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Case No: HP13E01725

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 02/09/2014

Before :

THE HONOURABLE MR JUSTICE SALES

- -

Between :

(1) Teva UK Limited	**Claimants**
(2) Teva Pharmaceutical Industries Limited	
- and -	
AstraZeneca AB	**Defendant**

Case No: HP14A01924

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Between :

(1) AstraZeneca AB	**Claimants**
(2) AstraZeneca UK Limited	
- and -	
(1) Teva Pharma BV	**Defendants**
(2) Teva Pharmaceutical Industries Limited	
(3) Teva UK Limited	

Simon Thorley QC & Thomas Hinchliffe (instructed by **Pinsent Masons LLP**) for the **Claimants** in HP13E01725 and for the **Defendants** in HP14A01924
Richard Meade QC & Kathryn Pickard (instructed by **Arnold & Porter LLP**) for the **Defendants** in HP13E01725 and for the **Claimants** in HP14A01924

Hearing dates: 11/6/14-18/6/14

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Approved Judgment

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

Mr Justice Sales:

Introduction

1. This case concerns a patent held by AstraZeneca AB as proprietor, and exclusively licensed to AstraZeneca UK Limited (I refer to the AstraZeneca companies as "AZ"), in relation to a treatment for asthma. The patent is European Patent (UK) No. 1,085,877, entitled "Use of a composition comprising formoterol and budesonide for the prevention or treatment of an acute condition of asthma" ("the Patent"). The priority date of the Patent is 11 June 1998.

2. Formoterol is a long-acting β_2-agonist ("LABA") with bronchodilator action. Budesonide is an inhaled corticosteroid ("ICS") with anti-inflammatory action. The Patent relates to the use of this combination of drugs both for the regular treatment of asthma, to keep symptoms in check (referred to as "maintenance" use), and for the treatment of acute attacks (referred to as "rescue" or "relief" use).

3. This is the joined hearing in two actions. The first is a revocation action in respect of the Patent, commenced in May 2013, brought by Teva UK Limited and Teva Pharmaceutical Industries Limited. The second is an infringement action, commenced in May 2014, brought by AZ against those companies and Teva Pharma BV (I refer to the three Teva companies as "Teva"). The Teva group manufactures and distributes generic pharmaceutical products. The infringement action was commenced when it emerged that in April 2014 Teva was granted marketing authorisations for two products, BiResp Spiromax and DuoResp Spiromax, falling within the claims of the Patent.

4. The Patent covers a therapy for asthma which combines formoterol and budesonide in a single inhaler which can be used both for maintenance and for relief. At trial and in the relevant scientific literature this was referred to as "SMART", standing for "Symbicort maintenance and reliever therapy for asthma" or for "single inhaler maintenance and relief treatment". "Symbicort" is the name of AZ's combined formoterol and budesonide inhaler. AZ's case is that the idea for having treatment for asthma for both maintenance and relief by means of a single inhaler, as set out in the Patent, is novel and was not obvious at the priority date for the Patent in June 1998.

5. AZ's primary position in the revocation action is that the Patent is valid. However, if it fails on that issue, AZ makes a conditional application to amend the Patent claims. It puts forward three sets of amended claims. The Patents Directorate of the UK Intellectual Property Office ("the IPO") has written a letter dated 28 May 2014 objecting to AZ's amended claims. The IPO did not seek to intervene to be heard in these proceedings.

6. In the event, there were no issues in the infringement action which required resolution by the court at this stage. AZ seeks *quia timet* injunctive relief against Teva. The Court has to address the existence and extent of any threat by Teva to infringe AZ's rights by reference to the circumstances as they exist at present. It is possible that there may be material changes of circumstances in future which might justify AZ in returning to court to seek injunctive relief in the light of those new circumstances.

7. It is agreed that there would be no infringement by Teva of AZ's second amended claim, but if the existing Patent is found to be invalid and AZ seeks to rely on the amended claims, the Court is required to scrutinise the validity of the second amended claim even though Teva does not find it necessary to argue against it.

8. I was informed that the Patent is currently the subject of opposition proceedings in the European Patent Office ("the EPO"). A decision of the Opposition Division, dated 15 March 2012, finding the Patent invalid on the ground of obviousness in the light of a piece of prior art relied on in these proceedings (a patent, "WO '773", dating from 1993 – "the 1993 Patent"), is currently under appeal. The resolution of that appeal will take some time. Meanwhile, the parties are agreed that I should address the issues in the proceedings before me on the basis of the evidence I heard, without reviewing or relying on the EPO proceedings.

The legal framework

9. Section 1(1) of the Patents Act 1977 sets out conditions which have to be satisfied before a patent can be issued. These include, at subsection (1)(b), that the relevant invention "involves an inventive step".

10. Section 2(1) and (2) provide:

> "(1) An invention shall be taken to be new if it does not form part of the state of the art.
>
> (2) The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way."

11. Section 3 provides:

> "An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above …."

12. Section 4A provides for the grant of patents in relation to methods of treatment or diagnosis. Section 4A(3) stipulates that in the case of an invention consisting of a substance or composition for use in a method of treatment of the human body, "the fact that the substance or composition forms part of the state of the art shall not prevent the invention from being taken to be new if the use of the substance or composition in any such method does not form part of the state of the art." Section 4A(4) makes similar provision in the case of an invention consisting of a substance or composition for a specific use in any such method.

13. Section 72 provides for a power to revoke patents on application, on grounds which include, at sub-paragraph (a), that "the invention is not a patentable invention", and at

sub-paragraph (c), that "the specification of the patent does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art."

14. Section 14 governs the making of an application for a patent. Section 14(5)(b) provides that the claim or claims in an application "shall … be clear and concise".

15. Section 75 provides that a patent may be amended following its grant. However, section 76(3) provides in relevant part that "No amendment of the specification of a patent shall be allowed under … section 75 if it – (a) results in the specification disclosing additional matter …".

The witnesses

16. I heard evidence from an expert in respiratory medicine on each side.

17. Professor Duncan Geddes was the expert witness for Teva. He holds the chair in Respiratory Medicine at Imperial College, London. He qualified in medicine in 1971 and has had a long career with a significant interest in the treatment of asthma. At the relevant times - in particular, in 1993, which is relevant for questions in relation to interpretation of the 1993 Patent, and in 1998, which is relevant for questions in relation to interpretation of the Patent in suit in these proceedings and the issue of obviousness in relation to that Patent - he was a practising clinician with a particular interest in and practice relating to asthma. He was not himself a research scientist, but occupied a middle position between such a scientist and an ordinary GP who might be called upon to treat patients with asthma in the usual course of their practice. He had a good understanding of the main currents of thinking in relation to the treatment of asthma in the 1990s.

18. In their submissions, AZ acknowledged that Professor Geddes was an honest witness (this was obvious), but were critical of his evidence in a number of respects. Contrary to these criticisms, I found Professor Geddes to be a good and reliable witness, with good and appropriate expertise to give evidence on the issues in the case.

19. AZ contended that under cross-examination Professor Geddes departed from his written evidence in certain respects. There is some force in this. The drafting of one or two statements in his reports was not quite so careful and clear as it might have been, and there was a significant acknowledgement by him in his oral evidence that it was not obvious to move from a particular article (Arvidsson et al., "Inhaled formoterol during one year in asthma: a comparison with salbutamol", *Eur. Respir. J.*, 1991 – "Arvidsson"), originally pleaded by Teva as critical prior art, to the invention in the Patent. Teva's pleaded reliance on Arvidsson as critical prior art was abandoned in the course of the trial. However, I found that this did not have a significant impact on the overall effect and reliability of Professor Geddes's evidence. For the most part, and particularly when giving his oral evidence, he was careful and precise; he sought to give a thoughtful, objective and at times self-critical account of the state of the art at the relevant times.

20. AZ said that Professor Geddes made inappropriate use of hindsight in giving his evidence. I was not impressed by this contention. I find that he approached his evidence with proper care in trying to address the state of mind of a person skilled in

the art at the distinct relevant times in 1993 and 1998, doing his best to avoid the effects of hindsight. This is not always an easy exercise, as he acknowledged, but I find that he did his best to approach matters in this way and that his evidence could be relied upon.

21. AZ also said that Professor Geddes's evidence was affected by sub-conscious bias in selecting materials for review as part of the common general knowledge ("CGK") of a person skilled in the art at the relevant times. In the course of preparing his evidence, Professor Geddes caused a search to be carried out on a leading online database of medical journals against various criteria. In checking the abstracts of articles thrown up by the search, he did not pick out review articles which went through the scientific literature regarding use of formoterol in the context of maintenance therapy, which was well known practice, but focused more on looking for papers which supported his own recollection that formoterol had been used for relief treatment as well. There is some force in this contention. Professor Geddes acknowledged the difficulty of excluding sub-conscious bias. Nonetheless, he did his best to adjust for this and gave fair and objective evidence about the other scientific papers which he had not selected, when they were put to him in cross-examination. Again, I do not consider that this had any significant effect on the force or reliability of his evidence.

22. AZ criticised Professor Geddes for adopting a careless approach in presentation of his evidence. At one point in his written evidence he said that formoterol was marketed in France in 1990, but in cross-examination he was shown documents which indicated that although a marketing authorisation had been obtained at that time, formoterol was not in fact placed on the market in France at that stage. However, in the overall context of Professor Geddes's evidence, I consider that this was a minor and insignificant lapse. He relied on information supplied to him by those acting for Teva, and readily acknowledged in his oral evidence that he himself had no recollection of it being marketed in France in 1990.

23. AZ further submitted that Professor Geddes's evidence regarding obviousness in 1998 was skewed by the fact that, as a clinical practitioner, he had prescribed a combined inhaler called Ventide which used a short-acting β_2-agonist ("SABA") and an ICS for maintenance treatment, and he had observed that some patients found it useful to use this for relief treatment as well, so that the idea of using a combination inhaler for both maintenance and relief was not something new to him at the time. However, I do not find that his evidence was distorted by this experience. He himself acknowledged that this was "rather specialised information", and did not say that his experience directly represented relevant CGK of the notional person skilled in the art.

24. AZ's expert witness was Professor Ian Pavord, who holds the chair in Respiratory Medicine at the University of Oxford. He also was a good and straightforward witness who, like Professor Geddes, did his best to assist the court.

25. Professor Pavord graduated in medicine in 1984. He has had an interest in respiratory medicine since then, and moved into research in the area in about 1990. Although the focus of his research at that stage was not on β_2-agonists or the use of ICS, which are central in this case, he was part of a research group which did a lot of work in this area. Later, his research interests became more focused on use of these drugs. Teva accepted that he had good expertise to assist the court in relation to the general understanding of the notional person skilled in the art in 1998, but claimed that his

expertise was less good than that of Professor Geddes in relation to 1993. In my view, however, Professor Pavord, like Professor Geddes, was well-placed to assist the Court with evidence regarding the general understanding of the skilled person in both 1993 and 1998.

