Neutral Citation Number [2009] IEHC 277

THE HIGH COURT

2008 3 PAP

IN THE MATTER OF IRISH PATENT NO. 65535 ENTITLED

"INHALATION MEDICAMENTS FOR TREATING RESPIRATORY DISORDERS" FILED ON 7TH SEPTEMBER, 1990 AND REGISTERED IN THE NAME OF GLAXO GROUP LIMITED

IN THE MATTER OF IRISH SUPPLEMENTARY PROTECTION CERTIFICATE NO. 1999/007 GRANTED ON 12TH AUGUST, 2003 AND REGISTERED IN THE NAME OF GLAXO GROUP LIMITED

IN THE MATTER OF THE PATENTS ACT 1992

AND IN THE MATTER OF COUNCIL REGULATION (EEC) NO. 1768/92 OF

18TH JUNE, 1992 CONCERNING THE CREATION OF A SUPPLEMENTARY PROTECTION CERTIFICATE FOR MEDICAMAL PRODUCTS PAB

JUDGMENT of Mr. Justice Charleton delivered on the 26th day of June 2009

1. The petitioner, Ivax International B.V. trading as Ivax Pharmaceuticals Ireland Limited, whom I will call Ivax, brings these proceedings to challenge an Irish patent for an asthma medicine that, when purchased in a chemist's, is commonly called Seretide. The patent is held by the respondent Glaxo Group Limited, whom I will call Glaxo.

2. The application for the patent was filed in Ireland on 7th September, 1990 and was granted on 12th October, 1995. Glaxo is entitled to a priority date as of 8th September, 1989. That priority date, I understand, arises by virtue of the filing in the United Kingdom patent office. In any event, the date is not in dispute. It is, however, very important as I have to look at the issues in this case as of that time. Glaxo obtained an extension of the term of the protection under the patent to 6th September, 2013 by reason of the grant on 12th August, 2003 of supplementary protection certificate number 1999/007.

3. Seretide is one of the best selling drugs in the world. It is administered by breathing in while firing a liquid to gas inhaler, or a dry powder inhaler, held in one's mouth. This gives a precise dose. It consists of a mixture, as opposed to a compound, of two solid but ground-up products; salmeterol xinafoate and fluticasone propionate. Both are in a carrier; lactose in the dry powder inhaler and a liquid which becomes gas on firing in the other. Fluticasone propionate is a steroid, specifically a medication which reduces inflammation in the lining of the trachea, a condition which is typical in asthma. Salmeterol xinafoate is a â 2-agonist and it relaxes the involuntary muscular spasm in the trachea that is also typical. In asthma, both spasm and inflammation are characteristic. In this preparation, it takes the salt form of salmeterol xinafoate, but other salt forms of salmeterol are also covered by the patent.

4. To be effective, steroids need to be taken regularly over a period of time, be it days or weeks or months. One is always given a prescription of a steroid to be taken regularly, like twice a day, for some period of time. This particular medication, fluticasone propionate, reduces inflammation only when taken regularly for some days; five was the estimate in evidence before me for the compound in issue. A â-agonist, like salmeterol xinafoate on the other hand, relaxes muscle spasm quickly. You use it when breathless. The evidence that I was given was that it is now understood that salmeterol xinafoate is effective within about twenty minutes. However, *Ullman and Svedmyr* [1988] saw "no significant differences in the time of onset between . . . salmeterol" and its analogue salbutamol. Salmeterol last for about twelve hours. Salbutamol, which I must mention again, has a swift onset but lasts for only about four hours. One is not always given a prescription by your doctor to take a â-agonist regularly. This is a central controversy in this case. The pharmaceutical preparation Seretide, which is covered by the patent in suit, is one that is to be taken regularly over a period of time for people with ongoing asthmatic problems. Taken twice daily, the inflammation of the trachea is reduced and the possibility of muscle spasm is both relieved and held off. When a medicine is prescribed to be taken once or twice or more per day this is referred to in scientific terms as regular use; or that expression can be replaced by saying twice daily or any number of times daily, meaning the same thing.

5. Ivax claims that Glaxo should never have been granted the patent for this preparation of the compounds. Glaxo hold, in addition to the patent for the drug combination in issue here, namely Seretide, the patents for the individual medicaments that make it up. There is no argument against these two individual patents for those components; salmeterol and fluticasone propionate. All are agreed that the development of fluticasone propionate and the long acting â 2-agonist salmeterol were inventive contributions to asthma medication. The issue is against the patent granted for putting them both into a single preparation. The argument by Ivax, essentially, is that the combining of these two medications into one product for use by those with ongoing asthma problems was obvious. In other words, that combining the two known drugs did not involve an inventive step. That is the crux of this case.

Patents Legislation

6. This case is to be decided under the Patents Act 1992 ('the 1992 Act'), as amended by the Patents (Amendment) Act 2006 ('the 2006 Act'). The provisions within the Act are mainly derived from the European Patent Convention of 1973, to which Ireland became a contracting party in 1992. There is thus a common system of substantive law of European patents. Our law is aligned to it, as is that of the United Kingdom. In this judgment I am relying extensively on principles developed within the jurisdiction of the neighbouring kingdom, principally under the Patents Act 1977, though the question of obviousness depriving a patent of protection goes back well before that particular legislation.

7. Article 56 of the European Patent Convention states that an invention "shall be considered as involving an inventive step, if, having regard to the state of the art, it is not obvious to a person skilled in the art". Articles 89 and 54(2) make it clear that everything made available to the public anywhere in the world before the priority date may become part of the state of the art as of the priority date; though whether it does or not is a matter for judicial determination. The United Kingdom Act of 1977, as to its material parts, are declared by s. 130(7) to have been framed as nearly as practicable to the corresponding provisions of the European Patent Convention. The supplementary protection certificate granted to this patent, and which extended its life, is governed by Article 15(1) of the Council Regulation (EEC) No. 1768/92. This provides for invalidity if the basic patent is revoked.

8. Section 18(2) of the 1992 Act requires a patent application to include "a specification containing a description of the invention to which the application relates". One or more claims must also be made for the patented invention. Under s. 20 these must "define the matter for which protection is sought, be clear and concise and be supported by the description". A patent must involve a new invention and, under s. 9(1) of the Act, it must be capable of industrial application. Under s. 58 of the 1992 Act, as amended by s. 11 of the 2006 Act, a patent may be revoked if the subject matter of the patent is not patentable; the specification in the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art; the matter disclosed in the patent extends beyond that disclosed in the application; or the protection has been extended by an amendment that should not have been allowed.

9. Something which is not inventive is not patentable. Most of the challenges to a patent, therefore, have arisen under the rubric of obviousness. In chapter 19 of *Pharmaceuticals Biotechnology and the Law* (London, 2009), Trevor Cooke argues that in the area with which I am concerned the requirement of an inventive step should be replaced by a test as to whether the product had secured marketing authorisation for a new pharmaceutical. As will be apparent, later in this judgment, the obtaining of authorisation to sell a pharmaceutical is an important step and one that is very difficult to achieve considered against the background of the research and development required. However, such a change would involve a new regime. I am obliged to direct my mind to the question of inventiveness.

10. Here, three sections of the 1992 Act are especially relevant. Section 11(1) states:-

> "An invention shall be considered to be new if it does not form part of the state of the art."

Section 13 provides:-

> "An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art."

11. It is clear that the background against which obviousness is to be judged, as of the priority date, is the state of the art. This is defined in s. 11(2) as follows:-

> "The state of the art shall be held to comprise everything made available to the public (whether in the state or elsewhere) by means of a written or oral description, by use, or in any other way, before the date of filing of the patent application."

Pumfrey J.

12. The issue of obviousness which arose in this trial also arose in England in the case of *Cipla Limited v. Glaxo Group Limited* [2004] R.P.C. 43, which also concerned Seretide. The action was heard before Pumfrey J. in January, 2004. The issue at trial was whether it was obvious to use this combination of drugs in an inhaler. The patent was revoked for Seretide in that litigation because of obviousness. Permission to appeal to the Court of Appeal was required but was refused, both by the judge and by way of what appears to me to have been some class of summary hearing seeking leave to appeal.

