step. This is a well known technique for extracting antibodies and separating them from the other components in a mixture. It does not distinguish between different kinds of antibody since it is based on the interaction between the constant region of the antibody and Protein A.

178. The product from the Protein A column is purified using the special reverse wash ion exchange method and the results are analysed. An example of a trace from an SPSFF ("SulphoPropyl Sepharose Fast Flow") ion chromatography column is given (fig 3):

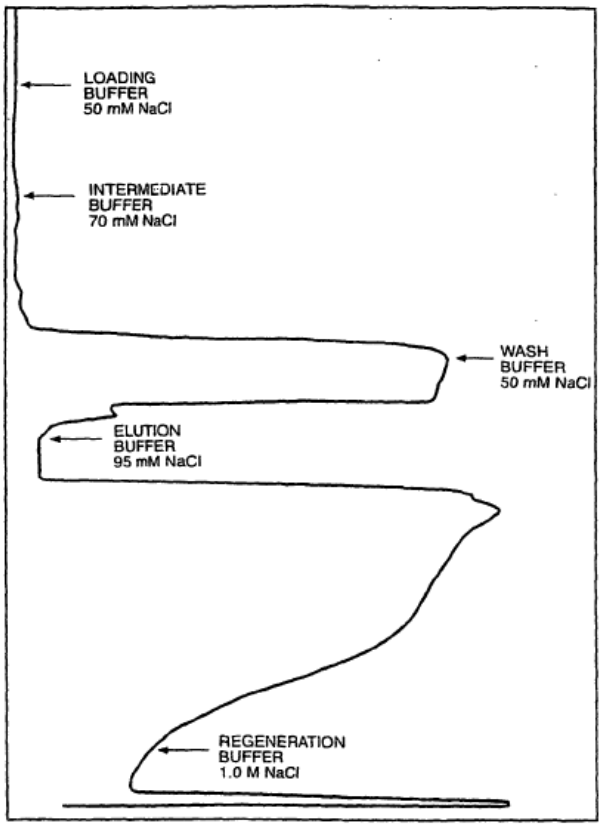

FIG._3

179. This figure is an UV absorbance trace showing what is eluting off from a column over time. Time is running downwards. At the start the composition to be purified is loaded onto the column using a buffer with a salt concentration of 50nM. The proteins, including trastuzumab, the acidic variants and other things, are now bound to the column. Next the salt concentration in the buffer is raised to 70mM. At this point there is still very little coming off the column and nothing to show on the absorbance trace. After a time the line moves to the right which indicates that protein is eluting off the column as the 70mM buffer takes effect. The next step is the reverse wash step. This is marked in fig 3 as the "wash buffer". Unusually, even though the previous change in salt concentration had been an increase, the wash buffer has a lower (50mM) concentration. After a time protein stops eluting from the column and the trace moves back to near the baseline. Then the salt concentration is raised again – to 95mM. This is the elution buffer and it is intended to be at the concentration at which the desired trastuzumab protein will elute. The trace rises again. There is a small shoulder on the leading edge of that peak. Then the trace drops again as all the protein which elutes at this concentration comes off. At the end a regeneration buffer is used with a high salt concentration (1.0M) to wash out any other proteins.

180. The material coming off the column is divided into fractions as it comes off and the fractions are analysed using an analytical chromatography technique. The analytical column is an HPIEX system (High Pressure Ion Exchange) system from Bakerbond. The results of the analysis are in Figure 5 and Table 3 of the patent. These analytical results show that compared to the starting material the reverse wash ion exchange process provides enrichment of the native trastuzumab antibody, no change in the level of certain basic variants and a reduction in the amount of deamidated Asn 30

variants. In other words the method leads to purification of the trastuzumab composition at the expense of the acidic variants. The method can produce a level of acidic variants of 13% or less which represents a 50% reduction from the starting material on the basis that it contains about 25% acidic variants (paragraph 113).

181. An important passage is paragraph 114. It explains the rationale for the reverse wash step in relation to handling acidic variants. It is as follows:

> "An absorbance trace from a cation exchange column run performed as described above is shown in Figure 3. This method resolved a deamidated variant of anti-HER2 antibody that differed only slightly from nondeamidated anti-HER2 antibody. The increase in conductivity from the initial conditions to the intermediate wash began to elute the deamidated anti-HER2 antibody. However, continued washing at this conductivity was found to elute nondeamidated anti-HER2 antibody, resulting in a loss of product. Proceeding directly from the intermediate buffer to the elution buffer was observed to result in either an unacceptably low removal of deamidated anti-HER2 antibody from the product if pooling began early or unacceptably low yields of anti-HER2 antibody product if pooling was delayed until the deamidated anti-HER2 antibody was reduced. It was discovered that by going back to lower conductivity as used initially, the elution of deamidated anti-_HER2 antibody continued, without significant anti-HER2 antibody product elution."