26. In summary, therefore, I found both experts to be good witnesses. There was no means to distinguish their evidence by reference to differences in their expertise or their approach to giving their evidence. The weight to be given to their respective evidence has to be assessed in the light of background information and materials to which reference was made by the parties.

Factual background

27. Asthma is a respiratory disorder characterised by narrowing and inflammation of the airways of the lungs. This causes symptoms such as breathlessness, wheezing, chest tightness and so on. The form and severity of symptoms covers a wide range. They may be chronic in nature, or take the form of acute flare-ups, or symptoms may be chronic with intermittent flare-ups. Acute symptoms can be very frightening for an individual.

28. It is recognised by practitioners that the narrowing of the airways associated with asthma is caused by two mechanisms: (a) irritation causing contraction of the muscle surrounding the airways (referred to as bronchospasm) and (b) inflammation of the airways (causing swelling of the airway wall and blockage from inflammatory secretions). These mechanisms interact with changes in the body according to natural daily rhythms, in particular during the night, when symptoms and liability to acute attacks may be worse (this is referred to as nocturnal asthma). They may also interact with environmental factors, such as the presence of irritants (like dust or cold air) or allergens or if the individual catches a cold.

29. Bronchospasm causes acute attacks that come on very quickly and may often occur at night. Persistent airway inflammation causes chronic symptoms which can persist for years. During an acute attack, an individual will often wish to use a bronchodilator drug which gives immediate relief by way of rescue or relief treatment. On the other hand, it will also be important that they keep long-term inflammation of their airways under control by use of maintenance treatment.

30. In the 1960s and 1970s the role of inflammation in asthma was not fully understood, and the focus of treatment was on bronchospasm, using bronchodilators such as β_2-agonists to give quick relief. These do not address the underlying inflammation, which became a focus of interest in the 1980s. By 1990, treatment of asthma was increasingly aimed at preventing inflammation, using maintenance therapies such as administration of ICS, alongside relief treatment.

31. At the priority date in June 1998, a typical and well-recognised form of relief treatment was by means of bronchodilators in the form of SABAs, which have a rapid onset of action but which wear off after a few hours, such as salbutamol. A typical and well-recognised form of maintenance treatment was by means of ICS, either by itself or in conjunction with a LABA as a combined maintenance treatment.

32. An example of a LABA which was used in this way is salmeterol. LABAs have a long period of action of about 10 to 12 hours which makes them well-suited for use in combination with ICS for maintenance, and provide general assistance in combating the effects of nocturnal asthma. Budesonide is an example of an ICS. Typically, a patient following this type of maintenance treatment will take a dose of ICS in conjunction with a LABA dose first thing in the morning and last thing in the evening. Depending on their symptoms and responsiveness to the maintenance treatment regime, a patient might also take two additional doses of ICS as part of their maintenance treatment during the day.

33. There is considerable variation between individuals in terms of their symptoms and how they respond to treatment. An individual on a maintenance treatment regime may still suffer flare-ups or acute attacks which require a response in terms of drugs to be taken, and may require relief treatment in addition to any ongoing maintenance treatment regime.

34. Salmeterol has a slow onset of action, which means that it is unsuited to use in relief treatment. A patient on a maintenance treatment regime involving ICS and a slow-acting LABA such as salmeterol will therefore typically need to use a SABA alongside that regime, for relief purposes. The patient may therefore need to use an inhaler for ICS, an inhaler for the slow-acting LABA and an inhaler for the SABA. Even if the ICS and LABA can be combined in a single inhaler (such as if the maintenance treatment requires only a combined dose of ICS and LABA first thing in the morning and last thing in the evening), without need for a further separate ICS inhaler, there is still a need to have a separate inhaler for a SABA for rescue treatment.

35. Formoterol is a LABA, but unlike salmeterol and other LABAs it has a rapid onset of action. Thus, formoterol takes effect quickly, while at the same time its effect is long-lasting, like other LABAs. Its long-lasting effect makes it potentially suitable for use as part of a maintenance treatment alongside an ICS, with good coverage in relation to nocturnal asthma. Its rapid onset of action makes it potentially suitable for use as a relief or rescue treatment, when a patient is subject to an acute flare-up of their asthma and needs immediate relief.

36. It is well known among practitioners that levels of patient compliance with long-term maintenance drug-taking regimes are often poor. Patients may forget or feel it is unnecessary to take their maintenance drugs if they appear free of symptoms. This has the effect that the long-term inflammation dampening effect of the ICS may be lost for a period, increasing the risk of flare-ups. Patients may also mix up their inhalers and drugs, thereby taking the wrong doses of drugs prescribed to them for maintenance.

37. Recognised to be associated with the issue of compliance is the phenomenon of masking, whereby if a rescue drug is taken which delivers prompt relief of symptoms, the patient may feel it is unnecessary to continue to keep up to date with the maintenance therapy. Conversely, if a patient is taking maintenance drugs but suffers an attack, in search of prompt relief he may take further doses of drugs (in particular, ICS) to try to deal with the attack which are beyond what is in fact necessary to control his asthma.

38. On the other hand, combination therapy with an inhaled fast acting β_2 agonist and ICS may improve compliance, precisely because the β_2 agonist provides an immediate beneficial effect and hence may motivate a patient to take their drugs as prescribed. This was noted in a leading textbook published in 1997, Barnes, Grunstein, Leff and Woolcock, *Asthma*, vol. 2, p. 2090.

39. As a general proposition, it is accepted that drugs should not be taken beyond what is needed to provide effective control of asthma (or, indeed, any disease or medical condition). Thus, the ideal dose of ICS is what is needed to control asthma in that particular patient, no more and no less. However, it is not always easy to work out what that dose is.

40. When a new patient first presents himself or when an existing patient appears to suffer an exacerbation in symptoms, a practitioner may choose a strategy of gradually increasing the dose of ICS until a level is found at which the symptoms are under control (the so-called "step up" approach) or may instead intervene with a significantly increased dose of ICS from the outset, and then gradually decrease the dose until the lowest level is found which is effective to control the symptoms (the so-called "step down" approach). The generally recommended approach throughout the 1990s was the step down approach, to try to bring the patient's symptoms under control as quickly as possible to give them relief and then slowly adjust the dosage to find the best level suitable for that patient. It is obviously inherent in the step down approach that ICS may be taken for a period at a level above what is actually required by the patient. Underlying that approach is a recognition that the safety profile of ICS drugs allows for a degree of excess dosing without undue ill-effects for the patient.

The person skilled in the art

41. As Arnold J explained in *Teva UK Ltd v AstraZeneca AB* [2012] EWHC 655 (Pat) at [2]:

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

42. The parties and the experts were eventually all in agreement as to the identification of the notional person skilled in the art relevant to the Patent. It is common ground that the Patent is addressed to a clinician with a specialist interest in the management and treatment of asthma. As Professor Pavord put it, in evidence which was accepted, such an individual would typically have a consultancy position at a hospital treating patients with respiratory disorders at the secondary care (specialist) level; in addition, they would typically be found conducting research in the medical schools of major academic institutions, and thus have both clinical and academic exposure.

The common general knowledge ("CGK")

43. There was a significant difference between the parties regarding the CGK which a person skilled in the art would be expected to have, both in 1993 and at the Patent priority date in June 1998.

44. It was common ground that CGK would include statements in standard reference works such as *Asthma* (see above) and in guidelines on the care of asthma issued by panels of experts. During the 1990s a number of groups with an interest in asthma treatment convened panels of experts to write summary guidelines for GPs, nurses and others. The panels reviewed the published literature and reached consensus opinions on the guidance to be offered to front line practitioners dealing with asthma patients.

45. The British Thoracic Society's Guidelines (1993) included, at Chart 1, details of a five step approach to treatment of asthma, on a spectrum with greater interventions (up to Step 5) as the severity of symptoms increases. Step 2 involved regular ICS for maintenance plus SABAs for relief; Step 3 involved regular ICS at an increased dose for maintenance plus SABAs for relief, with the possibility of adding LABAs for patients who had problems with increased ICS; Step 4 involved regular ICS at the increased dose level plus SABAs for relief, plus the possibility (among others) of trying inhaled LABAs. The type of LABA was not specified. Under Steps 3 and 4, a patient might need to have two or three inhalers using different drug preparations. The Guidelines also noted that it had become common practice to advise patients to double their ICS dose at the first sign of a cold or the deterioration of their asthma, which was thought to be of assistance albeit it had not yet been subject to clinical trials. (As with the step down approach, it is clear that this could mean that ICS might be taken for a period at a level above what is actually required by the patient, and it is likewise based on a recognition that the safety profile of ICS drugs allows for a degree of excess dosing without undue ill-effects for the patient).

46. These British Guidelines were issued in updated form in 1997. They again contained the recommendation to double the dose of ICS temporarily in case of cold or a deterioration of symptoms. They again included a five step approach broadly equivalent to that in the 1993 Guidelines (although this time salmeterol was mentioned by name as a relevant LABA). The notes for this stated that the aim is to achieve early control of the condition and then to reduce treatment (a reference to the step down approach). The 1997 Guidelines again noted that it was recommended to double the ICS dose if a patient's asthma deteriorated or at the first sign of a cold, despite the absence of controlled studies on this.

47. The US National Institutes of Health Guidelines for the Diagnosis and Management of Asthma (1997) similarly recommended the step down approach to treatment. They employed a four step approach to treatment (broadly similar to the five step approach in the British Guidelines), depending on the severity of the symptoms. SABAs were recommended for relief therapy. As in the British Guidelines, a doubling of the dose of ICS when a patient experienced a deterioration in symptoms was recommended. The US Guidelines included a table of comments on various medications. In the section headed in general terms, "Long-Acting $Beta_2$-Agonists", salmeterol and albuterol were mentioned by name (but not formoterol) and the commentary included the statement, "Should not be used for symptom relief or for exacerbations" (i.e. for relief therapy).

48. AZ relied strongly on the fact that the British and US Guidelines recommended only SABAs for relief treatment and that the US Guidelines contained a positive warning that LABAs should not be used for relief therapy. Therefore, AZ sought to suggest, the idea in the Patent of using a LABA (formoterol) for relief therapy was new.