13. It is powerfully argued on behalf of Ivax that I should follow the decision of Pumfrey J. In essence, the common system within Europe of patent protection and the respect that is owed by courts in different jurisdictions for decisions based on a common legal framework was presented as a sound foundation for such a course. Before me, however, substantially different facts were argued and new witnesses called. A large body of evidence was presented whereby it was contended that this combination of medicines had a greater-than-addictive effect and that this was foreshadowed in the patent. As it turns out, this claim was abandoned. Essentially, this occurred because there was no evidence that such an effect was in any way foreshadowed on any reasonable construction of the patent. In addition to that, however, a claim was made in this jurisdiction, which was not made in England, based upon a prejudice within the state of the art posited upon the mutual chemical reactivity of the two compounds. It would have been impossible, notwithstanding my respect for Pumfrey J. and for the courts of the neighbouring kingdom, to proceed towards a conclusion on the correctness of the decision in previous litigation without examining this evidence in detail and with an open mind. Since a finding on that issue could change the other aspects of evidence which may have been common between this case and that tried in the United Kingdom, a complete re-evaluation of all of the evidence was required in the present case. Furthermore, an argument was advanced that on the question of obviousness to try, at the least, the law stated by Pumfrey J. had been overtaken by the later judgment of the House of Lords in *Connor Medsystems v. Angiotech Pharmaceuticals* [2008] R.P.C. 716.

14. Before dealing with the question of obviousness, as a prelude to an analysis of the evidence, I need to outline the law and then to indicate my approach to the extraordinarily contradictory evidence proffered to the court on all of the central issues in this case.

The Patent

15. The law requires me to address my mind to the claim in the description in the patent application, as granted, and not to a vague paraphrase; *Conor Medsystems v. Angiotech Pharmaceuticals* [2008] R.P.C. 716. Therefore I need to refer to the patent and to the descriptions in it in some detail. Some explanations are also needed on the side, as it were, as part of this narrative.

16. The claimed invention states that it related to improvements in the treatment of asthma and respiratory disorders. The description proceeds:-

> "More particularly, it relates to the use of a bronchodilator drug 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. Asthma is a condition characterised by variable, reversible obstruction of the airways which is caused by a complex inflammatory process within the lungs. In most cases, this process is initiated and maintained by the inhalation of antigens by sensitive atopic individuals (extrinsic asthma). However, in some patients it is caused by other mechanisms which at present are poorly understood but do not involve an allergic process (intrinsic asthma). The disease has therefore two components, spasm of the bronchial or (breathing) tubes and inflammation or swelling of the breathing tubes".

17. The description goes on to give a history of earlier medications used to treat asthma and, in particular, it refers to individual preparations, not a combined treatment as here, of salbutamol, a â-agonist, and of beclomethasone dipropionate, a steroid. As it happens, the patents for these medications used individually were held by Glaxo. One of these was, and still is, commonly used, namely salbutamol under the pharmaceutical name Ventolin. Becotide was the pharmaceutical preparation of beclomethasone dipropionate. In the form of the pharmaceutical preparation Ventide, these two drugs were combined. Ventide consists of a short-acting, but quick relief, â-agonist

and a steroid in the same preparation for inhalation as an asthma relief medicine. Seretide is a long-acting, but slower relief â-agonist and a better steroid. I know nothing of the patent history of Ventide, though I need to look at this combination from the point of view of obviousness.

18. The description in the Seretide patent indicates that there were a number of disadvantages to Salbutamol. It being a short-acting â-agonist because of the short duration of dilatation the trachea, the spasm associated with asthma is reduced by salbutamol for about four hours. Therefore, it needs to be repeated several times during the day and night, if the patient's asthma is bad. Impaired sleep can result. Salbutamol is a â 2-agonist and beclomethasone dipropionate is a corticosteroid steroid. This steroid preparation, like all anti-inflammatory medication has the disadvantage in relation to the breathlessness problem of asthma that it takes some days for the reduction of inflammation to act on the underlying muscle spasm. Salbutamol, however, has an almost immediate effect in relieving breathlessness. The description in the patent continues:-

> "The present invention is based on the concept of a novel combination therapy which has markedly greater efficiency and duration of bronchodilator action than previously known combinations and which permits the establishment of a twice daily [...] dosing regimen with consequent substantial benefits in, for example, the treatment of asthma, particularly nocturnal asthma".

19. The description proceeds to set out the effect of salmeterol, the subject separately of patent 800, which is a â 2-agonist and can be expected to last for twelve hours. An asthmatic naturally reaches for breathing relief, but not so much for any prescribed anti-inflammatory. The treatment of the inflammatory condition in the trachea associated with asthma was regarded as useful, and still is, and essential in all but mild asthma, and this drug was to be combined in a new preparation with fluticasone propionate, separately the subject of patent 877, whereby the steroid preparation could act on what is thought to be the inflammatory trigger of the disease. The extended duration of the reduction in spasm by salmeterol, and the long term access to the anti-inflammatory fluticasone propionate while using it, is described as being "highly effective". The fundamental idea was the regular use of both active components, and not just on an as needed basis; this was in contrast with the way that asthmatics would typically use a Ventolin and perhaps not bother with any separate anti-inflammatory medication. The evidence I will refer to later will illuminate this. The description continues:-

> "Thus according one aspect of the invention, there are provided pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone propionate as a combined preparation for simultaneous or sequential administration by inhalation in the treatment of respiratory disorders. The invention additionally relates to the use of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone propionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous or sequential administration of salmeterol and fluticasone propionate by inhalation in the treatment of respiratory disorders."

20. The description goes on to indicate suitable physiologically acceptable salts of salmeterol. As it happens, salmeterol xinafoate is one of these. The effect of using a crystalline salt form is looked at later in this judgment. It is important to the chemistry issue. The patent indicates that the dose of these drugs will be metered so that they can be inhaled in a conventional manner either in the form of a dry powder composition or an aerosol spray formulation. It describes the ratio of the combination of salmeterol to fluticasone propionate as being in the range of 4:1 to 1:20; with each metered dose containing from 25 to 100 mcg of salmeterol and from 25 to 500 mcg of fluticasone propionate. The dosage, that is how many puffs, of course, might depend on age, weight and other underlying conditions that would be considered by a physician prescribing the drug. Ultimately, it would appear, a standard formulation has been arrived at in Seretide, and the patent had described the relevant range. The liquid to gas drug preparation is then set out as is the dry powder formulation.

21. There then follow the claims are made in the patent:-

> "1. Pharmaceutical compositions comprising effective amounts of salmeterol, (and/or a physiologically acceptable salt thereof) and fluticasone propionate as a combined preparation for simultaneous or sequential administration by inhalation in the treatment of respiratory disorders.
>
> 2. Compositions as claimed in claim 1, where in salmeterol is present as its 1- hydroxy – 2 – naphthoate salt.
>
> 3. Composition as claimed in claim 1 or claim 2 presented as a metered spray composition or a dry powder composition.
>
> 4. Compositions as claimed in any of claims 1 to 3 in dosage unit form containing 25 – 100 mcg of salmeterol (optionally in the form of a physiologically acceptable salt thereof) and 25 – 500 mcg of fluticasone propionate per dosage unit.
>
> 5. The use of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone propionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous or sequential administration of salmeterol and fluticasone propionate by inhalation in the treatment of respiratory disorders.
>
> 6. The use of salmeterol (and/or a physiologically acceptable salt thereof) and fluticasone propionate according to claim 5 in the manufacture of pharmaceutical compositions for administration on a twice daily basis.
>
> 7. Pharmaceutical compositions according to any one of claims 1 to 4 substantially as described herein by way example."

22. As to the manner in which this formulation of two compounds might be achieved, all of the evidence is agreed that no new formulation or delivery system is proposed or described. Instead the delivery systems implied, and the range of active compound to excipient, is completely standard and to be judged by the technology of the time.

The Experts

23. I am required to look at the issues objectively. Dr. Palmer, the actual inventor of this patented medicine, was not called as sadly he has since passed away. From the point of view of objective analysis, in any event, his evidence would only have had a limited role. Instead, a range of experts testified on the issues that I have outlined. I would confine myself, as far as possible, to indicating the weight which I have attached to their evidence. The evidence of each expert

has been analysed in the context of all the testimony in the case. Any conclusions I have reached is on the same basis and was not arrived at in isolation from any opposing viewpoint expressed by another expert. On many issues, both simple and complex, the experts on each side have taken determinately different stances. It would amount to a breach of their rights for me to attempt to figure out what their personal motive might be in arriving at apparent contradictions on matters of science. Instead, I am concerned with the validity of their opinion and its utility. I am not here to add to the science on this subject but, rather, to decide which piece of contradictory evidence I find to be the most likely. In preferring one opinion over another, I am simply indicating that one is more probable than another.