182. The skilled reader would understand that this passage was explaining the familiar trade off in protein purification between purity and yield and the effect of peak cutting. Without the reverse wash step, if the trastuzumab peak was cut too late then the purity with respect to acidic variants would be high but the yield would be too low whereas if the peak was cut to increase yield, then the material would include the acidic variant because it was still coming off the column and so purity would be reduced. It may be noted that paragraph 114 is written in qualitative terms. The patent clearly indicates that the reverse wash step is an improvement and produces yield figures for the use of the reverse wash step (paragraph 116) but no quantitative data are given for the trade off between yield and purity in relation to trastuzumab. The patent describes the yield or purity without the reverse wash as unacceptably low but does not state that trastuzumab with less than 25% acidic variants simply cannot be obtained without the step.

183. A number of points arise from the specification. There was an argument about where the disclosure sat on the range between an analytical scale, pilot scale and full manufacturing scale. Genentech contended for a larger scale and Hospira contended there was no such limitation. It is clear that the focus of the specification is on larger scale operations, although it is also clear that smaller scale purification methods are also mentioned. For what it may be worth I was not convinced Prof Titchener-Hooker was correct that the presence of some very small scale purification methods in a list of techniques in paragraph 81 would be understood as a reference to their use only as analytical techniques. The paragraph is not concerned with analytical methods, read in context and in its own words, it is concerned with purification steps

in order to produce protein. However in the end I am not convinced that this debate has anything to do with the true construction of the claims. Just because the focus of the specification is on larger scale operations that is not a reason to read limitations into the claims which are not there. The claims contain no language which the reader would think was an attempt to limit them to material made on any particular scale.

Claim construction

184. In this case claim 1 of 455 is in this form:

> A composition for therapeutic use comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof,
>
> wherein the amount of the acidic variant(s) is less than about 25%,
>
> and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,
>
> and wherein the anti-HER2 antibody is huMAb4D5-8,
>
> and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb405-8 converted to aspartate,
>
> and a pharmaceutically acceptable carrier.

185. The claim is to a composition with at least three components. There must be trastuzumab (because the anti-HER2 antibody is humMAb405-8), there must be one or more acidic variants and there must be a pharmaceutically acceptable carrier. Nothing turns on what sorts of things a pharmaceutically acceptable carrier must be but there is no doubt the composition must include something of this kind.

186. The acidic variants have to be variants of trastuzumab ("thereof") and have to be predominantly deamidated variants at the Asn 30 position.

187. The amount of the acidic variant(s) must be less than about 25%, which it is common ground means less that 24.5%.

188. As granted claim 1 was not limited to a composition "for therapeutic use" nor to one which comprised "a pharmaceutically acceptable carrier". There was a debate about the impact of the inclusion of these words in claim 1. Genentech contended that the words meant that the composition had to be suitable for therapeutic use. I agree. The debate was about the implications of that conclusion. At times it seemed as though Genentech argued that it meant the composition had to be one which had been made on a full manufacturing scale. I would not accept that. The claim is a claim to a product and would be understood as including any product with the relevant characteristics, however that product was made. If the patentee had wanted to make a claim relating to the process by which the product was made (including factors such as scale), it could readily have done so. The skilled reader can see that no such claim

has been made. For what it is worth there is a Divisional application related to the production method but that is irrelevant.

189. Genentech submitted that the limitation to a composition suitable for therapeutic use mean that the composition had to have a therapeutic effect and submitted that there was therefore a lower limit on the amount of trastuzumab in the composition below which the claim was not satisfied. The forensic purpose of this argument was to exclude from the claim compositions of trastuzumab which might be made during analytical work. Such compositions would contain only tiny (μg) amounts of the drug but otherwise satisfy the claim. Genentech avoided being drawn as to the lower limit of the amount but during the trial and after being pressed by Hospira submitted (and admitted) that a single 140mg dose of trastuzumab was therapeutically effective.

190. I am far from convinced this argument has been thought through. For example it seems to create opportunities for evasion about which a skilled reader would be doubtful. Could one avoid the claim by simply having two 70 mg vials (or ten 14 mg vials etc.) and infusing the two contents one after the other? The idea of a 140mg dose no doubt comes from taking the lower 2 mg/kg maintenance dose in the 4 + 2 q1w regimen (see the 115 patent above) and using the common 70kg assumption for the weight of an adult human. However the calculation assumes the therapeutic effect is to treat breast cancer in adult humans but the claim is not limited to that disease in that patient population. For all we know a much smaller dose is effective to treat other cancers in children. If so then the limit of the claim will be lower. Is it right to work on the basis that a single dose is effective at all? What if the dosing was conducted daily rather than weekly - in that case a single dose would be much less than 140mg. None of this was explored in evidence.

191. I strongly suspect the boundary of the claim is a lot lower than contended for by Genentech. Nevertheless I do accept that the skilled reader would not regard a material in μg amounts such as came off an analytical column, even if in fact the material was intact and was in a pharmaceutically acceptable carrier, as a composition of trastuzumab suitable for therapeutic use. It is not.

192. The other claims of the 455 patent which are relevant are:

> 2. The composition of claim 1, wherein the amount of the acidic variant(s) is less than about 20%.
>
> 3. The composition of claim 2, wherein the amount of the acidic variant(s) is less than about 13%.
>
> 4. The composition of claim 2, wherein the amount of the acidic variant(s) is in the range of about 1 to 18%.