49. However, although these Guidelines are relevant to assessment of the CGK, in line with the evidence of Professor Geddes I do not consider that they are a definitive statement of CGK of the relevant notional skilled person on this point. As he explained, the Guidelines are intended to provide guidance to the whole range of practitioners dealing with asthma patients, including in particular those (such as GPs or nurses) with less specialist knowledge of the field of respiratory medicine than the relevant skilled person would have and requiring clear instructions to inform their practice on the ground. In that context, it made sense to give instructions to use SABAs rather than LABAs for relief treatment. No full safety trials had been conducted into the use of any LABA (including formoterol) for relief therapy, and none had a marketing authorisation to be used for that purpose. It would not normally be right for general guidelines of this kind to recommend to non-specialists that they prescribe drugs off label for standard use. Moreover, most LABAs had slow onset of action and hence were inappropriate for use for relief therapy, and in guidelines which referred generally to LABAs and did not distinctly attempt to discuss formoterol as being in a separate class of its own, it would have risked confusion amongst ordinary practitioners to water down and render more complicated the advice to be given about relief therapy. These are, in my view, sufficient explanations for the form of guidance regarding relief therapy in these Guidelines.

50. By contrast, in 1993, and still more so in June 1998, the relevant skilled person whose CGK I have to assess would have had a more extensive and better-informed understanding than an ordinary practitioner of the different drugs available to treat asthma. The skilled person would have appreciated that, unlike other LABAs, formoterol had a rapid onset of action like a SABA and that, at the very least, this made it a potential candidate to be used as a relief drug. The Guidelines do not indicate that there was any prejudice in the relevant CGK at these times against using formoterol for that purpose.

51. It was also common ground that CGK would include the leading journal articles which addressed the treatment of asthma using ICS and β_2-agonists. Prominent among these were Sears et al., "Regular inhaled beta-agonist treatment in bronchial asthma", *The Lancet*, vol. 366 (1990), 1391-96 ("Sears"), Greening et al., "Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid" *The Lancet*, vol. 344 (1994) 219 ("Greening") and Pauwels et al., "Effect of inhaled formoterol and budesonide on exacerbations of asthma", *New England Journal of Medicine*, vol. 337 (1997) 1405 (the so-called "FACET study").

52. Sears suggested that use of SABAs alongside ICS as part of a maintenance regime could have detrimental effects on asthma, and led to β_2-agonists being somewhat under a cloud in professional opinion. However, Greening reported the positive outcome of a randomised, double-blind, parallel group trial to test two strategies for treating asthma symptoms which appeared despite maintenance treatment consisting of a low dose of ICS, namely an increase in the ICS dose and the addition of the inhaled β_2-agonist salmeterol, in each case taken regularly over a six month period (i.e. as a form of maintenance therapy), together in each case with a SABA prescribed for

relief treatment during the trial. It was found that while there were some beneficial effects from using the first strategy, there was greater improvement using the second; there was no significant difference between the groups in adverse effects or exacerbations of asthma. As Professor Pavord accepted, this lifted the cloud over use of β_2-agonists in the treatment of asthma.

53. The FACET study reported on a double-blind, randomised, parallel group trial to evaluate the effects of adding an inhaled LABA (formoterol) to doses of an ICS (budesonide), taken twice daily as part of a maintenance regime. The medications were inhaled together via separate multidose Turbuhalers. The results and conclusions were summarised as follows:

> "*Results* The rates of severe and mild exacerbations were reduced by 26 percent and 40 percent, respectively, when formoterol was added to the lower dose of budesonide. The higher dose of budesonide alone reduced the rates of severe and mild exacerbations by 49 percent and 37 percent, respectively. Patients treated with formoterol and the higher dose of budesonide had the greatest reductions – 63 percent and 62 percent, respectively. Symptoms of asthma and lung function improved with both formoterol and the higher dose of budesonide, but the improvements with formoterol were greater.
>
> *Conclusions* In patients who have persistent symptoms of asthma despite treatment with inhaled glucocorticoids, the addition of formoterol to budesonide therapy or the use of a higher dose of budesonide may be beneficial. The addition of formoterol to budesonide therapy improves symptoms and lung function without lessening the control of asthma."

The study indicated a lessening of need to use rescue medication during the night and also during the day. The reason for the reduction in the rate of severe exacerbations with formoterol was not clear, though possible mechanisms were suggested.

54. In addition to these leading studies, I find, in line with Professor Geddes's evidence, that a number of other academic articles were sufficiently prominent in the main academic journals in the field as to constitute part of the relevant CGK both in 1993 and 1998. These were Midgren et al., "Formoterol, a new long-acting β_2 agonist, inhaled twice daily, in stable asthmatic subjects", *Chest*, vol. 101 (1992) 1019 ("Midgren"), Wegener et al., "Rapid onset of action of inhaled formoterol in asthmatic patients" *Chest*, vol. 102 (1992) 535 ("Wegener"), and the proceedings of an international symposium at the First Annual Congress of the European Respiratory Society in 1991, edited by Professor S.T. Holgate and published in 1992, "Formoterol: fast and long-lasting bronchodilation" ("Holgate"). I refer to these articles as the "primary articles".

55. Midgren reported on a small trial to determine whether formoterol was clinically more effective than salbutamol (a SABA) in the maintenance treatment of asthma. The study indicated that a LABA such as formoterol was more effective as part of a maintenance therapy alongside an ICS than a SABA.

56. Wegener reported on a small trial to test the speed of onset of action of formoterol, which showed it had rapid onset of action and that tolerability of formoterol was good. The article included the following in the Discussion section:

> "Long-acting inhaled bronchodilators would be expected to be of benefit to asthma patients. It has been proposed that formoterol should be used in a twice-daily dose regimen. However, the severity of the asthma varies and asthma patients frequently also need to be able to prevent or treat the bronchoconstriction caused by cold weather, exercise, etc. For that reason they need a drug that also can be used as rescue medication (as required). Our results indicate that formoterol can be used both for regular maintenance therapy and for the treatment of incidental bronchoconstriction."

57. Holgate included material again indicating the rapid onset of action of formoterol, in contrast to the slow onset of action of another leading LABA, salmeterol. One of the published papers from the symposium, by Richardson and Bablok, reported on an open, multicentre trial to assess the use over nine months of formoterol as sole inhaled bronchodilator therapy, and concluded that a formoterol metered-dose inhaler "is effective in the prevention and relief of asthmatic symptoms" and is well tolerated by patients. Holgate also included a report of the general discussion at the end of the symposium involving those who had presented papers at it. In answer to a question from the audience, "Is formoterol recommended for regular use or as required?" (i.e. for maintenance or for relief), Dr Richardson replied:

> "Currently the recommendations [applicable in Switzerland] are for both, either 12-24μg twice daily regularly, or as required. Formoterol, whilst being longer acting, is also as effective as salbutamol in patients with exercise-induced bronchospasm. The only caveat is that patients taking steroids should not reduce the dose of steroid, even if they feel better."

58. I was also taken to a range of journal articles which were not in leading journals in the field of respiratory medicine, and would not have been likely to have been read by the notional skilled person in the ordinary course of keeping himself up to date. On the other hand, these materials would have been quickly identified by any person conducting a literature search and review into the use of formoterol and ICS in relation to the treatment of asthma. I refer to these articles as the "secondary articles". A question arises whether these materials should be taken into account in assessing the CGK of the notional skilled person. In my view, they should be.

59. In my opinion, for the purposes of assessing the attack on the Patent based on obviousness, this question essentially turns on the way in which a notional skilled person who is deemed to be unimaginative and uninventive would be expected to act if thinking about the general problem of possible treatments for asthma in 1993 and 1998. If considering in 1993 or 1998 how formoterol and an ICS might be used in combination (a possibility already known about in general terms from the primary articles), would the unimaginative and uninventive skilled person know that there was an obvious source of background information relevant to that question, without needing to make any inventive leap of imagination? In my assessment, both in 1993

and 1998 there was a sufficient well-established level of background CGK regarding the existence of formoterol as a LABA, the use of LABAs with ICS in the treatment of asthma, the fast onset of formoterol (in common with SABAs) and of academic interest in the area that the notional uninventive and unimaginative skilled person would have thought it obvious that he should conduct a literature search of the kind carried out on behalf of Professor Geddes in these proceedings.

60. The authorities indicate that CGK includes not just information directly in the mind of the notional skilled person, but such information as he would be able to locate by reference to well-known textbooks. This guidance needs to be adapted and kept appropriately up to date for the procedures for dissemination of scientific knowledge in the age of the internet and digital databases of journal articles. Searches of such databases are part and parcel of the routine sharing of information in the scientific community and are an ordinary research technique. In my view, if there is a sufficient basis (as here) in the background CGK relating to a particular issue to make it obvious to the unimaginative and uninventive skilled person that there is likely to be - not merely a speculative possibility that there may be - relevant published material bearing directly on that issue which would be identified by such a search, the relevant CGK will include material that would readily be identified by such a search.

61. Clearly, in some cases there may be a dispute about what might constitute relevant search criteria for a routine search. But in this case it was not suggested that Professor Geddes had used inappropriate criteria for his literature search, unrepresentative of those which a notional skilled person would have used.

62. Also, it will be relevant to identify what a literature search would have identified at the relevant time (in this case, most particularly in June 1998). This was a little hard to reconstruct in this case, since it was not clear when each article referred to did actually become available online for access via a routine literature search. However, by reason of the lapse of time between each article and the priority date for the Patent, it is probable that each of them was available in good time before that date.

63. Having made this assessment and before turning to the relevant articles, I should say that my judgment on the issue of obviousness does not ultimately turn on whether these further materials do or do not form part of the CGK of the skilled person. Of far greater importance, in my view, are the primary articles referred to above and the well understood features of formoterol in June 1998, namely that it was a LABA which could be used in combination with ICS for maintenance therapy and that, unlike other LABAs, it was fast acting, which made it a viable candidate for consideration for use as a rescue treatment as well.

64. The secondary articles included the following, in particular:

    i) Arvidsson (above), a report of a small trial (18 patients) of the use of formoterol in the treatment of asthma over a one year period. Professor Pavord and Professor Geddes agreed that the trial suffered from design flaws which made it difficult to draw conclusions from it. However, the article noted the fast action and long lasting effect of formoterol (in contrast to SABAs and other LABAs) and explained that during the trial formoterol was used “not only for regular treatment but also on demand” (i.e. for maintenance and for relief), and that patients expressed a strong preference for formoterol (as

compared with salbutamol), which indicated "that the patients were satisfied with the long-acting drug also for use when needed" (i.e. for relief). No long term problem associated with use of formoterol was found, save that one patient stopped taking his ICS dose due to the masking effect;

ii) Stam et al., "The onset of action of formoterol, a new β_2 adrenoceptor agonist", *International Journal of Clinical Pharmacology, Therapy and Toxicology*, vol. 31 (1993) 23, a small trial to study the characteristics of the onset of action of formoterol to see if it could be used as a "rescue drug" (i.e. for relief treatment) in cases of sudden asthma attacks. The fast onset of action of formoterol was identified. The discussion section ended with this:

> "Maintenance therapy with a drug like formoterol seems a step forward. To study if it could be used as a rescue drug in case of sudden attacks of airway obstruction, we studied the onset of its action. We wonder what the place of formoterol in our treatment strategy will be. Maintenance and/or rescue drug? We are conscious of the doubts raised by Cochrane [1990] in this respect."