24. The authorities are agreed on the purpose of an expert in a patent case it is to clothe the court in the mantel of expertise worn by the witness, so the court may make its own decision. In *Davey v. Magistrates of Edinburgh* [1953] S.C. 34 at 40, the Court of Session, through the Lord President, Lord Cooper, made this statement as to the correct approach to the testimony of experts:-

> "Expert witnesses, however skilled or eminent, can give no more than evidence. They cannot usurp the functions of the jury or Judge sitting as a jury, any more than a technical assessor can substitute his advice for the judgment of the Court – *S.S. Bogota v. S.S. Alconda* [1923] S.C. 526. Their duty is to furnish the Judge or jury with the necessary scientific criteria for testing the accuracy of their conclusions, so as to enable the Judge or jury to form their own independent judgment by the application of these criteria to the facts proved in evidence. The scientific opinion evidence, if intelligible, convincing and tested, becomes a factor (and often an important factor) for consideration along with the whole other evidence in the case, but the decision is for the judge or jury."

25. In addition, it should be noted that an expert is a human being. He or she may not have a perfect recollection as to the practice of their art twenty years ago. That is not a fault. To some extent, the scientific papers from that time may assist them; but even here, in some instances, the expert witnesses could not agree about the meaning of a text. A choice could not be avoided in this case. In making such a choice, I am deciding on weight and on recollection. I am not, in saying that I prefer one witness on an issue to any other, attacking their credibility or their professional brilliance. My thanks go to all of the witnesses. I have had the expert assistance of Dr. John Stephens, lecturer in organic chemistry at the National University of Ireland, Maynooth, in assessing this evidence. His help has been invaluable, but the decision in this case is mine.

Obviousness

26. An obvious step is the antithesis of an inventive step. Since this patent is being attacked by Ivax, they bear the burden of proving that the combination of molecules in Seretide was obvious. The task of the court is to weight up the evidence and to decide whether the invention was obvious. This is what the statute requires. Novelty is not the same as inventiveness. A product may be new, but it may not have involved an inventive step because that novelty would have been obvious, as of the priority date, to a person skilled in the art. There may be many variables between the claimed invention and the state of the art as of the priority date. What is, or what is not, obvious to a person skilled in the art involves an identification of the step that is alleged to be inventive against the background of the common general knowledge of an objective person skilled in the art, in the light of any relevant prior art. What the nature of that difference might be, and so constitute an inventive step, was well explained by Lord Hoffmann in *Biogen v. Medeva* [1997] RPC 1 (HL) 34:-

> "Whenever anything inventive is done for the first time, it is the result of the addition of a new idea to the existing stock of knowledge. Sometimes, it is the idea of using established techniques to do something which no one had previously thought of doing. In that case the inventive idea will be doing the new thing. Sometimes it is finding a way of doing something which people had wanted to do but could not think how. The inventive idea would be the way of achieving the goal. In yet other cases, many people may have a general idea of how they might achieve a goal but not know how to solve a particular problem which stands in their way. If someone devises a way of solving the problem, his inventive step will be that solution, but not the goal itself or the general method of achieving it.".

27. Much of the case law on the notion of inventiveness, and its antithesis obviousness, warns against the adaptation of a form of words that becomes a substitute for the statutory test. The written submissions in this case helpfully point up the differences in approach between the Boards of Appeal of the European Patent Office and the English Courts. The former generally, but not necessarily exclusively, adopts a problem and solution approach. This is not a rule of law but, rather, a method of furnishing the tribunal with the correct mental reference to answer the fundamental question as to whether an alleged inventive step was obvious. The three main stages involve:-

1. Determining the closest prior art;

2. Establishing the technical problem to be solved;

3. Starting from the closest prior art and the technical problem, then considering whether or not the claimed invention would have been obvious to the skilled person.

28. While this approach is useful, especially as the question of obviousness is assessed from the position of the state of art at the relevant time, I note the four stage test used by the courts in England has been approved in this jurisdiction. I would prefer in future to use the European test but as the parties have agreed the English test, I regard it also as helpful as a point of reference. Neither test changes the result by its application. No test, however, can be designed or applied in any way that moves the court away from its statutory duty to consider the question of obviousness. Fundamentally, I bear in mind the following statement of Kitchin J. in *Generics (U.K.) Limited v. Lundbeckas* [2007] R.P.C. 32 at para. 72:-

> "The question of obviousness must be considered on the facts of each case. The court must consider that 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 which the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

29. In *Pozzoli S.P.A. v. B.D.M.O. S.A.* [2007] F.S.R. 37, 872 at 879, Jacob L.J. restated the traditional four step English test in a manner in which I regard as acceptable, as follows:-

"1 (a) Identify the notional "person skilled in the art";

(b) Identify the relevant common general knowledge of that person;

2. Identify the inventive concept of the claim in question or if that cannot readily be done, construe it.

3. Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;

4. Viewed without any knowledge of alleged invention as claimed, do these differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

30. The test of obviousness cannot, as a matter of law or as correct reasoning, be approached with the benefit of hindsight. I warn myself about being misled by the simplicity of any solution into believing that it must have been obvious. If one falls into that error in looking at an inventive step, the concept of the common general knowledge becomes completely distorted. Rather, my task is to consider whether it would have been obvious to a person skilled in the art, and therefore having common general knowledge, to take the new long acting â-agonist salmeterol, an analogue of salbutamol, perhaps in a physiologically acceptable salt form, and to combine it with the new steroid fluticasone propionate in a pharmaceutical preparation. In the light of the common general knowledge, and the relevant cited prior art, can this be regarded as an invention? Over this issue, the previous combination preparation for asthma produced by Glaxo, as Ventide, looms large.

31. Simply because the research avenue is sensible, it does not follow that if it produces a novel outcome that a claimed invention is to be condemned as obvious. Where a number of sensible lines of inquiry present themselves, but without a clear indication as to which may be successful, an issue can arise as to whether it was obvious to try the strategy that produces the novel result for which the patent is claimed. It may be obvious as a matter of business investment to try a huge number of different avenues of inquiry. After all, the more experiments that are done, or the more combinations that are tried, the expectation of success is increased, at least statistically. The difficulty here is that in using a concept like 'obvious to try', one may be substituting an incorrect test in place of the concept of obviousness that the court is required to consider. What I am attempting to do is to weigh up the evidence with a view to deciding whether this invention was obvious. I am not in a position to comment of the judgment of Pumfrey J., which I respect but cannot follow. An argument was advanced, however, that were this case being tried now before him that the test as to whether a combination was obvious to try would be qualified by the concept that the skilled person would have to have a reasonable expectation of success. After all, in the field of pharmaceuticals, commercial interests may drive the trial of a huge number of combinations. This does not necessarily mean that they are obvious. I think it is important for me to approve the up-to-date analysis of the concept of obviousness, in terms of obvious to try, presented by Lord Walker of Gestinghorpe in *Connor v. Angiotech*, at paras. 46-50. For the purpose of this judgment I adopt it:-

"I venture to add a few remarks on the notion of "obvious to try," and its relevance to this appeal.

46. Its origin was in the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, a case about a method for production of asbestos cement. After referring to two items of prior art Diplock LJ said at p 495:

> "It is enough that the person versed in the art would assess the likelihood of success as sufficient to warrant actual trial. . . . The Superintending Examiner and the Patents Appeal Tribunal were both of opinion that, filtration processes being common to many industries, these documents, although addressed primarily to the mining and paper industries respectively, were likely to be read by those concerned with the asbestos cement industry, and that such readers would have realised that here was a newly-introduced flocculating agent which it was well worth trying out in their own filtration process. I can see no grounds which would justify this court in reversing this concurrent finding by two expert tribunals."

Diplock LJ was not here expounding a technical doctrine. On the contrary, he was at pains to stress the need to avoid generalisation. A little earlier in his judgment he had said (at pp 494-495):

> "I have endeavoured to refrain from coining a definition of 'obviousness' which counsel may be tempted to cite in subsequent cases relating to different types of claims. Patent law can too easily be bedevilled by linguistics, and the citation of a plethora of cases about other inventions of different kinds. The correctness of a decision upon an issue of obviousness does not depend upon whether or not the decider has paraphrased the words of the Act in some particular verbal formula. I doubt whether there is any verbal formula which is appropriate to all classes of claims."