193. No issues of construction arise in relation to these claims. Each claim sets a different limit on the concentration of acidic variants of trastuzumab of less than about 25% of claim 1; 20% (claim 2) and 13% (claim 3). Claim 4 requires a range of from 1% - 18%.

Novelty

194. To deprive a claim of novelty the prior art must make an enabling disclosure of the invention. The twin requirements of disclosure and of enablement were discussed by Lord Hoffmann in *Synthon* [2006] RPC 10.

Andya

195. Andya is a patent application which describes pharmaceutical formulations of antibody huMAb4D5-8 (i.e. trastuzumab). The trastuzumab is to be used to treat diseases such as breast cancer.

196. The formulations are made by reconstituting lyophilised (freeze dried) trastuzumab protein. The application discloses the results of stability tests carried out on reconstituted trastuzumab formulations. The formulations are stable.

197. Andya described the ways in which trastuzumab degrades in the liquid state and mentions two kinds of degradation. One is deamidation of the Asn30 amino acid of the light chain in the antibody. It is described as a major degradation route. Analysis of the trastuzumab deamidation is carried out by cation exchange chromatography on a Bakerbond HPLC system.

198. The stability test results are depicted in figures 5 to 8. For example figure 5 is:

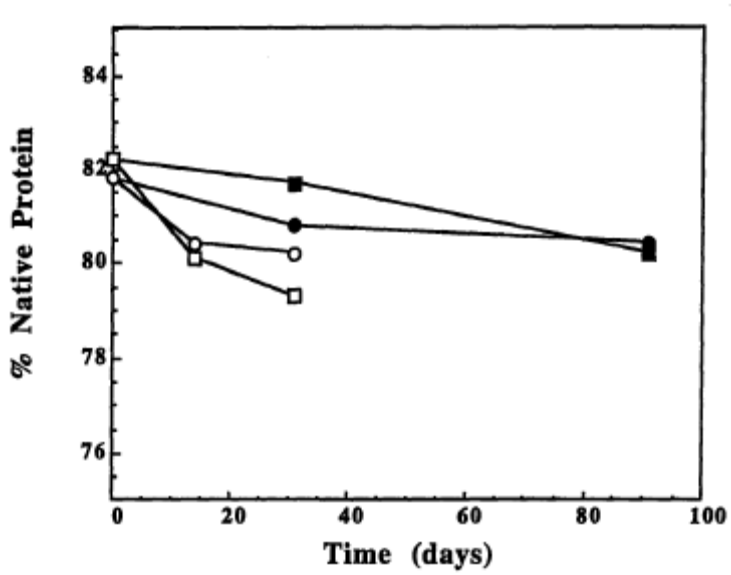

FIG. 5

199. This figure shows the results of tests on trastuzumab lyophilized at a concentration of 25mg/ml in a particular solution. A vial of lyophilised trastuzumab consisted of about 450mg protein. The samples were reconstituted in BWFI (Bacteriostatic Water For Injection). The squares and circles represent samples made up in different ways. The samples are stored at 5°C (solid symbols) or 25°C (open symbols) and degradation of the protein is monitored over time.

200. Figure 5 shows that at the start of the tests 82% of the protein in the reconstituted formulation was native trastuzumab. Thus the maximum level of acidic variants in that composition was 18%.

201. Andya states that the formulations described provide an acceptable rate of degradation under refrigerated storage conditions.

The disclosure of Andya compared to claim 1

202. The lyophilised vials of trastuzumab disclosed by Andya are compositions of trastuzumab for therapeutic use. The amount of trastuzumab in the individual lyophilised vial is 450mg. The lyophilised compositions include pharmaceutically acceptable carriers. The composition has no more than 18% acidic variants but Genentech pointed out that Andya does not state the composition of that 18%. It is likely to include both acidic and basic variants. Andya does not state expressly that the acidic variants are predominantly deamidated Asn30 protein. Genentech accepted for the purposes of this action that the acidic variants would satisfy the claimed requirements relating to being predominantly deamidated asparagine with the Asn 30 converted to aspartate.

203. Thus Andya discloses a composition within claim 1. The real issue is whether that is an enabling disclosure.

204. Andya provides a clear teaching to the skilled person to make a formulation of the kind described. The skilled person has a clear target to aim at. It is a composition of trastuzumab with 82% native protein.

205. A recombinant cell line would have to be created, probably in CHO cells, which produced trastuzumab on a substantial scale. To do this would be a very substantial amount of work but there is no evidence it presented undue difficulties. The material produced by the cell culture would have to be purified. The skilled team would select suitable purification methods in order to produce the quantities of trastuzumab needed to create the formulations.

206. Prof Titchener-Hooker was asked about this in cross-examination. His view was that the skilled team could make a trastuzumab composition with 18% or fewer acidic variants on gram scales. The significance of gram scales is that that would be enough material to make the formulations described in Andya. That view has two important qualifications. First it was expressed on an assumption that the reader of Andya would understand that the analytical results showed that it was possible to resolve the native protein from the acidic variants. Second Prof Titchener-Hooker made clear that the composition which would be produced could well have a different balance of acidic to basic variants in the 18% which was not native trastuzumab as compared to the composition actually tested in Andya.