The reference to Cochrane is to an article, "Bronchial asthma and the role of β_2-agonists", *Lung* (1990) Suppl. 66-70, which discussed the use of SABAs and LABAs (formoterol and salmeterol). It noted that an early study of LABAs in New Zealand suggested that there might be a danger of serious side-effects associated with them, which required study. This concern was much reduced by Greening in 1994. Cochrane also noted the possibility of a masking effect and that the LABAs might be slower acting, which made them suitable for a role in maintenance treatment rather than relief treatment. Later work on formoterol, however, showed that, unlike salmeterol, it has a fast onset of action. By June 1998, Cochrane's conclusion that the new LABAs "are not to be misused as rescue bronchodilators with possible tachyphylaxis or other significant side effects" had been overtaken by other research in the field;

iii) Schultze-Werninghaus, "Long-term treatment with inhaled formoterol over one year", a paper at the 8th Congress of the European Society of Pneumology, published 1990, reporting on a study involving more than 200 patients, using formoterol essentially for maintenance but also allowing patients to use it for relief therapy. The results showed that formoterol is an effective and well tolerated therapy. The published paper included a report of a discussion involving Schultze-Werninghaus and some leading researchers, including Dr Pauwels and Professor Barnes. Dr Pauwels said that it was reasonable to use formoterol for relief therapy, since its onset of action was as fast as the SABAs. Professor Barnes's view was that when LABAs are introduced into clinical practice they should be used mostly for maintenance therapy, with SABAs used for relief, since "otherwise there could be difficulties with management" (which seems to be a reference to the possible masking effect from using LABAs);

iv) Falck et al., "Formoterol Turbohaler 72 and 120µg (delivered doses 54 and 90µg respectively) daily during three days was safe in patients with asthma",

Eur. Respir. J. (1997), 10 Suppl. 25, 103s, a short report of a trial to determine the clinical safety of use of formoterol for relief therapy, which showed that formoterol proved to be safe and well tolerated. The report noted that LABAs were used for maintenance therapy and observed, "As inhaled formoterol has a rapid onset of action, it has also the potential to be used as a reliever of acute bronchoconstriction" (i.e. for relief therapy); and

v) Palmqvist et al., "Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency", *Eur. Resp. J.* (1997), vol. 10, 2484, reporting on a trial to compare these two LABAs. Formoterol was again found to have a fast onset of action, unlike salmeterol. As a result, in the discussion section it was noted, "It could be argued that formoterol … can be used as an occasional rescue medication in asthma. However, the safety of such a treatment has not been studied."

65. Teva relied on the secondary articles as indications of obviousness in respect of the inventive step involved in the Patent as at the priority date. In my view, in the circumstances of this case, the range of references in the literature to possible use of formoterol as a relief drug was so extensive that it provides corroborative evidence that it would have been obvious to the notional skilled person that formoterol could well be of use as a relief drug and that, since it is also a LABA, its use as a relief drug could well be integrated with its use as a drug alongside an ICS for maintenance therapy. The secondary articles reinforce my primary conclusion, that the recognised fast onset of action of formoterol made the idea of trying it out for both relief and maintenance therapy in combination with an ICS obvious to the notional skilled person. Like the primary articles, they indicate that there was no prejudice in the CGK against such use of formoterol and show that the Guidelines cannot be regarded as a definitive statement of the relevant CGK.

66. Within the secondary articles, AZ particularly sought to rely upon:

i) Bartow et al., "Formoterol – An Update of its Pharmacological Properties and Therapeutic Efficacy in the Management of Asthma", *Drugs,* February 1998: 55(2): 303-322 ("Bartow"). This reported on the effects of formoterol and supported its use in aspects of maintenance therapy as recommended in the current Guidelines, noting that despite its fast onset of action it is "not recommended [sc. in the Guidelines] as rescue treatment …"; observed that because of its long duration of action it "may mask signs that more aggressive therapy is warranted", but went on "However, the use of formoterol in the acute setting has not been evaluated"; and further noted that "Further studies to evaluate the earlier use of formoterol in patients with mild to moderate asthma are needed to determine the role and long term safety of formoterol in the management of asthma". I do not consider that Bartow assists AZ. As to formoterol not being recommended for rescue therapy, it does not add to the position to be derived from the Guidelines, discussed above. The reference to formoterol's fast onset of action and use in the acute setting not having been evaluated implicitly acknowledges that it might well be found to be useful for rescue use, which supports Teva's case on obviousness. The significance of the point on the need for testing of the long term safety of formoterol is discussed further below; and

ii) Moore et al., "Long-acting Inhaled β_2-Agonists in Asthma Therapy", *Chest* (April 1998), 113, 4: 1095-1108 ("Moore"), a review of existing literature on studies involving salmeterol or formoterol. The article noted the fast onset of action of formoterol. However, its conclusions included that patients should be instructed not to take LABAs between scheduled doses (i.e. should not use LABAs for relief). This was on the basis of a safety concern if LABAs were used excessively. In my view, Moore does not assist AZ. The reasons for not recommending use of formoterol for relief therapy were related to safety concerns, in advance of trials to establish long term safety (see further below). Those concerns do not indicate that it was not obvious (to the requisite legal standard) to think that formoterol might well be useful for relief therapy.

67. Apart from the primary and secondary articles, both sides sought to rely upon what I will call "tertiary articles". These were articles published or available only after the priority date and hence did not form part of the CGK at the relevant time, but which were said to be indicative of what a notional skilled person would have thought in light of the available literature as at the priority date. The court has to be very careful in assessing a submission like this. Researchers and writers of articles may often have the inventive and imaginative features which are to be excised from the personality of the notional skilled person.

68. Tertiary articles particularly relied upon by Teva included the following:

i) Politiek et al., "Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction", *Eur. Respr. J*, vol. 13 (1998) 988, submitted for publication in April 1998 but published shortly after the priority date, a trial to investigate the effects of formoterol and salmeterol on acute bronchoconstriction, which confirmed the rapid onset of action of formoterol, in a manner equivalent to a SABA, showing (as noted in the discussion section) that formoterol might be an alternative for the SABA salbutamol for relief therapy, and noting that this was in contrast to the international guidelines. It concluded, "However, additional safety studies with long-term treatment of formoterol 'as needed' [i.e. for relief] are required, before considering changing asthma management strategies". I discuss the significance of this point further below; and

ii) Tattersfield et al., "Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial" *The Lancet*, vol. 357 (2001) 257, in the discussion section noted, "Four small, short studies have compared formoterol and salbutamol taken as needed [i.e. for relief] in addition to twice-daily maintenance treatment, and all showed improvement in asthma control with formoterol." The studies referred to were Arvidsson and another article by him, Midgren, and Wallin et al., "Formoterol, a new long acting beta$_2$ agonist for inhalation twice daily, compared with salbutamol in the treatment of asthma", *Thorax* vol. 45 (1990) 259.

69. Tertiary articles particularly relied upon by AZ included the following:

i) A chapter entitled "Future Therapies for Asthma" by Barnes et al. in the 3rd edition of a book entitled *Asthma: Basic Mechanisms and Clinical Management*, published in 1998 ("Barnes 1998"), which reviewed the range

of available treatments and drugs for asthma available at the time, including formoterol. In the conclusion, it was noted that "For some patients a fixed combination β_2-agonist and steroid inhaler may be a useful development, since they will improve compliance of inhaled steroids (which is poor because of the lack of immediate bronchodilator effect)". AZ emphasised that Professor Barnes, a leading researcher in the field, did not suggest as a future development the sort of formoterol/ICS combined inhaler for relief and maintenance which is the subject of the claims in the Patent. AZ said that this indicated that the Patent did indeed set out a relevant non-obvious inventive step meriting protection. However, I do not think that much weight can be given to the extremely short and very abstract conclusions in this paper. Professor Barnes did not refer to the fast acting nature of formoterol, even though that was well known by this time and was part of the CGK. He did not say anything to rule out the possibility of use of formoterol in the way contemplated by the Patent. If anything, his reference to use of formoterol in a combination inhaler with an ICS to improve compliance with the ICS regime is indicative of the currency of thinking at the time about the possible benefits of using formoterol in this sort of way. In fact, it reflects an idea in a previous article he had published in 1995 (P. Barnes et al., "Use of a Fixed Combination β_2-agonist and Steroid Dry Powder Inhaler", *Asthma Am J Respir Crit Care Med* 151: 1053-1057 – "Barnes 1995"), in which he referred to the problem of compliance with therapy and proposed combination of a fast acting β_2-agonist with an ICS in an inhaler, to improve compliance with maintenance therapy;

ii) An issue of *Am J Respir Crit Care Med* in 2005 containing a study of the efficacy of the use of SMART therapy involving a combined formoterol/ICS inhaler for both maintenance and relief therapy and an editorial by Professor Barnes ("Barnes 2005"), in which he noted "The remarkable and somewhat unexpected finding" that the treatment markedly reduced the number of severe exacerbations and the need for oral corticosteroids and offered improved symptom control and lung function. Barnes 2005 offered possible explanations for this and suggested that the study could lead to changes in the paradigm of asthma management, by a switch to the SMART therapy; and

iii) Professor Barnes again emphasised that SMART treatment was a departure from conventional approaches to treatment of asthma in Barnes, "Scientific rationale for using a single inhaler for asthma control", *Eur Respir J* 2007, 29:587-595 ("Barnes 2007"), in which he said that SMART treatment "will revolutionise asthma therapy."

70. AZ sought to rely on Barnes 2005 and Barnes 2007 to show that, at the priority date in June 1998, the idea in the Patent was novel and was not obvious. In my view, however, Barnes 2005 and Barnes 2007 do not show this. The fact that the benefits of using SMART therapy, as particularly referred to in Barnes 2005, went beyond what the relevant informed community might have expected in 1998 (sometimes called a "bonus effect": see *Glaxo Group Ltd's Patent* [2004] EWHC 477 (Ch); [2004] RPC 43, [113]) does not show that the use of a formoterol/ICS combined inhaler for both maintenance and relief therapy was not an obvious idea to try in the circumstances of June 1998. AZ put forward no teaching in the Patent to explain that the further benefits of using SMART type treatment referred to in Barnes 2005 and Barnes 2007

which were not obvious in June 1998 could be expected to follow from use of its invention, and cannot claim that the Patent is made valid simply because such unanticipated and unexplained additional benefits happened fortuitously to be found to follow from use of such treatment: see *Glaxo Group Ltd's Patent* at [113]-[115] per Pumfrey J.