47. *Johns-Manville* was decided over forty years ago, and was concerned with a fairly low-tech process. During the last forty years the volume of high-tech research has increased enormously, especially in the fields of pharmaceuticals and biotechnology. The resources committed to research are enormous, because the potential rewards in world-wide markets are so great. Competition is fierce. In this climate "obvious to try" has tended to take on a life of its own as an important weapon in the armoury of those challenging the validity of a patent.

48. The process has been vividly described in observations made out of court by Sir Hugh Laddie, Patents - what's invention got to do with it? (Chapter 6 in Intellectual Property in the New Millenium, p.93):

> "When patents and patent applications succumb to invalidity attacks, obviousness is the most common cause. This inevitably generates friction between the community of patentees and applicants on the one hand and patent offices and national courts on the other. A company which has spent millions of dollars on research and has produced a valuable new drug will be understandably irritated when, say, a court declares the patent invalid for obviousness, thereby opening up the market to competitors who are free to copy. That irritation is likely to be particularly acute when the raison d'être of the patent system is said to be the economic encouragement of research and development.

> The problems can be approached by considering first the concept of 'obvious to try'. The classic statement of this principle is set out in the judgment of the Court of Appeal in *Johns-Manville Corporation's Patent*. It was said that a development should be treated as obvious if 'the person versed in the art would assess the likelihood of success as sufficient to warrant actual trial'. Statements to similar effect have been made by the EPO.
>
> On its face, this produces an unworkable or irrational test. If the reward for finding a solution to a problem and securing a monopoly for that solution is very high, then it may well be worthwhile for large players to examine all potential avenues to see if one gives the right result, even though the prospects of any one of them succeeding are much less than 50/50. What makes something worth trying is the outcome of a simple risk to reward calculation. Yet, if the reward is very large, the avenues worth trying will be expanded accordingly. So, the more commercially attractive the solution and the more pressing the public clamour for it, the harder it will be to avoid an obviousness attack. In those circumstances a solution which is quite low down a list of alternatives, all of which are more or less worth trying, will fail for obviousness; a consequence which is consistent with the decision in *Brugger v Medic-Aid*."
>
> Sir Hugh goes on to suggest that as technology advances rapidly, this is a serious and growing problem.
>
> 49. In the Court of Appeal in this case Jacob LJ (paras 39-45) made some comments to the same general effect, with a useful anthology of citations from different jurisdictions.
>
> 50. This background helps to explain the question which the judge asked himself (at the end of para 61 of his judgment), including the reference to testing a product "without any expectation of success" (which Lord Hoffmann refers to as an "oxymoronic concept"). The judge sought to answer the question (para 62) by assessing the contribution to the art made by the specification, and decided (para 64) that the only real contribution was a proposal for testing (and no more). In this way arguments that would normally be regarded as relevant to insufficiency crept into a challenge on the ground of obviousness."

32. Earlier, Lord Hoffman had also approved of the earlier authorities. He noted that Jacob L.J. had correctly summarised the question as to when an invention could be considered obvious on the grounds that it had been obvious to try. The conclusion was that the notion of something being obvious to try "was useful only in a case in which there was a fair expectation of success. How much of an expectation would need to be decided upon the particular facts of the case".

Prejudice

33 In considering the nineteen very long days of testimony in this case, it is clear that most of the evidence was directed either for or against whether the common general knowledge of the skilled person would include the prejudices, preferences and attitudes of that time, such that the person skilled in that art would reject the combination in Seretide at discussion stage; or would simply reject it out of hand. That prejudice might, or would it is argued, be such so as to lead away from an item of prior art as a point for innovation. In other words, the core issue here is was there a prejudice against this combination by reason of the thinking as of 8th September, 1989; the priority date? As I shall shortly make clear, by referring to a person skilled in the art, I am referring to a team. Nonetheless, it is as well to deal with this legal issue of prejudice at this point. As a matter of law, a prejudice in the state of the art may mean that even trying a combination of two drugs may not necessarily be obvious, it may in fact be inventive. As I seek to remind myself constantly, in the light of the extraordinarily detailed evidence, obviousness is what Ivax, as petitioner, must show. Here, I quote some passages from the legal submissions of Glaxo, as respondent on this issue. This is their case on prejudice in the common general knowledge, as amplified by oral submissions and as presented through evidence:-

> "1. This case concerns a life-transforming medicine, *Seretide*®, created by the Respondent ("Glaxo") after years of costly medical research, which has allowed people with debilitating respiratory disorders such as asthma and chronic obstructive pulmonary disease to lead normal lives. *Seretide* represents the best of medical innovation not least because, at the time it was created, skilled workers:
>
> > (a) Would have expected the two components to exhibit chemical reactivity and instability, such that they would not have expected that the two medicines could form a stable formulation that could sit on pharmacy shelves or in warehouses for months before use;
> >
> > (b) Could not have predicted the synergistic activity of the two components;
> >
> > (c) Would have had no clinical motivation to create a combined preparation of the two components, as they would have had serious concerns about the regular use, in combination or otherwise, of â-agonists in asthma therapy.
>
> 188. In the patent, Glaxo claims a composition of two compounds that could not have been expected to be capable of co-formulation into a stable pharmaceutical composition and that, prior to the invention, could not have been thought to be anyway worthwhile combining in terms of arriving at a useful treatment for asthma. It is submitted that now that the inventor's instincts as to this particular combination as a treatment for asthma have been borne out - the composition having been shown to have produced a revolutionary and practice-changing therapy for asthma - it should be judged to merit the patent protection initially granted."

34. Any issue as to the synergistic activity of the two components in this drug preparation is not now being pursued. Nonetheless, I am grateful Professor Ian Adcock for the illumination which he brought to these complex issues. I refer to my conclusions on it later in this judgment. The issue of chemical reactivity could have been removed from my analysis of the evidence in this case, were I to decide against the amendment to the patent sought by Glaxo. This seeks to remove the words "or sequential" when it occurs in the patent after describing the "simultaneous" taking of the two compounds. In the event of an incorrect conclusion of law on that issue, however, the parties on appeal are entitled to the benefit of whatever factual analysis would enable the Supreme Court to finally decide the case. Hence I leave the issue of amendment over to the end of this judgment.

35. Since a huge body of evidence has been directed in favour of and against the prejudices alleged to be inherent in the

common general knowledge of the time, I should clarify what those I am now concerned with involve: firstly, the potential chemical reactivity between salmeterol and fluticasone propionate so as to prejudice a combination; secondly, the issue as to whether the medical community had a prejudice against the regular use of â-agonists in asthma therapy; and, thirdly, whether there was also a prejudice against using combined preparations of trachea muscle relaxants and anti-inflammatory medications as a combined preparation, particularly â-agonists and steroids. If these prejudices are shown to be unwarranted by the evidence, I must nonetheless decide whether this alleged invention was obvious. That, however, is a much easier task if these prejudices are disposed of by reducing them to the rank of mere allegations.

36. In this regard, I adopt as correct the analysis by Jacob L.J. in *Pozzoli S.P.A. v. B.D.M.O. S.A.* [2007] FSR 37, 872 at 879:-

> "24. Sometimes a patentee seeks to defend his invention from a charge of obviousness by saying that there was a technical prejudice against it. Such an argument was run here. The Judge said:
>
> > Mr Carr submitted that the idea of overcoming a prejudice must consist in overcoming a false prejudice; in other words a mistaken technical belief that deters the unimaginative skilled person from pursuing a particular path. Mr Carr characterised this kind of false belief as a "lion in the path" (see Bunyan: The Pilgrim's Progress, The Third Stage: "Fear not the lions, for they are chained, and are placed there for trial of faith where it is, and for discovery of those that have none: keep in the midst of the path, and no hurt shall come unto thee."). In such a case the patent reveals that the belief was mistaken, and thus contributes to the art. If on the other hand the perceived technical problem exists in the same form both before and after the claimed invention, then the prejudice has not been overcome at all. In such circumstances overcoming the prejudice cannot be part of the inventive concept, although the technical means for dealing with the perceived problem can be. I accept this submission.
>
> 25. I would not analyse it that way myself. There is an intellectual oddity about anti-obviousness or anti-anticipation arguments based on "technical prejudice." It is this: a prejudice can only come into play once you have had the idea. You cannot reject an idea as technically unfeasible or impractical unless you have had it first. And if you have had it first, how can the idea be anything other than old or obvious? Yet when a patent demonstrates that an established prejudice is unfounded – that what was considered unfeasible does in fact work, it would be contrary to the point of the patent system to hold the disclosure unpatentable.
>
> 26. I put it this way in *Union Carbide v B.P.* [1998] RPC 1, 13:
>
> > Invention can lie in finding out that that which those in the art thought ought not be done, ought to be done. From the point of view of the purpose of patent law it would be odd if there were no patent incentive for those who investigate the prejudices of the prior art.
>
> 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.
>
> 29. This analysis does not require a different way of looking at the inventive concept depending on whether or not the patentee has shown the prejudice is unjustified as the Judge thought at [67]. It is simply that in the former case the patentee has disclosed something novel and non-obvious, and in the latter not. The inventive concept, as I have said, is the essence of what is in the claim and not dependent on any question about a prejudice being overcome."