207. On the first point, Dr Gottschalk's evidence explained that the analytical results in Andya showed that the native trastuzumab protein had been separated from the variants using a Bakerbond cation exchange CSX column. So the 82% figure reported in Figure 5 was the peak area of protein relative to the total peak area measured by chromatography. This might have been a matter for Prof Zhuo to consider since he was an analytical protein chemist but he did not give evidence. I find that the assumption put to Prof Titchener-Hooker by counsel was justified. The skilled reader of Andya would understand that cation exchange chromatography could separate native trastuzumab from the variants. This would be operating on an analytical scale.

208. I accept Prof Titchener-Hooker's second point. Andya does not report an analysis of the mix of particular acidic and basic variants in the balance of the trastuzumab compositions apart from the native protein. There is no guarantee that a composition of trastuzumab made by a skilled team following Andya would have the same mix as whatever the mix was in the substance analysed in Andya. However there is no suggestion in the evidence that it is likely that such a composition, with 82% native trastuzumab, would fall outside the claims because, for example, the remaining 18% contained only acidic variants of the wrong kind. It is clear as a matter of fact that the deamidation of Asn30 is an important degradation pathway of trastuzumab. It is more likely than not that a composition of 82% trastuzumab made this way would satisfy the relevant elements of claim 1.

209. I turn to address the other lesser points which were taken against the allegation of lack of novelty by Andya.

210. First, it is correct that Prof Titchener-Hooker was set the task of making 140mg of trastuzumab rather than being referred to the reference to 450mg in the document. This is not important given that Prof Titchener-Hooker was focussing here on making gram scale quantities. That would be enough for 140mg vials or 450mg vials.

211. Second, it is true that Hospira did not produce experimental data to back up their case that separating trastuzumab from the variants without the reverse wash step could be done or could be done at a certain yield. If Prof Titchener-Hooker's evidence had been different this might have been a point of more significance. As it is I do not regard this as a strong point.

212. Third, it is true that another aspect of the questioning involved Prof Titchener-Hooker considering the Herculean task of making 140mg of trastuzumab by repeatedly carrying out the analytical scale separation of trastuzumab. The analytical columns deal in µg quantities. Conceivably the multiple runs might involve hundreds of runs of an analytical column. Genentech pointed out that the analytical column result reported in Andya was operating at 40° C and might lead to degradation of the protein. Multiple runs might also lead to degradation of the column. Prof Titchener-Hooker considered repeated runs of an analytical column in re-examination. However I do not have to delve into the debate about multiple runs of an analytical chromatography column because Prof Titchener-Hooker gave a clear answer when focussed on the gram scale.

213. Fourth, one of the assumptions put to Prof Titchener-Hooker was that yield was immaterial. That was an important element in Prof Titchener-Hooker's evidence. He said "*Because you have told me I can sacrifice yield all the way through, I think you will be successful*". In my judgment this point does not assist Genentech at least when considering novelty. The purpose of the law of novelty is to prevent the state of the art being patented again. A composition of 82% trastuzumab is described in Andya. The fact that it could be rather tedious to make gram quantities of that composition does not matter unless the hurdles are so severe as to place an undue burden on the skilled team seeking to carry out its teaching such that the document is not enabling. I do not accept the burden would be undue.

214. Fifth, a point was taken that the questioning focussed on a MonoS chromatography column and the FPLC technique. I do not accept that anything turns on this. Prof

Titchener-Hooker understood they were being put forward as examples. His view was not expressed on the basis that success depended on the particular kind of column or method the skilled team would use.

215. Sixth, a rhetorical question was asked: why focus on the 82% result in Andya and not for example the 78% figure in Example 6? The answer is that for novelty, it is irrelevant although the issue is capable at least in principle of being important in relation to obviousness.

216. Seventh, similarly the question of motivation was mentioned. Again that is a matter of inventive step rather than novelty. The question is whether there is an enabling disclosure of the 82% composition referred to in Andya.

217. In my judgment the case for anticipation by Andya is proved. Andya makes an enabling disclosure of an 82% composition of trastuzumab. The composition enabled by Andya will comprise acidic variants of trastuzumab of the relevant kind but will contain no more than 18% acidic variants. Thus claims 1, 2 and 4 of the 455 patent lack novelty.

Obviousness

218. There are four obviousness attacks: Waterside, Andya, common general knowledge in general and common general knowledge based on Protein A. The issues of claim construction and common general knowledge have been considered already. There is no need to consider an inventive concept separately from the terms of the claims, properly construed.

Waterside

219. The Waterside prior art consists of slides presented at a conference by Reed Harris from the Analytical Chemistry Department of Genentech. The slides relate to analysis of trastuzumab in the context of Phase III clinical trials of that agent for breast cancer. The fact that trastuzumab is being manufactured in CHO cells at a full production scale (12,000L) is also mentioned.

220. Slide 4 presents three analytical chromatograms of trastuzumab on a MonoS cation exchange column. The presence of a variant deamidated at Asn 30 is described. The slides would be understood to show that native trastuzumab and the deamidated Asn 30 variant can be separated at an analytical scale on a MonoS system.