71. Overall, I did not find any of the tertiary articles of great assistance in relation to assessment of the CGK in 1993 or at the priority date in 1998. Those relied on by Teva had a tendency to support my conclusions arrived at by reference to other evidence that it was CGK that formoterol was a LABA with fast onset of action which might well be capable of being used in combination with an ICS for both maintenance and relief. Those relied on by AZ had a tendency to indicate that use of formoterol with an ICS in a combination inhaler for both relief and maintenance was an important advance in the effective treatment of asthma. But in my view the inference cannot be drawn from this that it would not have been obvious to the notional person skilled in the art in June 1998 that use of formoterol in this way was something well worth trying out. In the light of the primary and secondary articles, I consider that this was in fact something which would have been obvious to the notional skilled person.

72. Finally under this heading, there was in both 1993 and 1998 a well-established and common practice, part of the CGK, of administering ICS and SABAs or LABAs in combination, via an inhaler. For example, a familiar product on the market in the 1990s, Ventide, used a combination inhaler, and AZ's Turbuhaler product could clearly be used in that way. Use of combined inhalers was well known: Barnes 1995 and Barnes 1998, for example, both recognised the possibility of using combination inhalers, and noted the possibilities for offering improvements with issues of compliance through using them.

The 1993 Patent

73. The 1993 Patent is relevant to Teva's challenges to the validity of the Patent both as based on anticipation and on obviousness.

74. The 1993 Patent included the following:

> "Abstract: Effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are used in combination for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder. …
>
> Field of the invention
>
> This invention relates to improvements in the treatment of mild as well as severe asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active

ingredients. It emphasizes the use of a long-acting bronchodilator which provides rapid relief of symptoms.

Background of the invention

…

The most common cause for poor control of asthma is poor compliance with the long-term management of chronic asthma, particularly with prophylactic treatments, such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β2-agonist inhalers, since these provide rapid relief of symptoms, but often do not take prophylactic therapy, such as inhaled steroids, regularly because there is no immediate symptomatic benefit. They also counteract down regulation of β2-adrenoceptor agonists.

Formoterol, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy phenyl)-1-methylethyl] amino] ethyl] phenyl] formamide), is an adrenoceptor agonist which selectively stimulates β2-receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by endogenous mediators, and increased mucociliary clearance. Inhaled formoterol fumarate acts rapidly, usually within minutes, which gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of both β-agonist and steroid. Inhaled formoterol also exerts a prolonged bronchodilation, which in clinical trials has been demonstrated as up to 12 hours.

Budesonide, (16, 17-butylidenebis(oxy)-11, 21-dihydroxypregna -1, 4-diene-3, 20-dione), may be given in a high inhaled dose (up to 2 mg daily) with very low systemic effects, possibly because of its rapid metabolism. The high rapid systemic elimination of budesonide is due to extensive and rapid hepatic metabolism. Long term clinical studies have shown that inhaled budesonide is a pharmacologically safe drug. High doses of inhaled budesonide are highly effective and well tolerated when used in oral steroid replacement therapy. Budesonide represents a logical safe and effective therapy for long term control of asthma.

The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects. The drawbacks of the currently available bronchodilators are their relatively short duration of action. By using a compound with long duration e.g. formoterol it would be possible to avoid the nocturnal asthma, which so often causes considerable anxiety and debility to the patients. Formoterol gives less nocturnal waking than the commonly

> used short-acting agonists like salbutamol, terbutaline and the like. Formoterol has been registered for oral administration in Japan since 1989.
>
> Pharmaceutical combinations of long-acting β2-agonists and steroids are disclosed in two European applications, EP 416950 which discloses the combination of salmeterol and beclomethasone, and EP 416951 which discloses the combination of salmeterol and fluticasone propionate. …
>
> Outline of the invention
>
> The present invention is based on the concept of a novel combination therapy whereby formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administrated [sic] simultaneously, sequentially or separately by inhalation. This combination has not only a greater efficiency and duration of bronchodilator action but the combination also has a rapid onset of action. This new feature is of utmost importance in order to establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies life for patients considerably and makes life more comfortable and secure. The rapid onset of the long-acting β2-agonist gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of both β2-agonist and steroid. Since the use of formoterol instead of salmoterol gives a much more rapid onset the combinations according to the invention have a number of advantages compared to the combinations disclosed in EP 416950 and EP 416[9]51. The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma.
>
> The present invention provides a medicament containing, separately or together, (i) formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder. …
>
> The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 μg with a preferred dose of 6-48 μg and the suitable daily dose for budesonide is 50 to 4800 μg with a preferred dose of 100-1600 μg. The particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc). …"

75. For Teva's case on anticipation, the parties are agreed that it is necessary to interpret the 1993 Patent as at 1993. That is to say, for this purpose the court dons the mantle of the relevant skilled person and reads the 1993 Patent in light of the CGK of such a

person in 1993. The question, then, is whether the 1993 Patent, so interpreted, clearly anticipates the claimed invention set out in the Patent in suit.

76. For Teva's case on obviousness, it is common ground that the issue has to be addressed as at the priority date in June 1998. The question is whether the claimed invention in the Patent would have been obvious to the skilled person with the CGK of such a person as at that time, and in light of the state of the art (including prior art relevant under section 2(2) of the Act) at that time.

The Patent in suit

77. The Patent includes the following disclosure:

> "BACKGROUND OF THE INVENTION …
>
> **[0003]** In spite of modern maintenance treatment too many asthmatic patients are undertreated for a number of reasons with a negative impact on their quality of life. Too complicated therapy with different medications and devices may lead to misunderstanding and communication problems between patient and doctor. Poor compliance is a common phenomenon. Improved patient education may partly counteract this, but does not completely solve the problem. A new and more simple approach to asthma treatment could thus be of tremendous help for many patients suffering from respiratory disease, particularly asthma. The combination of budesonide and formoterol in the same device as suggested in PCT applications WO 93/11773 and WO 98/15280 (both to Astra AB of Sweden) offers a favourable pathway to improve today's asthma management with an excellent safety profile. However, although having an adequate regular, e.g. bid, treatment with such a combination, many patients will now and then run into acute situations with a higher frequency and severity of exacerbations, when additional medication is needed. Such an additional medication is often a β2-adrenoceptor agonist with fast onset, normally terbutaline or salbutamol. A second medicament is thus needed, and this can negatively affect the overall compliance of the patient. There is thus need for a neat way of handling maintenance treatment together with the treatment of acute situations. …
>
> SUMMARY OF THE INVENTION…
>
> **[0011]** The recommended dose regimen described in the prior art as disclosed above is twice a day. This dose recommendation was a result of a concern not to have too high an administration of the active compounds. However, in the present invention it has been found that it is possible for the patient to administer this mixture as often as needed.

[0012] The combination of formoterol and budesonide can be used as a rescue medication. Worsening of symptoms can be counteracted by incremental use of the combination for symptom relief, e.g. during exacerbations with the additional steroid component coming in as early as possible to suppress the enhanced airway inflammation. The long duration of formoterol will reduce the risk of too frequent dosing. When taking the combination budesonide/formoterol when needed the severity of exacerbations can be reduced. The as needed use (Pro Re Nata, PRN) will also minimize the difficulty of predicting which patients will be controlled on a low dose of inhaled steroid rather than increasing the steroid dose before adding a long-acting β2-agonist. Under-treatment with inhaled glucocorticosteroids following a too low maintenance dose will be more or less "self-corrected" by the rescue usage according to the present invention. The PRN use of the combination will always give some beneficial anti-inflammatory effects even if it is used by the patient only for rescue purposes. A treatment for patients suffering from respiratory disease, particularly asthma (including allergic conditions, e.g. episodic or intermittent asthma), will therefore be to use the combination formoterol/ budesonide for maintenance therapy as well as on an as needed basis (for rescue purposes), e.g. for prevention of exercise and/or allergen induced asthma.

DETAILED DESCRIPTION OF THE INVENTION…

[0016] A suitable unit dose of formoterol (as fumarate dihydrate) is in the range of from 1μg to 48 μg, preferably from 2 μg to 24 μg, and more preferably between 3 μg and 12 μg. The daily dose of formoterol (as fumarate dehydrate), including maintenance therapy, should be in the range of from 1 μg to 100 μg, preferably from 2 μg to 60 μg, and more preferably from 3 μg to of [sic] 48 μg.

[0017] A suitable unit dose of budesonide is in the range of from 20 μg to 1600 μg, suitably from 30 μg to 800 μ, preferably from 50 μg to 400 μg, and more preferably between 100 μg and 200 μg. The daily dose of budesonide, including maintenance therapy, should be in the range of 20 μg to 4800 μg, preferably from 30 μg to 3200 μg, and more preferably from 40 μg to 1600 μg. The particular dose regimen will depend on the patient (age, sex, weight etc.) and the severity of the disease (mild, moderate, severe asthma etc.). …

[0021] Administration may be by inhalation orally or intranasally. The ingredients of the system are preferably adapted to be administered from a dry powder inhaler, a pressurized metered dose inhaler, or a nebulizer. …

Examples of use of the claimed invention were set out. These included, in particular, Example 5, as follows:

> **[0030]** A patient on maintenance treatment with the fixed combination formoterol fumarate dihydrate/budesonide in a dose of 4.5/80 μg or 4.5/160 μg bid additionally uses the same combination either for rescue purposes once or twice daily to treat sporadic breakthrough symptoms, or as needed to treat exacerbations during one or two weeks, with a maximum daily dose of 36/640 μg (8 puffs of 4.5/80 μg) and 36/1280 μg (8 puffs of 4.5/160 μg), respectively. …

The claims set out in the Patent included the following:

> 1. Use of a composition comprising, in admixture
>
>   a. a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
>
>   b. a second active ingredient which is budesonide;
>
> for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma **characterised in that** the use is for symptomatic relief, when needed, in addition to treating chronic asthma on a regular basis.
>
> 2. Use according to claim 1 wherein the composition is used for the manufacture of a medicament for use in the prevention or treatment of an acute condition of asthma.
>
> 3. Use according to claim 1 wherein the composition is used for the manufacture of a medicament for use in the prevention or treatment of intermittent asthma.
>
> 4. Use according to claim 1 wherein the composition is used for the manufacture of a medicament for use in the prevention or treatment of episodes in chronic asthma. …
>
> 8. Use according to any previous claim, wherein a unit dose of formoterol lies in the range from 1 μg to 48 μg, preferably between 3 μg to 12 μg, calculated as formoterol fumarate dihydrate.
>
> 9. Use according to any previous claim, wherein the daily dose of formoterol, including maintenance therapy, lies in the range of from 1 μg to 100 μg, preferably from 2 μg to 60 μg, calculated as formoterol fumarate dihydrate. …

> 11. Use according to any previous claims, wherein a unit dose of budesonide lies in the range of from 20 μg to 1600 μg, preferably between 50 μg to 400 μg.
>
> 12. Use according to any previous claim, wherein the daily dose of budesonide, including maintenance therapy, lies in the range of from 20 μg to 4800 μg, preferably from 30 μg to 3200 μg. …"

The validity challenge to the Patent: discussion

(a) Anticipation

78. In relation to Teva's case based on anticipation, I accept the submission of Mr Meade QC for AZ that Teva has to show that the claimed invention in the Patent was clearly and unambiguously anticipated by the 1993 Patent. I also accept Mr Meade's submission that Teva has failed to establish this.