37. The issues put forward by Glaxo illustrate, to my mind, how an expectation of reactivity, in the context of the necessity for certainty of ingredients within the long life of a pharmaceutical preparation, or a clinic prejudice against a combination therapy or regular doses of â-agonists, may be such that overcoming it involves invention. As was stated by Michael Fyshe Q.C. giving the judgment in *Dyson Appliances Limited v. Hoover Limited* [2001] All E.R. (D) 37 at 156:-

> ". . . common general knowledge has both positive and negative aspects… For the present purposes, the addressee is nonetheless deemed to have been presented with (in effect) three items of prior art wherein it is proposed to clean dirt laden air by means, not of bags, but of cyclonic action alone. He is also assumed to take some interest in them, however inimical the proposals may be to his likely way of thinking at the time. In terms of its impact on the issue of obviousness, I believe that this negative thinking which… amounted to prejudice would at least have caused the addressee to regard modification to any of these prior art proposals with considerable reserve if not overt scepticism. This likelihood must, I think, be given due weight, in my view of the matter. I cannot think that any cited prior art would *ex facie* be likely to have the led the addressee at the relevant date with any enthusiasm to effect the often substantial changes which would bring these proposals within a claim of the patent"

38. I am conscious as well, however, that a debate is not necessarily a prejudice. It may be, however, that within a situation of apparent debate that a prejudice may sometimes be found where the side of the debate representing the anti-prejudice camp is overwhelmed in such a decisive way that the issue seems to be clearly settled.

39. Finally, I note that the patent says nothing about any novel solution for the purpose of combining two apparently reactive compounds, namely salmeterol and fluticasone propionate. Nor does the patent teach that the new combination of these drugs would be a clinical advance in respect of the ingestion of regular â-agonist drugs. Any decision as to obviousness, however, must depend upon an analysis of the evidence. I now turn to the question of the person skilled in the art. This person, as in almost all pharmaceutical cases, would be a team.

The Team

40. The 1992 Act, requires me to consider an inventive step from the point of view of a person skilled in the art. This is an objective test. It is clear that under s. 11(2) the state of the art extends beyond the boundaries of the State. In that regard, the opinion expressed by Dr. Conor Burke as to clinical practice in Ireland from 1986 through to 1994 is of very limited benefit. I am satisfied, instead, that I am obliged to consider the objective test as to the state of the art globally, and not simply in accordance with what a skilled and highly committed asthma specialist would have found in Ireland as of the priority date. As Clarke J. remarked in *Ranbaxy Laboratories Limited v. Warner-Lambert Company* [2007] I.E.H.C. at 4.5:-

> ". . . it is also appropriate to note that each case must be determined on the evidence presented to the court concerned. For the reasons which I have already analysed, that evidence should be confined to demonstrating what the knowledge of the skilled addressee would have been as of the priority date. Given that the relevant knowledge is international it would be surprising if there were very significant differences between the conclusions which could properly be arrived at from one country to the next as to what the knowledge of the skilled addressee as of that date would have been. However, the court is, nonetheless, bound by the evidence presented to it."

41. As I have said, the person skilled in the art in this case would be a team. Nonetheless, that team is regarded as a kind of objective legal person for the purposes of considering what the state of the art would be. The European Patent Office Guidelines, Part C. Chap. IV, s.11.3 characterises such a person as an ordinary practitioner in the field of technology who is aware of what was common general knowledge in the art as of the relevant date. My task is properly put by Fletcher Moulton L.J. in *British R. Syndicate Limited v. Minerals Separation Limited* [1909] 26 R.P.C. 124 at 128, as being:-

> "To arrive as closely as it can as the mental attitude of a well-instructed representative of the class to whom the specification is addressed, and no more. In other words, in the performance of this part of its task it has to ask itself what ought fairly to be considered to be the state of knowledge in the trade or profession at the date of the patent with respect to the matters in question, and if any facts or documents or such that in ordinarily probability they would not be known to competent members of such trade or profession, they ought not to be taken, either for against the public on the one hand, or the inventor on the other, as forming part of public general knowledge."

42. A piece of knowledge becomes general knowledge when it is generally regarded as a good basis for further action; *General Tyre and Rubber Company v. Firestone Fire and Rubber Company Limited* [1972] R.P.C. 457 at 483.

43. The common general knowledge is the technical background of the notional man in the art against which the prior art must be considered. This is not limited to material which he has memorised and has at the front of his mind. It includes all that material in the field in which he is working which he knows to exist, which he would refer to as a matter of course if he cannot remember it and which he understands is generally regarded as sufficiently reliable to use as a foundation for further work or to help understand the pleaded prior art. That does not mean that everything on the shelf which is capable of being referred to without difficulty is common general knowledge, nor does it mean that every word in a common textbook is either. In the case of a standard textbook, it is likely that all or most of the main text will be common general knowledge. In many cases, common general knowledge will include, or be reflected, in readily available trade literature which a person skilled in the art would be expected to have at his or her elbow and regard as basic reliable information.

44. I further accept that to common general knowledge must be added any knowledge that a skilled person would acquire before he embarks on the problem to which the patent purports to provide the solution; *Novartis Attorney General v. Ivax Pharmaceuticals UK Limited* [2006] E.W.H.C. 2506 at 27. In addition to common general knowledge, I must examine what the prior art on the issues in this case teaches the skilled team. Since pulling together several pieces of prior art may itself amount to innovation, a mosaic of several pieces of prior art is not inherently likely to be obvious. Where a cross reference exists in prior art, however, it may be otherwise. Where a piece of information is common to the team in this area, such may be common general knowledge. Where a member of the team has a piece of prior art, properly so considered, it is to be expected for him or her to share it with the team. As the team will have different sub-specialities, I see no reason why they would not add to the discussion as to the prior art, provided the team remains uninventive. The caution against mosaicing is an aspect of the proper approach to obviousness. By unthinkingly applying that caution, the statutory test of obviousness may be lost sight of. Let us remember what a mosaic is. It is an inventive and carefully thought-through arrangement of different colours so as to create a work of art. From the micromosaics of Byzantium, that approach in artistic brilliance even our own Book of Kells, to the less elaborate artworks of recent eras, the inventive nature of a mosaic is manifest in varying degrees: but, that aspect of invention, of imaginative agglomeration, and non-obviousness as to the design, is always there. Taking a few pieces of the existing state of the art and coming up with a new step cannot always properly be referred to as mosaicing. The nature of the interaction between the pieces of prior art must be such as to require an inventive step before the test for registration of a patent under the 1992 Act, and under the Convention, can be met. It can be argued that to put together (a) and (b), having regard to an existing opinion in prior art as to the utility of (c), involves a mosaic. I do not think that this is always so. The question is not: are there a number of parts to this patent which claim statutory protection because it is inventive? Rather, the question is: is there anything about putting together (a) and (b), or whatever number of pieces of prior art, which is inventive? My view in this case is that the use by the team of the pieces of prior art cited does not attract the caution reminding me that a mosaic is, of its nature, inventive. This patent is not in place because of a mosaic, properly so described.