221. Slide 9 (p7 of the exhibit) is entitled Deamidation of Light Chain Asn-30. It is as follows:

• $p185^{HER2}$ binding assay: peak 1 82% specific activity
peak 3 100% specific activity
• 25% of pool has deamidated Asn-30:
25% @ 82% specific activity
75% @ 100% specific activity
pool @ 95% specific activity
• Decided not to remove the deamidated material.
• Deamidation increases when HCCF is held even at 2-8C
so harvests are taken straight through to purification

222. Peak 1 is the deamidated Asn 30 acidic variant. Peak 3 is native trastuzumab. The slide is explaining that the deamidated Asn30 variant has 82% of the specific activity (activity per unit mass) of native trastuzumab in an assay. There was a debate about the precise meaning of the second bullet point. I find that it would be understood to mean that if a pool of nothing more than 75% pure trastuzumab and 25% pure deamidated Asn 30 acidic variant was considered, that pool would have 95% specific activity (because arithmetically 95 = 25x82 + 75x100). The slide would be understood as recording that Genentech decided not to remove the deamidated variant (3^{rd} bullet) but also decided to harvest the cell culture fluid (HCCF) straight away in order to minimise deamidation.

223. Thus as compared to the claims of the 455 patent, Waterside discloses the idea of a trastuzumab composition for therapeutic use. The skilled person might infer that Genentech believes its product is likely to have a level of deamidated Asn30 variant of 25% but the slides do not state that explicitly and do not address the levels of any other acidic variants.

224. Stated simply the difference between Waterside and the claims is that no level of acidic variants is stated in Waterside at all. At best the level might be inferred to be 25% in which case the composition is outside the claim.

225. The skilled team reading Waterside would be motivated to make a composition of trastuzumab for therapy. They would believe that it was possible to make the antibody in CHO cells at the 12,000 litre scale. They would expect to be able to set up a CHO cell production system. It would be a lot of work but would not involve an inventive step.

226. The team would know that the protein had to be purified. The methods which would be selected would include at least two steps: Protein A affinity chromatography would be used to separate antibodies from other material in the cell culture medium and conventional ion exchange chromatography would be used to purify the material produced from the Protein A chromatography. The ion exchange chromatography would be conventional in the sense that it would not use the special reverse washing step disclosed in the 455 patent. None of this involves an inventive step either.

227. At this point it is convenient to consider the question of a product specification. In considering the level of acidic variants in trastuzumab, the skilled team presented with Waterside would:

i) See that the deamidated Asn30 variant existed and had a lower specific activity than native trastuzumab;

ii) See that Genentech had decided not to remove the deamidated Asn30 variant.

228. I find that the level of acidic variants in the composition to be made would be specified by the skilled team. The specification would be the province of clinical, regulatory and analytical members of the team rather than the bioprocess engineer. The engineer would only play a role if the specification seemed to him to be unachievable. However I find that the fact that the charge difference between trastuzumab and the Asn 30 variant is very small would not be enough for a skilled bioprocess engineer, a priori, to think that a specification of levels of acidic variants ranging from less than 13% to more than 25% was unachievable to such an extent that they would question such a purity profile.

229. Genentech made the point that since Waterside explains that Genentech decided not to remove the deamidated material, there would be no reason for the skilled team to set a specification which required a reduction in the level of acidic variants. That is a reasonable point in Genentech's favour.

230. Genentech also pointed to later materials highlighting the infancy of the business of making therapeutic monoclonal antibodies on a manufacturing scale at the relevant date and the fact that variants in general are not necessarily regarded as components which must be removed. These are also reasonable points in Genentech's favour.

231. However balanced against the factors which might suggest that the skilled team would not seek a low level of acidic variants is the point that the Asn 30 variant was located in the CDR region of the antibody. It affects antibody binding. Dr Gottschalk's evidence was that the skilled team would be concerned about this. He used the term "red flag". It was put to him that the results in Waterside showed that Asn-30 variant had 82% specific activity and so the skilled team would not be unduly concerned but he maintained that it was a "red flag".

232. Furthermore even if the only consequence of a composition containing appreciable amounts of Asn 30 variant is a reduction in specific activity overall, that in itself is not desirable since such a composition would need to be administered in higher amounts than would be achieved with pure trastuzumab, risking side effects.

233. Despite the points in Genentech's favour, in my judgment the nature and location of the Asn 30 variant means that a skilled team working without hindsight at the relevant time would seek to minimise the level of acidic variants. It would not be inventive to specify a level of acidic variants which was at any level within the range of numbers considered in this case. Assuming (see the Protein A argument below) that the level of acidic variants in the material after Protein A affinity chromatography was higher than 25%, it would not be inventive to decide to reduce the concentration of acidic variants below that level. Setting as a target a concentration lower than 25%, lower than 18% or lower than 13% would be a routine matter for a skilled team.