79. In my judgment, there is no clear and unambiguous statement in the 1993 Patent that formoterol and budesonide should be used in combination (in particular, in a combination inhaler) for both maintenance and relief purposes, which is the essence of the claimed invention in the Patent in suit. In my view, the statement in relation to the "Field of the invention" that the 1993 Patent emphasises the use of a LABA which provides rapid relief of symptoms is, in the context of the 1993 Patent as a whole, a reference not to use of the combination for relief therapy but rather a reference to other benefits of using a fast-acting LABA in conjunction with an ICS identified in the 1993 Patent in the "Background of the invention" and the "Outline of the Invention". These are: immediate confirmation for patient that he has taken an adequate dose, avoidance of "overdosing of both β-agonist and steroid" and that rapid onset of action of formoterol "is of the utmost importance in order to establish a higher compliance for patients …". This distinguishes the claimed invention in the 1993 Patent from the other European patent applications to which it refers, which were for use of a combination of salmeterol (a slow-acting LABA) with an ICS.

80. This interpretation of the disclosure in the 1993 Patent is strongly supported by the statements in the "Outline of the Invention" section that "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma" and "The intended dose regimen is a twice daily administration [etc]". These are clearly references to use of the combination for maintenance therapy, not relief therapy.

81. Against this, Mr Thorley QC for Teva sought to emphasise the passage in the "Outline of the Invention" section which says, "This new feature [i.e. the combination of an ICS with a LABA with rapid onset of action] … provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies life for patients considerably and makes life more comfortable and secure." He submits that this is a claim that the combination of formoterol and the ICS referred to in the 1993 Patent can be used for relief therapy, as is emphasised by the reference to avoiding the need for the patient to carry two different inhalers. This, he says, is, in

the context of the CGK of the skilled person in 1993, a reference to the need for a patient to have an ICS inhaler for maintenance and a separate SABA inhaler for relief. On this reading, Mr Thorley submits, the 1993 Patent was saying that a patient needed to use only the formoterol and ICS combined inhaler for both maintenance and rescue purposes.

82. In my view, reading the 1993 Patent as a whole, the invention it disclosed did not go this far. I accept that the words "rescue medicine" would have been interpreted in 1993 as a reference to relief therapy. However, Mr Thorley had no good explanation to offer for the other features of the 1993 Patent referred to above. In the context of those other statements, I think the better interpretation of what is being said here is that at the time when the patient takes his twice daily maintenance dose of the combination (typically first thing in the morning and last thing at night) he is relieved from having to have two inhalers to hand – an ICS inhaler and a SABA inhaler - to get some relief (particularly in relation to nocturnal asthma, which may cause discomfort during the night or first thing in the morning).

83. In that regard, it is also noticeable that the relevant passage in the 1993 Patent says that the rapid onset of action of formoterol "is of utmost importance" for compliance purposes (i.e. compliance with maintenance therapy), not "rescue". Clearly, in the relevant sentence, "rescue" is a subordinate potential benefit, which in my view is properly interpreted as something incidental to the twice daily use of the combination dose referred to in the 1993 Patent.

84. This is to do one's best to understand the teaching of the 1993 Patent, read as a whole. But even if it is difficult to spell that meaning out of the document, it is equally or more difficult to spell out the meaning which Mr Thorley sought to tease out of this passage, read in the context of the whole document.

(b) Obviousness

85. Nothing had changed in the period between the issue of the 1993 Patent and the priority date of the Patent in suit in 1998 in relation to CGK relevant to interpretation of the 1993 Patent to change its teaching (as it would be interpreted by the relevant skilled person) in respect of the use of formoterol between those dates. For the reasons already given in relation to Teva's case on anticipation, the 1993 Patent taken by itself does not show that the idea of SMART therapy, the use of a formoterol/ICS combination for both maintenance and relief, was obvious in June 1998. Nor does it constitute an item of prior art which in itself invalidates the Patent. However, it did disclose that formoterol and an ICS could be used in combination, including in a combination inhaler, for maintenance therapy and that there could be a rescue effect (see paras. [79] and [82]-[83] above). The significant difference between the disclosure in the 1993 Patent and the invention in the Patent in suit is the use of such a combination, including by way of a combination inhaler, for relief therapy at other times.

86. However, the gap between the disclosure in the 1993 Patent and the Patent in suit is bridged by the CGK in 1998 at the priority date. So, by reference to the 1993 Patent read in the light of the CGK at the priority date, I find that the teaching in the Patent in suit was obvious as at the priority date and that the Patent is invalid.

87. In my view, on the issue of obviousness, it is appropriate to apply the four stage approach set out in the judgment of Jacob LJ in *Pozzoli Spa v BDMO SA* [2007] EWCA Civ 588; [2007] FSR 37 at [23}:

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

88. For examination of the notional skilled person and the relevant CGK, see above. The inventive concept in the Patent appears from the passages cited above. The essence of it is that formoterol and budesonide (an ICS) can be used in a combination (including in the same inhaler) for both maintenance and relief therapy, and that this can improve overall compliance by patients with their therapy regime (including by what was referred to as "self-correction" of any under-use of inhaled ICS through its being inhaled during relief use as well).

89. For discussion of the third and fourth steps, it is necessary to refer to the guidance of Kitchin LJ in relation to this sort of patent case in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234, at [89]-[93], as follows:

> "89. It is step (4) which is key and requires the court to consider whether the claimed invention was obvious to the skilled but unimaginative addressee at the priority date. He is equipped with the common general knowledge; he is deemed to have read or listened to the prior disclosure properly and in that sense with interest; he has the prejudices, preferences and attitudes of those in the field; and he has no knowledge of the invention.
>
> 90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which

are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.

91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way. Lord Hoffmann summarised the position in this way in *Conor* [*Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49; [2008] RPC 28] at [42]:

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

92. Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. In *Generics (UK) Ltd v H Lundbeck*, [2008] EWCA Civ 311, [2008] RPC 19, at [24] and in *Conor* [2008] UKHL 49, [2008] RPC 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in *Lundbeck*:

> "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."
>
> 93. Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling within the claim. As Aldous LJ said in *Norton Healthcare v Beecham Group Plc* (unreported, 19 June 1997):
>
> > "Each case depends upon the invention and the surrounding facts. No formula can be substituted for the words of the statute. In every case the Court has to weigh up the evidence and decide whether the invention was obvious. This is the statutory task."

90. In the light of the examination of the state of the CGK at the priority date set out above - and taking into account the evidence of Professor Pavord and, in particular, Professor Geddes, whose evidence was more in line with the scientific literature at the priority date - Teva's case on obviousness is made out. In my judgment, the relevant skilled person at that date would have regarded it as obvious to pursue the particular approach of combining a dose of formoterol with an ICS (such as budesonide) for both maintenance and relief therapy with a reasonable or fair expectation (as opposed to a hope) of succeeding in securing effective treatment of asthma by such means, in assisting in improving compliance with treatment and in establishing through phase 3 clinical trials (extensive safety trials of the kind required, for example, to secure marketing authorisation for such use of these drugs) that such therapy was safe. The invention in the Patent was obvious to the requisite standard set out in *MedImmune Ltd*.

91. By June 1998, the fast onset of action of formoterol was well known. This made it an obvious candidate to be tried for use in relief therapy. Use of LABAs (including formoterol) in maintenance therapy along with ICS was also well known. The use of such drugs in combination, in particular by use of combination inhalers, was well known. The desirability of doing anything possible to improve patients' compliance with therapy was also well recognised, as was the likelihood of patients improving their intake of ICS maintenance drugs if they received an immediate perceived beneficial effect from doing so at the same time as they used a fast-acting β_2-agonist such as formoterol. There was nothing striking or unusual about thinking about all these things in combination together. On the contrary, it would have been obvious to a person skilled in the art to do so.

92. There was no special learning or technical contribution deployed by AZ in the idea of "self-correction" of under-administration of ICS as part of a maintenance regime. The problem of compliance with such a regime (of which masking through use of a LABA is one aspect) was well-known, and it was obvious that if patients could be persuaded to take ICS more frequently by being incentivised to do so through combining an ICS with securing immediate relief from an aggravation of their symptoms by use of a LABA or SABA, that would tend to correct that problem. The idea of "self-correction" went no further than this.

93. It should be noted that using an ICS in a combination relief treatment as proposed in the Patent by a patient who *had* followed all the directions they had been given for maintenance treatment (and hence who, in the course of their maintenance treatment, was properly administering the appropriate amount of ICS they required) would lead to use of the ICS beyond what was required for them, contrary to general recommendations regarding the use of drugs. But what made that acceptable was background CGK (as reflected, for example, in the step down approach recommended in the Guidelines) that it would be safe to over-administer an ICS in this way.

94. Similarly, the idea that early increased use of ICS could help nip an aggravated episode of asthma "in the bud" (as Mr Meade put it) was part of the CGK, as reflected in the recommendations made in the Guidelines. AZ added no technical contribution in that regard by what it said in the Patent.

95. In reaching this conclusion on obviousness, I bear well in mind the warnings against using hindsight and ex post facto analysis of which I was forcefully reminded by Mr Meade: see *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC and *Terrell on the Law of Patents*, 17th ed, Richard Miller QC et al., paras. 12-69 and 12-70, pp. 382-383. In my view, judged purely at the priority date, the inventive idea in the Patent was obvious, indeed clearly so.

96. The impediment to widespread adoption and implementation of SMART therapy in June 1998 (in particular, the use of formoterol for relief therapy) was not its lack of obviousness as an idea, but the fact that phase 3 clinical trials had not yet been carried out in relation to it. This meant that it was inappropriate for inclusion in the therapy Guidelines referred to above and that various commentators felt it necessary to make cautionary statements about the need for further testing of the kind set out above.