45. I do not propose to embark on any discussion, or to make any findings, concerning what is alleged to be the difference in evidence between the Glaxo presentation of the skilled team in the United Kingdom and in this jurisdiction, Ireland. Instead, I am assessing the evidence in this case through the eyes of a skilled but unimaginative team. As a matter of law, a novelty is not properly patented through finding public material showing that solution and what is obvious in conclusion of a consideration. The team with common general knowledge that comes upon a piece of prior art cannot claim statutory protection in respect of it, or of anything that is obvious in consequence of it. The members of the skilled team are those who have a practical interest in the subject matter of the invention and it is to them that a patent is addressed. Since it is well settled that the skilled person can be a team, the kind of individuals with different skills and knowledge are proposed must be described in order to make a finding of fact as to the makeup of that skilled team.

46. Between the parties, there is little difference. Ivax submits that the skilled team would comprise clinicians who have an interest in asthma, clinical pharmacologists and formulation scientists. I accept that I am obliged to take a realistic view as to what that makeup of this skilled but unimaginative team would be. In the original formulation of a team by

Ivax, no medical chemist was included. I need to explain the logic behind this. During the course of evidence, it was conceded by Professor Graham Buckton for Ivax that the team would consult a medicinal chemist. Glaxo's submission is that the skilled team would not only include, but would be led by, a medicinal chemist. Either he or she would be chairing the meetings or a leading role would be ascribed to him or her so that any opinion expressed from that source would carry weight, and probably be an important voice. Glaxo's submission is that a medicinal chemist would immediately notice the alleged problem concerning the reactivity of the two compounds in Seretide and caution against fluorinated thioesters as acylating agents. This is an issue which I have to address in some detail, but shortly. My view on this matter is that the team would include a medicinal chemist and that that view of the section of the team would carry considerable weight. My view is also, however, that Professor Graham Buckton is correct that the formulation scientists would probably have an answer to any concern that he or she might have raised. I also regard it as important that the members of the skilled team, though uninventive, would be persons of wide knowledge of their individual subjects. A caution raised by the medicinal chemist would, on the evidence as I analyse it, be capably answered by the formulation scientist.

Asthma

47. My understanding of the nature of asthma, which is important to the decision that I must make in this case, is derived from the evidence of the experts before the court, particularly Dr. Conor Burke, and from references in the evidence to *Barnes* [1989], *Drazen and Others* [1996], and *Page* [1987]. Asthma affects 5 % to 7% of the population of North America and Europe according to conservative estimates. About 60% to 70% of patients with asthma have mild conditions and tend to be treated with inhaled â-agonists taking these in inhaled form, usually as prescribed on an as needed basis. Some people would take one puff per week; others would take one per day. These are the less severe cases. Quantifying asthma in a community is difficult but it is also challenging to quantify in patients. One can have bad symptoms one month and not the next. One may be off an inhaler for years. However, one will still be classified by the medics as an asthmatic. The disease has been recognised for some centuries. According to some surveys it can affect up to 25% of a population if one includes wheeze resulting from infection. It is an illness with considerable morbidity. In children it is one of the most common diseases and is responsible for considerable absenteeism from schools. While deaths from asthma are relatively uncommon, they have been the subject of many scientific papers. In the 1980s it was found that deaths from asthma were on the rise in many countries, including the United States. As *Page* [1987] indicates:-

> "Somewhere, somehow, something is going wrong which may relate to a whole range of factors, including under-diagnosis, under or inappropriate treatment and poor compliance…"

48. It is against this background that the two active compounds in Seretide made their appearance. Autopsy examinations of patients dying from asthma tended to show: gross inflammatory changes of the airways with oedema of the sub-mucosal tissue and airway wall; infiltration with inflammatory cells; mucus plugs; and bronchial smooth muscle hyperplasia. Asthma can apparently be an inherent condition within a patient, not caused by an external stimulator of inflammation or, it seems more commonly, it can be caused as a kind of allergic reaction or reaction to disease whereby the lining of the trachea becomes inflamed and so causes spasm of the muscles. This is not yet completely understood. I quote from *Page* [1987]:-

> "Asthma has been considered for many years to have at least two major pathological components: bronchospasm of airway smooth muscle and airways inflammation. Traditionally, asthma has been seen as reversible airway obstruction with emphasis on smooth muscle bronchoconstriction. It is now becoming increasingly apparent that asthma should be considered an inflammatory disease with a component of chronic airflow obstruction and therefore treated as such."

49. Since this case is concerned with the state of art that existed on filing the patent, and September 1989 was the priority date, it makes sense to give a brief initial survey as to the approaches to treating asthma current in the 1980s. Two basic forms of treatment were possible in theory. These related to the trachea muscle and to the lining of the trachea. The lining of the trachea could be treated, as I have indicated, over a period of time, by steroids and corticosteroids and the patient could also be treated by antihistamines as a basic anti-allergy medicine. To deal with the spasm of the trachea muscle, anti-cholinergics could be, and often were, used as was xanthine, a drug which is part of the chemical family that also includes caffeine, and by â-agonists. â 2-agonist drugs can be problematic, but were certainly more problematic in the earlier stages of drug development. The â receptors in the heart are called â 1-agonists, whereas those in the trachea are â 2-agonists. By using a general â-agonist medicine, the problem was that the heart and the trachea could both be affected and, over time, this could have dangerous effects. It was therefore a serious advance when a â 2-agonist drug could be identified and prepared so that the trachea muscle could be treated as to its â 2 receptors without, at the same time, affecting the working of the heart. Salbutamol, a â 2-agonist, was therefore a welcome development in the treatment of asthma. Because salmeterol acts for much longer in relieving bronchial muscle spasm it, in turn, was a serious advance on salbutamol. No one disputes this. Steroids reduce inflammation of the trachea lining. If corticosteroids were taken for too long, or in too high dosages, however, the body might reduce its own cortisone production and that too could be serious. The search was also on for better steroids. These issues need to be considered in more detail in attempting to answer the central questions in issue and in assessing the scientific evidence.

The Drugs

50. I now wish to give some basic information in relation to salmeterol and fluticasone propionate, the drugs that are combined in Seretide, and their predecessors. Ventolin is the brand name for salbutamol. This is a â 2-agonist. It has almost immediate effect, about 5 minutes, but its bronchodilator action lasts only about four hours. Its analogue salmeterol, part of Seretide, takes about 20 minutes to affect bronchodilation. That may not have been known as of the priority date. I ascribe, however, little importance to the gap in bronchodilation as between five minutes or less for salbutamol (because that is used somewhat more as a rescue than as a maintenance medication, notwithstanding advertisements from 1989) and salmeterol, which has a bronchodilation time for relief of about 20 minutes (and which is clearly a maintenance, and therefore a regularly taken, medication). On the evidence, salbutamol, was developed some time in the late 1960s by Glaxo and it is an early and very good example of a â 2 -agonist. In 1990, the official figures show sales in the United Kingdom of 19,328,200 units of Ventolin.

51. Becotide is the brand name for beclomethasone dipropionate. This is a corticosteroid and it works by reducing the inflammation of the trachea. This drug seems to have been developed some time around 1971 and, on its own, takes about seven days to reduce the inflammation of the lining of the trachea to an acceptable level. When it does that, the effect will usually assist bronchodilation. The patents for both of these drugs are also owned by Glaxo. In 1990, the sales for Becotide in the United Kingdom were 7,860,600 units. Ventide is a combination of these two drugs: beclomethasone dipropionate and salbutamol. Compared to the sales of these two previous drugs, its take-up was poor though, perhaps, improving. On the evidence, the sales in the United Kingdom for Ventide in 1989 were 250,000 units and in 1990 these had reached 425,000 units. If there was an increase in sales, I attach no importance to it. I accept, however, that compared to the combined sale of Ventolin and Becotide, the sale of Ventide was low.

52. It is of limited significance to what follows, on the issue of medicinal combinations in asthma, and regular use of inhaled â-agonist therapy for asthma, that Ventide was granted an authorisation under the Medical Preparations (Licensing, Advertisement and Sale) Regulations (S.I. No. 210 of 1984), on the 14th May, 1990 for sale in Ireland. This occurred a year after the priority date and at a time, as will be seen, when it is argued that any medical doctor believing in combined therapy for asthma or in regular â-agonist therapy for asthma was way out of date. The drug was launched in Ireland in April, 1991. It was withdrawn in April, 1996. The relevant sales figures have been produced to me. As of the year ended December, 1993, Ventide had sales in Ireland of 85,549; as of December, 1994, sales of 99,596; as of December, 1995, sales of 72,167; and as of December, 1996 (the year it was withdrawn from the market), sales of a much lower amount. I bear these figures in mind when coming to the issue of both national and international practice on the issues of combined medication and regular ingestion of â-agonists in asthma therapy. Beclomethasone dipropionate as Becotide had very good sales in Ireland during this time. As of December, 1993, it sold over 4 million units. Ventolin, which has the active ingredient salbutamol, was selling from 1993 to 1996, the years when I have the figures, in figures that were surprisingly aligned with Becotide.