234. The next element to consider is the purification itself. The team would understand from Waterside that native trastuzumab and the deamidated Asn30 variant could be separated, effectively to baseline, on a MonoS column operating at an analytical scale. They would not know the conditions which had been used but this information gives the skilled team two key pieces of information. The first is the fact that the Asn 30 variant can be separated by ion exchange chromatography at all. Thus the site of the

variation must be at or near the surface of the molecule and not buried deep within it where it might have been inaccessible to use as a basis for separation. Second they would know the kind of ion exchange chemistry which allowed for separation. MonoS is a cation exchange system using a sulfonate ligand and the skilled team would know that. They would know as a matter of common general knowledge that prepacked MonoS columns were available on a range of scales. MonoS columns are all relatively small scale but they include preparative scale columns, that is to say columns in which the protein is being purified to be prepared for use and not simply being analysed. They would also know that for even larger scales, such as moving to IND and BLA scales, the manufacturer made available columns with the same chemistry as MonoS in order to facilitate scale up.

235. The skilled team would not expect to maintain the same resolution available at analytical or smaller preparative scales as the scale of the purification method increased and would also know that as scale increased, the balance between purity and yield would shift.

236. Prof Titchener-Hooker's evidence was that the answer to the question of whether trastuzumab could be prepared with a minimised level of acidic variants on larger scales depended on economics. His view was that separating the acidic variant from trastuzumab was not a route the skilled team would pursue because the team would find it difficult to be confident on the end result at a realistic investment of time, cost and resources.

237. Dr Gottschalk accepted there would be a loss of resolution at higher scales and accepted many of the detailed reasons why that was so which were put to him. However he maintained that the skilled team would expect to be able to undertake routine optimisation of the chromatography conditions to achieve separation.

238. It seems to me that Prof Titchener-Hooker's evidence, while it will reflect the views of real bioprocess engineers, does not reflect the position of the notional skilled team in this case. Commercial factors like cost and the resources needed to carry something out are not necessarily irrelevant when considering obviousness but their role needs to be kept in its place. If a step is technically obvious, it should not be the subject of a patent even if commercially it may not be a sensible thing to do.

239. I also bear in mind that the 455 patent states that without the reverse washing step the yield of trastuzumab was unacceptably low if the peak was cut so that the level of acidic variants was reduced. However this does not mean that one simply could not make a given composition of trastuzumab at all nor was there any evidence that that was the case. As I understood Prof Titchener-Hooker's evidence, if he had thought that as a technical matter the making of a composition of trastuzumab to a given specification of acidic variants was simply not possible on a large scale without the reverse wash step, he would have said so and would have answered counsel's questions differently.

240. The skilled team would expect to be able to produce, on a full commercial scale, a composition comprising native trastuzumab protein. There is no doubt about that. I find that the skilled team would also expect that they could produce such a composition to any specified level of acidic variants by trading off between yield and purity. In other words the skilled team would expect that if a higher purity of native

trastuzumab vs the acidic variants was required, it could be produced by sacrificing yield. Conversely a higher yield could be produced albeit the material would have a higher level of acidic variants. A composition of trastuzumab to any specified level of acidic variants is technically obvious. There is no actual or perceived technical barrier to its production.

241. It may be that to make trastuzumab at a full 12,000 litre scale one would have to tolerate a yield much lower than the typical overall 70% yield Prof Titchener-Hooker explained was the norm in industry but that does not make the composition itself inventive. An improvement in yield might very well provide the basis for an inventive step in the context of a new method of carrying out an industrial process but it seems to me that it does not confer inventiveness on a product which is defined in such a way that it can be made by any process, whatever the yield.

242. This reasoning applies to all the relevant claims of the 455 patent i.e. claims 1, 2, 3 and 4. Accordingly I find that all the claims of the 455 patent lack an inventive step over Waterside.

Andya - obviousness

243. The only claim Andya does not anticipate is claim 3. I do not see how Andya can add anything to most of the argument over Waterside in relation to that claim. If anything it is a more difficult case. Claim 3 requires less than about 13% acidic variants. For that to be obvious the skilled team would have to want to make a composition of 87% native trastuzumab but there is nothing in Andya to lead a skilled team to seek to make such a composition. Andya discloses compositions in the range 78% to 82% native trastuzumab. That provides a clear target for the skilled team. It is not clear to me that there is any reason over Andya to seek to make a purer composition than that. They could make it if they wanted to but I am not convinced the motivation to do so exists over Andya. I would hold that claim 3 was not obvious over Andya.

244. Since I have found Andya to anticipate claims 1, 2 and 4, I will not conduct a laborious analysis of inventive step of those claims over Andya. In case this matter goes further I will mention motivation, yield and scale.

245. As regards motivation I think the skilled team reading Andya would be highly motivated to set about making an 82% native trastuzumab composition for therapeutic use. A number of the examples have formulations consisting of 82% trastuzumab. The skilled team would believe that Genentech clearly regarded 82% purity as achievable without undue effort. There is nothing in Andya to suggest it is problematic to make such a composition.

246. As regards yield, I have dealt with that above. There is nothing about starting from Andya which makes a difference to the argument about the balance between yield and purity as the scale of production increases.

247. As regards scale, Andya describes 450mg vials of trastuzumab. It would be obvious to aim to make trastuzumab on a gram scale in order to produce such vials.