97. It is at this point in the analysis that it is necessary to recall the basic function of monopoly protection by patent, which is to incentivise and reward inventive steps which are explained and made available to the public in the teaching of the patent. Where, as here, a patent is sought in relation to a new use of an existing drug or combination of drugs, patent protection will only be justified if the patentee discloses sound reasons, not recognised or known before, for thinking that new use will be effective to secure the object for which it is put forward: compare *Conor Medsystems* at [27]-[30] per Lord Hoffmann; *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly and Co Ltd* [2009] EWCA Civ 1362; [2010] RPC 9 at [44]-[52] per Jacob LJ (the fundamental question is, "… has the patentee made a novel non-obvious technical advance and provided sufficient justification for it to be credible?", [50]) and [98]-[100] per Lord Neuberger MR (referring to the principle articulated by the EPO that "the extent of a patent monopoly should correspond to and be justified by the technical contribution to the art", [98]); and *Pozzoli* at [27]-[28], where Jacob LJ said this:

> "27. Patentability is justified because the prior idea which was thought not to work must, as a piece of prior art, be taken as it would be understood by the person skilled in the art. He will read it with the prejudice of such a person. So that which forms part of the state of the art really consists of two things in combination, the idea *and* the prejudice that it would not work or be impractical. A patentee who contributes something new

> by showing that, contrary to the mistaken prejudice, the idea will work or is practical has shown something new. He has shown that an apparent "lion in the path" is merely a paper tiger. Then his contribution is novel and non-obvious and he deserves his patent.
>
> 28. Where, however, the patentee merely patents an old idea thought not to work or to be practical and does not explain how or why, contrary to the prejudice, that it does work or is practical, things are different. Then his patent contributes nothing to human knowledge. The lion remains at least apparent (it may even be real) and the patent cannot be justified."

98. In the Patent, AZ disclosed nothing to explain why use of formoterol and an ICS in combination for both maintenance and relief therapy would be safe. As referred to above, it was the common understanding within the CGK that there could safely be a level of dosing with ICS above that strictly necessary for the individual patient, so using an ICS in a single inhaler each time formoterol was used for relief purposes was not thought to be problematic and AZ in the teaching in the Patent added nothing to human knowledge on that score. Similarly, use of formoterol to some extent was already believed in the CGK to be safe.

99. More importantly, AZ had not carried out any phase 3 safety trials to establish the safety of the treatment beyond what a person with CGK in June 1998 would have believed to be the case, nor announced the results of any such trials to show that the treatment was safe to that standard. AZ was in the position that it did not wish to incur the very large costs of conducting such safety trials unless it had assurance that it would have a patent monopoly in relation to the treatment should it incur the expense of carrying out the trials and succeed in demonstrating its safety so as to secure wider acceptance of it as a therapy for asthma. This is the sort of problem discussed in the speech of Lord Walker of Gestingthorpe in *Conor Medsystems* at [45]-[51], in *Regeneron Pharmaceuticals Inc. v Genentech Inc.* [2013] EWCA Civ 93; [2013] RPC 28, in particular at [103] per Kitchin LJ, and in *Hospira UK Ltd v Genentech Inc.* [2014] EWHC 1094 (Pat) at [56]-[64] per Birss J. However, in order to justify being allowed a patent monopoly before proceeding to the expense of phase 3 trials, AZ had to produce a novel and non-obvious idea which would be amenable to further examination by such trials. AZ has failed to do this.

100. In my view, in June 1998 it was obvious to the notional skilled person that a SMART type approach to asthma therapy involving a combination of formoterol and ICS for maintenance and relief was very well worth trying, albeit it might require a company with deep pockets to carry out the more extensive research to establish a fully robust safety profile to exclude unforeseen and unpredicted hazards, of a type which emerged with thalidomide, and which might make it a candidate for marketing authorisation and so forth. Further work needed to be done to get to that level of assurance regarding safety. Everyone in the field knew that. AZ offered no explanation in the teaching in the Patent to suggest that it could already demonstrate safety to that level. Safety to the lower level of allowing skilled persons to think that this was a therapy well worth trying had already been demonstrated, in particular by Greening in 1994 and by the FACET study, and was by June 1998 part of the CGK.

101. So the safety issues regarding the use of the SMART treatment had been overcome for the purposes of examination of the issue of obviousness by June 1998 and, to the extent that further safety issues were known to remain at that stage, AZ had revealed nothing in the teaching in its Patent to explain that it had overcome those issues. Accordingly, AZ had not provided an account going beyond what was already obvious on the question of safety to justify upholding a patent monopoly in its favour in respect of the SMART treatment.

102. For these reasons, I conclude that Teva's challenge to the Patent on grounds of obviousness is made out. I find that the Patent is invalid.

AZ's alternative claims to amend the Patent

103. If AZ fails in its efforts to maintain the validity of the Patent, as I find it does, it seeks to amend the claims in the Patent in three ways:

    i) The first set of amended claims is based on an amendment to the first claim in the Patent (see above) to refer specifically to formoterol fumarate dihydrate as the active ingredient form of formoterol (nothing turns on this) and to add a reference to a specific dosage regime in these terms: "… and wherein the formoterol fumate dihydrate and budesonide are administered in a unit dose of 4.5/80 μg or 4.5/160 μg formoterol fumarate dihydrate/budesonide" ("Amended Claim 1");

    ii) The second set of amended claims is based on a varied version of this, adding the following text at the end of the first claim in the Patent: "… and wherein the formoterol fumarate dihydrate and budesonide are administered in a unit dose of 4.5/80 μg formoterol fumarate dihydrate/budesonide" ("Amended Claim 2");

    iii) The third set of amended claims is based on a yet further version, adding the following text at the end of the first claim in the Patent: "… and wherein the use for treating chronic asthma on a regular basis is b.i.d. (twice daily) maintenance treatment; the use for symptomatic relief is as needed to treat exacerbations during one or two weeks; the formoterol fumarate dihydrate and budesonide are administered in a unit dose of 5.4/80 μg or 4.5/160 μg formoterol fumarate dihydrate/budesonide, and the maximum daily dose of formoterol fumarate dihydrate/budesonide is 36/640 μg (8 puffs of 4.5/80 μg) or 36/1280 μg (8 puffs of 4.5/160 μg)" ("Amended Claim 3").

104. Teva does not accept that its proposed competitor for AZ's product based on the Patent would infringe Amended Claims 1 or 3. But it is agreed that it is premature to address that question at this stage. AZ accepts that Teva's activities would not involve infringement of Amended Claim 2, and Teva has no direct interest in that amended claim. However, AZ seeks to amend in the form of Amended Claim 2, notwithstanding the objections of the IPO, since it may provide them with patent protection against other potential competitors.

105. The issues which arise before me in relation to the amended claims are whether the amended claims are allowable under the 1977 Act (which reflects the European

Patents Convention) and whether, if allowable, they would make any difference to the outcome of the challenge to the Patent on the grounds of obviousness.

106. On the first issue, it is suggested that AZ's amended claims (i) are not clear and concise to the standard required by section 14 of the Act and/or (ii) they involve adding matter, and hence that by virtue of section 76(3)(a) they are not allowable. What the Act seeks to do by this provision is "to prevent a patentee altering his claims in such a way that they claim a different invention from that which it disclosed in the application … provided the invention in the amended claim is disclosed in the application when read as a whole, it will not offend against section 76 …": see *Southco Inc v Dzus Fastener Europe Ltd* [1990] RPC 587, 616 per Aldous J, cited in *LG Philips LCD Co. Ltd v Tatung (UK) Ltd* [2006] EWCA Civ 1774; [2007] RPC 21, at [30].

107. By its letter dated 28 May 2014, the IPO said that it considered that amendments to the first claim in the Patent were sufficiently clear for the purposes of section 14. However, it stated that it considered that each of Amended Claims 1 and 3 was not allowable, as it added matter.

Clarity

108. I agree with the view of the IPO that the amended claims do not offend the requirement of clarity derived from section 14.

109. A claim in a patent does not need to be drafted to a standard which removes all conceivable doubt about what it means, but it "needs to be as clear as the subject matter reasonably admits of": *LG Philips LCD Co. Ltd v Tatung (UK) Ltd*, at [20] per Neuberger LJ; see also [26]. Absolute clarity would impose an unreasonable standard and would undermine fair protection for inventions under the patent system. On the other hand, a patent defines an intellectual property right and the scope of the patentee's legally protected monopoly, and potential competitors are entitled to fair warning and a reasonable indication from the face of the patent what its scope is.

110. Teva submitted that the amended claims do not make it clear whether, in giving dose quantities, they are referring to the metered dose (the amount of a drug put into an inhaler) or the delivered dose (the lesser amount of the drug actually delivered via an inhaler into the patient). I do not accept this.

111. In my judgment, it is clear from a reading of the amended form of the claims in the context of the Patent as a whole that the unit dose being referred to is the delivered dose, i.e. the amounts of formoterol and budesonide which are actually taken into the body of the patient. The Patent is not for a combination treatment which *must* be taken via an inhaler, but for a combination which *may* be taken via an inhaler but which can be taken in some other way: see para. [0021]. It is only in relation to an inhaler that the difference between metered dose and delivered dose is significant. Thus, since the invention in the Patent does not necessarily involve use of an inhaler, the reference to "unit dose" in the claims cannot sensibly be read as meaning the (higher) metered dose which is used when filling an inhaler. It can only realistically be read as a reference to the administered or delivered dose which would be supplied under any of the methods of delivery covered by the Patent.

Added Matter

112. AZ submits that the amended claims do not include added matter. The detail which they include is already contained in the Patent, in particular in what is said in Example 5. Teva, on the other hand, submits that AZ's Amended Claims 1 and 3 do add matter, in that AZ seek to spell out something new in those Amended Claims so that they fall foul of the problem given the label of "intermediate generalisation", that is to say that Amended Claims 1 and 3 seek to extract the dose amounts from Example 5 and give them a generalised form in a patent claim disregarding critical and non-severable aspects of the detail given in Example 5. (Teva is neutral on Amended Claim 2, but that amended claim does have to be considered by the court).