53. Flixotide is the brand name of fluticasone propionate. This has patent 877 registered to Glaxo and was initially, apparently, developed for use on inflamed skin. In 1988 it came to be recognised for use in the airways as a steroid treatment for inflammation associated with asthma. Both fluticasone propionate and salmeterol were announced in the pharmaceutical industry journal 'Scrip' in 1987 and again mentioned in 1989. In 1987, salmeterol was announced as an analogue of salbutamol in 'Scrip'. This journal is widely read in the pharmaceutical industry. I regard this as important on the issue of obviousness. Serevent is the brand name of salmeterol, which has the 800 patent. When described by *Coleman and Others* [1988], salmeterol was welcomed by those in the field of asthma therapy. I accept the evidence of Dr. John Costello on the notice taken of these drugs in the therapeutic community, of which he is and was a distinguished part. It was a new drug which, compared to salbutamol, and was much longer lasting in its effects. Instead of four hours, one could expect twelve hours relief in bronchodilation. Again, it was developed by Glaxo. As we know, Seretide is the brand name for the preparation in issue here, of salmeterol and fluticasone propionate. This combines the â 2 -agonist with the steroid and is designed to be taken twice a day, once every 12 hours, by asthma sufferers. As of the priority date, it was published that both drugs were in phase III clinical trials.

54. The announcement in 'Scrip' of 4th March, 1987, is cited as part of the prior art. Since it is accepted by me as such, and since it is important to my decision, I now quote the relevant section describing salmeterol and fluticasone:-

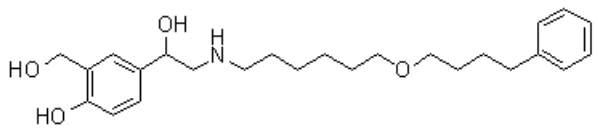
> "The beta 2 stimulant, salmeterol, and the anti-inflammatory steroid, fluticasone, are the resultant product candidates from research to improve salbutamol (Ventolin) and beclomethasone dipropionate (Beclovent/Becotide).
>
> Salmeterol, a chemical analogue of salbutamol is specifically designed for inhalation – its bronchodilating action in asthmatic patients at 50-200mcg is at least as intense as that of salbutamol 200mcg with a duration of action about four times longer than salbutamol according to Dr. David Jack, Research Director (Glaxo Holdings). Bronchodilation is maintained for at least 12 hours he said.
>
> The company believes that salmeterol's duration of action and selectivity makes it the ideal bronchodilator for maintenance treatment in chronic asthma 'because for the first time maximal bronchodilation is achievable without side-affects throughout the day and night with simple twice daily dosage'. Dr. Jack stressed the control exercised by the drug on the diurnal variation in respiratory function in asthmatic patients, which causes acute attacks in early morning. He also pointed out that it did not alter heart rates.
>
> The clinical trial comparing the effects of inhaled salmeterol and salbutamol will soon be extended to include comparison of salmeterol with oral theophylline. Glaxo expects to file for marketing approval of salmeterol in the last quarter of 1989.
>
> Fluticasone dipropionate is substantially more active than beclomethasone dipropionate as a vasoconstrictor and anti-inflammatory agent on human skin but has no greater suppressive effect on the hypothalamic/pituitary/adrenal system, Dr. Jack said. It may therefore, he added, have a more intense anti-inflammatory effect in the lungs at tolerated doses. Comparative studies with beclomethasone dipropionate are under way. Product licence applications could be filed early in 1989."

55. Salmeterol was described in *Thorax* [1988] by Ullman and Svedmyr. This is cited as part of the prior art. It is accepted by me as such. The abstract reads:-

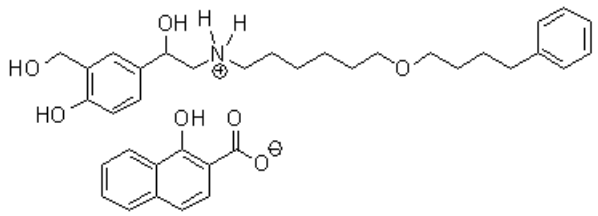
> "Salmeterol is a new inhaled â 2 Adrenoceptor agonist which has been shown in animal experiments to produce a more prolonged bronchodilator effect than currently available â 2 Adrenoceptor agonist. It was studied in eight adult asthmatic patients. Each patient received on separate days salbutamol 200 mcgs and salmeterol 50, 100 and 200 mcg according to a randomised, double-blind, cross-over design. FEV 1, peak expiratory flow (PEF) heart rate, blood pressure and tremor were recorded in the clinic for six hours after drug inhalation: PEF was recorded for a further six hours at home. All three doses of salmeterol produced peak increases in FEV 1 (meaning 0.5 – 0.8l) and FEV (71 – 100 l/min) similar to those produced by salbutamol 200 mcgs (0.51 and 74 l/min). After salbutamol FEV 1 and PEF had returned to base line within six hours, but after all three doses of salmeterol, more than half of the maximum bronchodilator effect remained after twelve hours. The effects of salbutamol and the two lower doses of salmeterol (50 and 100 mcg) on cardiovascular measurements and on tremor were similar, whereas after salmeterol 200 mcg, there was a small decrease in diastolic blood pressure and an increase in heart rate and tremor. Thus inhaled salmeterol has a long acting bronchodilator action in asthmatic patients. This effect may be of value in the treatment of asthma, particularly in patients with nocturnal symptoms."

56. The relevant chemical formula for salmeterol was produced together with the chemical formula for salbutamol underneath it. This showed a secondary alcohol hydroxy OH group and a secondary amine, the nitrogen group, together with a primary alcohol CH^2 OH group in the chemical structure. Both salmeterol and fluticasone propionate were quite new drugs as of the priority date for Seretide.

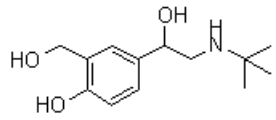
57. Here are the diagrammatic representations of salmeterol, one of its salt forms as salmeterol xinafoate, and salbutamol:



Salmeterol



Salmeterol xinafoate



Salbutamol

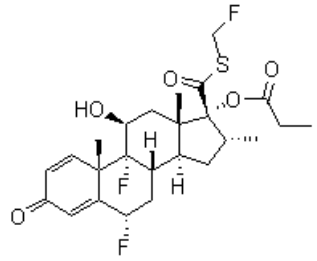
58. It is fair to say that salmeterol caused considerable excitement among physicians specialising in asthma medicine when it appeared. This is reflected in the article by *Deuchar* [1989] where he said:-

> "A highly selective â 2 stimulant, inhaled salmeterol has been shown in early clinician trials, not only to control symptoms in a regular twice daily – dosage, but also to abolish virtually any need for intermittent rescue puffs of the more traditional salbutamol inhalers. Professor Margaret Turner – Warwick, Consultant Physician at the Brompton Hospital and President of the Royal College of Physicians, thinks the drug has great potential and stresses the "staggering improvement in early morning peak expiratory flow rates". That the drug appears to have enlisted in Phase II trials. But she has pointed out that there could be problems with tachyphylaxis and rebound phenomena which have yet to be overcome. "We must not get carried way with the notion that this drug is the be all and end all. It should be prescribed in combination with inhaled steroids in the case of there being any doubt at all about the efficacy of monotherapy", she says.".