Obviousness over common general knowledge in general

248. Given the finding over Waterside, this approach does not add anything and I will not address it further.

Obviousness over common general knowledge based on Protein A

249. The 455 patent describes the purification of a trastuzumab composition which had been derived from CHO cells and purified by Protein A affinity chromatography. After the Protein A step the material is subjected to the reverse wash on an ion exchange column. The patent specification states that the material loaded onto the column contained about 25% acidic variants. Analysis of that material is shown in figure 5. Hospira argue that in fact when the data is considered carefully, the level of acidic variants in the LOAD sample was less than 25%. Hospira contend it was 23.5% and that Genentech's own approach to the figures, analysed correctly, sets the level at 24.2%. Thus Hospira reasons that the material produced after the Protein A column already had the level of acidic variants called for by claim 1. Accordingly even if the ion exchange chromatography step had no effect vis a vis the level of acidic variants, the product produced would be a product within claim 1. Since it was obvious to use Protein A and ion exchange chromatography together to purify trastuzumab based on common general knowledge alone, claim 1 is obvious over common general knowledge alone.

250. This Protein A argument has two important aspects. First there is a major debate, based on the data in the patent, about what the level of acidic variants in the LOAD sample actually is. This involves Dr Gottschalk's evidence and the effect of his cross-examination. Second there is a question about what the level of acidic variants would be in material harvested from cell culture.

251. Dr Gottschalk derived the level of acidic variants in the LOAD sample in the following way. Figure 5 of the patent is as follows:

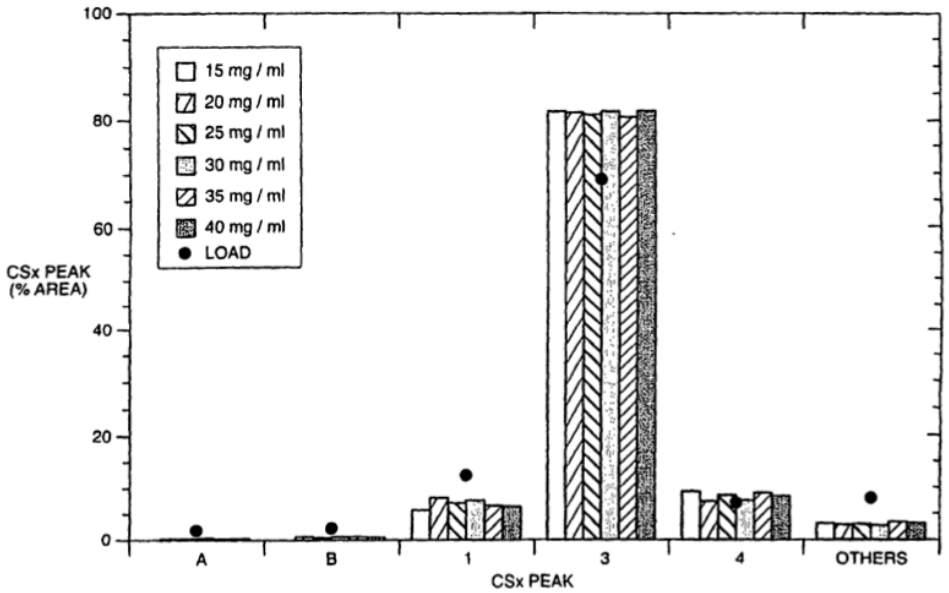

FIG._5

252. The block represents the results of the chromatography at various loading levels and the black circles represent the LOAD sample. Peak 3 is native trastuzumab. Peaks A, B and 1 are acidic variants. Peak 4 is basic variants. The "Others" consists of a

mixture of acidic and basic variants. Measuring the heights of the peaks on the figure Dr Gottschalk arrived at 68.3% for LOAD peak 3 and 6.4% for LOAD peak 4. If one knew what the proportion of acidic variants was in the "Others", one could work out what the level of acidic variants was in the LOAD sample.

253. Based on information from chromatograms disclosed by Genentech which came from the actual laboratory work undertaken by Genentech scientists which was reported in Figure 5, Dr Gottschalk worked out that a conservative estimate of the content of basic variants in the "Others" expressed as an overall percentage was 1.8%. I accept his calculations based on the chromatograms and I accept that they are conservative.

254. Thus Hospira contend one can say that the level of acidic variants in the LOAD sample was 23.5% (i.e. 100% - (68.3% + 6.4% +1.8%)).

255. Dr Gottschalk had also performed a different calculation taking a figure for the "Others" from Figure 5. This was in effect assuming that all the "Others" were acidic variants and operated as a kind of worst case calculation. It was the subject of cross-examination and I am not satisfied that Dr Gottschalk's figure for the height of the "Others" peak is accurate enough to make the finding Hospira contended for in that context. However it does not matter because given the disclosure from Genentech there is no need to decide what the height of the "Others" peak is.

256. Genentech also put to Dr Gottschalk that his figures taken from Figure 5 could only be expressed to the nearest whole percentage. Dr Gottschalk did not really disagree with that in general terms although there was a disagreement in detail about the height of the "Others" peak. He accepted that expressed to the nearest whole percentage the height of the peak 3 represented 68% and peak 4 represented 6%. Using those numbers in the calculation gives the level of acidic variants in the LOAD sample as 24.2% (i.e. 100% - (68% + 6% +1.8%)). Hospira submitted it was still appropriate to use the 1.8% figure derived from consideration of the Genentech chromatograms. Whether that is right or not does not matter because using a rounded figure of 2% (instead of 1.8%) works in Hospira's favour.