113. Kitchin LJ addressed the issue of intermediate generalisation in *OYJ (Nokia Corporation) v IPCom GmbH & Co KG* [2012] EWCA Civ 567; [2013] RPC 5 at [56]-[60], as follows:

> "56. Turning to intermediate generalisation, this occurs when a feature is taken from a specific embodiment, stripped of its context and then introduced into the claim in circumstances where it would not be apparent to the skilled person that it has any general applicability to the invention. "
>
> 57. Particular care must be taken when a claim is restricted to some but not all of the features of a preferred embodiment, as the TBA explained in decision T 0025/03 at point 3.3:
>
> > "According to the established case law of the boards of appeal, if a claim is restricted to a preferred embodiment, it is normally not admissible under Article 123(2) EPC to extract isolated features from a set of features which have originally been disclosed in combination for that embodiment. Such kind of amendment would only be justified in the absence of any clearly recognisable functional or structural relationship among said features (see e.g. T 1067/97, point 2.1.3)."
>
> 58. So also, in decision T 0284/94 the TBA explained at points 2.1.3-2.1.5 that a careful examination is necessary to establish whether the incorporation into a claim of isolated technical features, having a literal basis of disclosure but in a specific technical context, results in a combination of technical features which is clearly derivable from the application as filed, and the technical function of which contributes to the solution of a recognisable problem. Moreover, it must be clear beyond doubt that the subject matter of the amended claim provides a complete solution to a technical problem unambiguously recognisable from the application.
>
> 59. It follows that it is not permissible to introduce into a claim a feature taken from a specific embodiment unless the skilled person would understand that the other features of the

> embodiment are not necessary to carry out the claimed invention. Put another way, it must be apparent to the skilled person that the selected feature is generally applicable to the claimed invention absent the other features of that embodiment.
>
> 60. Ultimately the key question is once again whether the amendment presents the skilled person with new information about the invention which is not directly and unambiguously apparent from the original disclosure. If it does then the amendment is not permissible."

114. In my view, the skilled addressee would not be able to derive from Example 5 that the dose amounts set out there are capable of abstraction from the details of the factual scenario set out in that Example so as to provide "a complete solution to the technical problem". Example 5 is truly what it says it is – an example. It is not, on a proper interpretation, capable of generating generalisable patent claims. It merely addresses a possible use of the patented invention by a patient with particular characteristics, by way of specific illustration of how the invention in the Patent might be used.

115. There is considerable variation in asthma symptoms between patients, resulting in different drug use and dose profiles between patients depending on their individual responsiveness and the severity of their symptoms. Example 5 takes as an example one patient with a particular established maintenance regime and indicates how the patented combined maintenance and relief regime might be adapted for use by such a patient, for illustrative purposes. A reader of the Patent, whether skilled or lay, cannot derive from this that AZ was making any assertion that the use proposed in Example 5 is generally suitable for the treatment of asthma. It does not propose "a complete solution to the technical problem". I therefore agree with the view of the IPO as regards added matter in relation to Amended Claims 1 and 3.

116. The IPO did not say that Amended Claim 2 was objectionable on this ground, but gave no reasons for distinguishing between that amended claim and Amended Claims 1 and 3. Since Teva was neutral on Amended Claim 2, it did not address it in argument. I therefore did not receive much direct assistance on this point in relation to Amended Claim 2. However, in my judgment, Amended Claim 2 suffers from the same objection that it contains added matter as a result of intermediate generalisation from Example 5 and for that reason cannot be allowed.

Obviousness

117. The issue of obviousness in relation to Amended Claims 1 to 3 involves a slightly artificial exercise, difficult to separate out from the issue of added matter. For example, if (contrary to my view above) Amended Claim 1 were a discrete allowable claim to be included in the Patent, then in a sense it might be said that the full detail of the dosage regime set out in it was not something which was obvious to the notional skilled person.

118. But reflection on this tends to support my conclusion on added matter. AZ offered no distinct explanation of reasons why one would expect the relief use of a combination of formoterol and an ICS as set out in Example 5 should be particularly beneficial,

other than for the same (obvious) reasons that one would generally expect it to be possible to use formoterol in an effective way for both maintenance and relief therapy.

119. Moreover, the Court of Appeal in *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly and Co Ltd* [2009] EWCA Civ 1362; [2010] RPC 9 explained the relevant sense in which an obviousness objection to the main claim would also apply in this sort of case. Selection of a random sub-class or member taken from a prior art published class (or, I would add, from what is already taken to be a wider class regarded as obvious in the CGK) is taken to be obvious where it provides no technical contribution, so mankind can learn nothing new from it: see [44]-[52] per Jacob LJ and [93]-[106] per Lord Neuberger MR. In the present case, therefore, the obviousness in relation to the wider class claim equally covers the narrower claims in Amended Claims 1 to 3, since AZ offered no additional plausible explanation for any other grounds why those narrower claims should be expected to be effective, if implemented according to their terms.

Conclusion

120. For the reasons given above, I reject Teva's challenge to the Patent based on alleged anticipation in the 1993 Patent; I find that Teva's obviousness challenge to the Patent is made out and that the Patent is invalid; and I reject each of the amended claims put forward by AZ.

Post-script

121. When I distributed this judgment to the parties in draft, Counsel for AZ submitted that the judgment contained an error, in that I had made a finding of obviousness based on CGK alone, which they said AZ had not appreciated was an issue at trial. Rather, the case on obviousness presented against AZ was based on the 1993 Patent read in light of the CGK. They properly raised this matter with me, following the guidance in *Re M (A Child) (Non-accidental injury: burden of proof)* [2008] EWCA Civ 1261 at [36]-[40].

122. In the discussion of the obviousness challenge in the draft version of the judgment, I had put the teaching in the 1993 Patent to one side (in the draft version of paras. [85]-[86]), since my view was that the case on obviousness was fully made out by reference to the CGK. The 1993 Patent did not, taken by itself, make out a case of obviousness. It was therefore unnecessary to discuss the 1993 Patent further in that context.

123. I had thought that this approach was uncontroversial, because Teva's pleaded case on obviousness relied on both the 1993 Patent and (it appeared) the CGK, without restriction. The expert evidence and parties' submissions also ranged very widely over the topic of the CGK, not always pegging the discussion to a starting point in the 1993 Patent.

124. However, when the draft judgment was distributed, Counsel for AZ referred me to correspondence between the parties in which Teva made it clear that, notwithstanding the terms of the formal pleading, on the obviousness part of its challenge it did not rely on a case of obviousness stemming purely from the CGK, but rather presented its case as obviousness based on the 1993 Patent read in the context of the CGK. Counsel for Teva accepted this.

125. In the light of this, I was satisfied that this was an exceptional case (see the discussion in *Robinson v Fernsby* [2003] EWCA Civ 1820, in particular at [82]-[98]) in which it would be appropriate for the relevant part of the draft judgment to be amended in the final version, so as properly to reflect the case which was in issue at trial.

126. I had the benefit of submissions from the parties about the changes to the draft judgment which should be made. Mr Meade QC for AZ submitted that the outcome should be that I give a judgment rejecting the obviousness challenge, since I had only relied on the general CGK as the basis for my finding of obviousness. Mr Hinchliffe, who presented the submissions on this point for Teva, submitted that the final judgment should still include a finding that the obviousness challenge was made out, but on the basis of a combination of the 1993 Patent and the CGK, rather than on the basis of the CGK alone. In other words, whereas in the draft judgment it had appeared appropriate to put the 1993 Patent to one side when considering the case on obviousness since it was unnecessary to rely upon it in analysing that case, that could not be regarded as appropriate once the limited nature of the case presented by Teva was understood. But on consideration of that more limited case, Teva's submissions on obviousness were fully made out on the facts and ought to be accepted.

127. I accept Mr Hinchliffe's submission on this issue. In the light of it, I have reviewed the analysis on the issue of obviousness and have made alterations to reflect a situation in which it is not appropriate simply to let the 1993 Patent to drop out of the equation by putting it to one side, as had been done in the draft judgment. I agree with him that Teva's case on obviousness on the more specific basis of an argument relying on the 1993 Patent read in the light of the CGK has been made out. I was fully equipped as a result of the evidence and submissions at trial to review the case in this way; I simply had to undo the intellectual shortcut I had made at paras. [85]-[86] in the draft judgment and bring the 1993 Patent back into the picture for the purposes of analysing the case on obviousness.

128. Accordingly, I have amended paras. [85]-[86] in this final version to achieve that. There is a compelling case, based on fairness to both parties and application of the overriding objective in CPR Part 1, that this is the proper way to proceed. In my view, it would be absurd (and deeply unfair to Teva) to proceed as Mr Meade contended, and to reject a case on obviousness which I am satisfied has been properly made out by Teva on the basis on which it presented its case at trial, namely by reference to the 1993 Patent as read in the light of the CGK in June 1998.

129. I have given careful consideration to the question whether it would be unfair to AZ to make this amendment to the judgment. I am satisfied that there is no unfairness involved. AZ had a fair opportunity to meet the case as presented against it by Teva. The point I sought to make in the draft judgment was that it was unnecessary to rely on the 1993 Patent for the case on obviousness if one could simply refer to the general CGK, not that the 1993 Patent was irrelevant to a case on obviousness. The amendments to paras. [85] and [86] do not involve a reversal of any finding of fact made by me; they reflect a modification in the analysis which is necessary and appropriate once it is appreciated that it should take the teaching in the 1993 Patent into account rather than simply leaving it to one side. I have reviewed the whole judgment and I am satisfied that, with that modification, the analysis on the issue of obviousness reflects the relevant findings to be made in light of the evidence and submissions on Teva's case at trial.

130. Mr Meade submitted that there was unfairness to AZ, because the whole process of reasoning changed as between (inappropriate) analysis by reference to the general CGK in the draft judgment and the analysis by reference to the 1993 Patent and the CGK as proposed by Mr Hinchliffe for the final judgment. Mr Meade said that there was inadequate review of the terms of the 1993 Patent in the judgment to allow for such a change in focus.

131. I reject that submission. As regards the terms of the 1993 Patent, there is a close review of what it said and did not say in the section of the judgment which deals with the case on anticipation. There is no difficulty about referring to that review in the section which deals with obviousness based on the 1993 Patent read in the light of the CGK. At trial, there was uncertainty about what the court might hold regarding the meaning of the teaching in the 1993 Patent, and hence uncertainty about the extent of the gap between the 1993 Patent and the invention in the Patent in suit which might need to be bridged by the CGK. This no doubt explains the wide-ranging evidence and submissions which I heard about the content of the CGK. On Teva's obviousness case, it was always clear that some element of CGK was being relied upon, which would be more extensive or less extensive, depending on the court's holding regarding the meaning of the 1993 Patent. AZ had a fair opportunity to adduce evidence and make all the submissions it wished in response to that case. I consider that the analysis and findings which are appropriate in reviewing Teva's case on obviousness, understood as a case based on a combination of the 1993 Patent and the CGK (rather than as including also a case based purely on the CGK) are those now set out in the final judgment. No other changes or modifications would be appropriate.

132. I therefore confirm my conclusion at para. [120] above, after taking account of the submissions made by the parties regarding the contents of the draft judgment distributed in advance of handing it down.