257. I find that the level of acidic variants in the LOAD sample described in the patent was no more than 24.2%. It was therefore within claim 1. Thus even if the ion exchange chromatography step in the patent had made no difference to the level of acidic variants in the sample loaded onto the column, the result would have been a composition of trastuzumab with no more than 24.2% acidic variants.

258. This leads to the second point. Hospira has established to my satisfaction that the material in the LOAD sample of the patent had no more than 24.2% acidic variants in it. Since Protein A affinity chromatography will not distinguish between different antibodies, it is a solid inference to draw that the material prior to the Protein A affinity step had no more than 24.2% acidic variants expressed as a percentage of antibody overall. In other words the material from Genentech's harvested CHO cell culture fluid (or at least after any processing Genentech use after cell culture) will have had this level of acidic variants too. So Hospira argues that since it would have been wholly obvious to make trastuzumab in CHO cells, harvest the culture fluid and purify it with Protein A and ion exchange, the result would have been within claim 1 even if the skilled team made no effort to reduce the level of acidic variants.

259. Genentech contended that Hospira had simply failed to prove a key element in this case. Hospira had not proved what the level of acidic variants would in fact be if a skilled team set up their own CHO cell culture and harvested the result. The fact that the level of acidic variants in the LOAD sample in the patent might be below 25% does not mean that that would be the level of acidic variants in another context. Genentech submitted that Dr Gottschalk agreed that cell line and cell culture conditions could affect the level of acidic variants. A different cell line and different conditions could lead to higher levels of acidic variants. As Genentech pointed out, in the claim for a declaration of non-infringement it appears that Hospira have purified trastuzumab with levels of acidic variants from 25% up to 29% so it cannot be inevitable that any recombinant trastuzumab cell culture fluid will have less than 25% acidic variants.

260. Hospira's response to this was to argue that:

i) The point was kept back until the middle of the cross examination. It was not actively supported by any Genentech witness and was not noticeable in Genentech's opening written skeleton. It seems to be an afterthought of the lawyers.

ii) It should be within Genentech's knowledge as to whether the particular conditions it used did have a material effect on the level of charge variants but it has adduced no evidence on this point.

iii) There is no reason to suppose that Genentech's cell line or culture conditions were in any way unusual and no suggested reason was put to Dr Gottschalk during cross examination.

iv) There is no reason to suppose that, if cell line and culture conditions do affect acidic variant levels, Genentech's parameters are at the low end of resulting acidic variants. It would seem extremely likely that other routine cell lines or culture conditions would produce acidic variant levels still lower than Genentech did. That being so, the ordinary skilled team simply using protein A purification for its known purpose with such routine cell line and conditions would produce material within the claims and the Patent is obvious.

v) If the skilled team, without knowledge of Genentech's proprietary information, would generate trastuzumab with a materially different acidic variant profile, this raises the prospect that the skilled team would not be able to reproduce Example 1 of the Patent.

261. I agree that there is no reason to suppose that Genentech's cell line or culture conditions were unusual nor is there any reason to suppose that Genentech's parameters are at the low end of resulting acidic variants. However neither point makes up for the lack of proper evidence on this issue. The point of the Protein A argument is to contend that even if the skilled team was not focussing on acidic variants, they would make a product within claim 1 in effect by accident or inevitably. The evidence simply does not make that good. It is certainly not inevitable.

262. I do not accept point (v) because the patent provides a method of making the claimed composition – using the reverse wash step.

263. As for points (i) and (ii), in some ways Genentech ran a risk by not adducing positive evidence on the point but in the end the burden of proving the case on this was on Hospira. I do not know why Hospira assumed that proving what the composition of the LOAD sample in the patent was would necessarily be enough for their obviousness attack. It ought to have been apparent to them that there was another step in the reasoning to take that result and apply it more generally. The point is open to Genentech to take and for that reason and that reason alone, the Protein A argument fails.

Declaration of non-infringement

264. Hospira sought a declaration of non-infringement in relation to five formulations of trastuzumab (A to E). The levels of acidic variants in those formulations is 25%, 26%, 27%, 28% and 29%. Plainly none of those formulations could infringe any of the claims of the 455 patent since the limit of the claim is 24.5%.

265. At one stage in these proceedings Genentech submitted that the declaration should not be granted because it was in effect hypothetical. However Hospira explained that the levels of acidic variants are "*hypothetical yet realistic percentages selected to provide a convenient way of ascertaining the boundaries of the claim. The percentages reflect levels identified in testing product batches.*" Since the levels reflect levels identified in testing the declaration sought is not hypothetical and there is no reason to refuse it on that ground.

266. During the proceedings Genentech resisted accepting that the declaration should be given until various details of the measurement technique had been given. Hospira provided detailed answers and the details of the measurement technique used were incorporated into the declaration sought.

267. By 14th March 2014 Hospira had answered all the questions about the measurement technique which it was open to Genentech to ask. Thus at that point there was no reason not to make the declaration and I did so.

Conclusion

268. I find that both the 115 patent and the 455 patent are invalid.