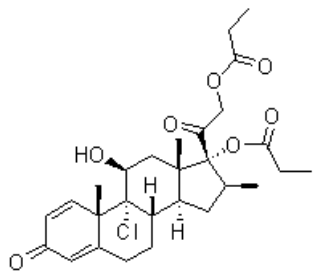
59. The effect of the new drug fluticasone propionate, in comparison to beclomethasone dipropionate, was noted in a paper by *Bauer* [1988]. Since this appeared at a Congress of the European Society of Pneumotology, it can be expected to have been noted. I find the evidence of Dr. Costello persuasive in that regard. The problem with beclomethasone dipropionate was that the taking of corticosteroids in large doses tended to suppress the production of cortisone in the body. The advantage of fluticasone propionate was that it did not at that stage show serious side effects. I quote from the relevant paper:-

> "Fluticasone Propionate is a new corticosteroid which has greater topical activity than beclomethasone dipropionate and minimal systemic activity after oral dosing. We have performed a multicentre randomised double-blind parallel group study comparing BDP 750-1500 mcg with the same dose of FP in 97 patients with severe asthma who were symptomatic at entry to the study. After a run-in period on BDP, patients were randomised to received equal doses of either FP or BDP for a four week period. Lung function was recorded at clinic visits after two and four weeks; in addition patients recorded symptoms and twice daily PEFR on diary cards. Plasma cortisol estimations were made before and after injection of synthetic ACTH at the beginning and end of the study period. Lung function improved in both groups during the study, those treated with FP having a significantly higher FEV1 at 4 weeks 69.2% vs 62.5% predicted, p = .032 for FP and BDP respectively. Morning PEFR(L/min) in the FP treated group was significantly higher than BDP during each two week period…as was evening PEFR during the first two weeks… Evening PEFR for weeks 3-4 was 381 vs 361… symptoms scores also improved but did not reach statistical significance. There were no significant changes recorded in HPA function during the study period. The majority of adverse events reported appeared unrelated to treatment with the inhaled corticosteroids. These data provide evidence that both inhaled FP and BDP are effective in the treatment of severe asthma but that FP is more potent when given in equal dose. FP may therefore offer advantages over BDP in these severe patients."

60. I now show the relevant chemical structures for fluticasone propionate and beclomethasone dipropionate:



Fluticasone propionate



Risk of Reactivity

61. I am satisfied that I should ask myself this question: was the chemistry involved in the two compounds of fluticasone propionate and salmeterol, or a relevant physiologically acceptable salt preparation in the human body like salmeterol xinafloate, such that, at the state of knowledge in 1989, the team considering developing a combination product would have rejected an attempt to combine these? This question involves me looking at the issues as to the potential for chemical reactivity between these drugs as they would have been seen at that stage. This also leads me to ask a second question: would the skilled team proceed to testing in order to determine stability notwithstanding these issues? And then I consider with those questions the nature and cost of such testing. I turn first to the nature of the tests and then consider the chemistry that might be anticipated between these compounds in 1989. My reason for looking at the tests first is that in considering the reactivity the team would have to know what kind of tests they would be facing and what kind of expense. These are practical issues, but important ones nonetheless. The team would judge any issue on the reactivity in accordance with whether there were very simple or very expensive tests anticipated in order to confirm any such prejudice, if it existed. I have also looked at this central issue the other way around, and I arrive at the same result.

Testing

62. I accept the evidence of Professor Alexander Miximovich Klibanov that the basic principle of medicine is to do no harm. In consequence, the stability of a preparation is crucial. He, together with other witnesses, testified that the chances of actually marketing a pharmaceutical for sale are around the level of 1: 10,000 for every compound invented. Most fail because of toxicity and instability issues. When a pharmaceutical decays, which is a serious risk over time, it becomes something else. Resulting compounds may be toxic. One of the crucial issues, however, is the length of time that decay, resulting in an impurity, takes. A pharmaceutical team doesn't need to worry about decay in several years time: it does have to worry about decay over several months. Since water is everywhere, the reactivity of compounds in the presence of water is very important. So is their state as presented in the medicinal preparation; this can be as solid or in solution. A very high level of stability is required over one to two years, as an absolute minimum, he said, by regulatory authorities, particularly the Food and Drug Administration, the FDA, in the United States. International standards are pretty consonant with that. The preparation must remain both efficacious and non-toxic. Any other situation would not be acceptable. Anything beyond 0.1% degradation over the shelf-life of a product requires identification and testing as to what the product is and as to what its effects are. In other words, it becomes a substance which the patient is ingesting and therefore needs to be tested and authorised. Although there was some confusion as to the precise standard as between Professor Graham Buckton and Professor Martyn Davies, I am content to take the most stringent standard. The regulatory authorities in the United States, and probably elsewhere, require to know what the 0.1% is and what it does.

63. Since the development of a product takes place over a period of years, a development team would not lightly run a risk of degradation, it is claimed, because by doing so they would be spending a great deal of money on the early and later stages of development with a consequence of waste, failure and lost opportunity for the development of other medicines, should the product fail these necessarily strict standards. The perception of risk of reaction between salmeterol and fluticasone propionate at the level of knowledge in 1989, was therefore at issue. Professor Klibanov, Professor Stephen Davies and Professor Martyn Davies were the main witnesses, all for Glaxo, in favour of the team not proceeding to any testing of a combination of salmeterol and fluticasone propionate.

64. Whereas Professor Klibanov told me that shelf life for a drug was determined over one to two years at room temperature, all the evidence is agreed that a drug company developing a medicine could not wait that time. The next phase of developing a drug, therefore, after the discussion stage as to the potential of the molecules in terms of their possible mutual reactivity, is to begin an early form of testing. With salmeterol and fluticasone propionate, it would be fair for the team to infer the inherent stability of each over a relevant shelf-life since each of these compounds had been patented. In any event, since both of these compounds are Glaxo products, the drug company can be predicted to have done all the relevant tests on each compound that made, at a minimum, a product sufficiently stable and useful so as not to be rejected in the early stages of development but to be brought on to Phase III clinical trials and to be patented before the priority date in 1989. As noted previously, at the priority date, these drugs were in Phase III clinical trials. My interpretation of the evidence also supports this conclusion.

65. The next phase beyond invention and discussion of a combination product of any two, or more, compounds is to test the stability of the two compounds in relation to each other over a time period that is accelerated, notionally, by increased temperature, solvent state, high light radiation, and water exposure conditions. There is a serious conflict of evidence here between the two formulation chemists who gave evidence in this case, namely Professor Graham Buckton and Professor Martyn Davies. Professor Buckton told me that the usual test condition is to hold the products together at 45º or 60º C using relatively high humidity levels. These are chosen because of the degrading effect of water on compounds. That takes a few weeks. Further stability tests over longer periods of time are then done. These take further weeks or months. The compounds are also tested with excipients, which are the medium in which they are stored as a pharmaceutical preparation and delivered into the body. By this I refer to the lactose, for instance, that makes up most of the dry powder inhaler in Seretide, about 98%, and to the liquid in which the solid particles of the drug are held as a suspension in the aerosol inhaler. If these tests are passed then the compounds, at some stage, have to be tested at room temperature. This may be done while clinical trials are on-going on small, then on larger, human populations. They are, of course, subject to the proviso that the results up to that time have been sufficiently satisfactory. Professor Martyn Davies disagreed with this scheme of testing. Professor Buckton told me that the relevant cost for the initial stress testing would be in the region of £5,000 to £10,000. His level of testing was different in concentrating on stress testing and in consequent expense than that suggested by Professor Martyn Davies. His figure came out at just under $200,000.

66. I need to refer briefly to Professor Martyn Davies' evidence on this. The tests that he would require would all be done together. Of the battery of possible tests he would do the equivalent of a stress test, a photolysis test, a hydrolysis test and an oxidation test. All of these would then be subject to chemical analysis as to the peaks found on chromatography, and the molecular weights of any degradation products would be identified. The data would then be collated, reviewed, and signed off by the senior member of the team assigned to testing. There was not much difference between his evidence and that of Professor Buckton as to what the stress test would involve. Any difference does not influence me.

The products would be heated at 50º and then from that temperature in 10º intervals until degradation was observed. This, he said, would take one to two months. These impressive conditions were designed to force degradation purposely and, in that respect, his evidence does not differ in principle from that of Professor Buckton. Where it does differ is that Professor Martyn Davies believed that photolysis would be performed at the same time on the mixture of the compounds. This would involve exposure to forced conditions and would involve confirmatory studies concerning, for example, packaging. The duration of this test would be 21 days, but it would be run at around the same time as the stress testing. The purpose of this would be to see whether or not the product should be protected from light. Then, at the same time, according to Professor Martyn Davies, a hydrolysis test would be carried out wherein the compounds would be exposed to an acid and to a base, perhaps separately but certainly together as this is a proposed combination product. This would be done at room temperature. Finally, the mixture of the two compounds would be exposed to hydrogen peroxide at 3% for one to two weeks at two different concentrations. When this was done it would be necessary to test the excipient compatibility. Since both a dry powder inhaler and a pressurised metered dose inhaler were contemplated here, both tests would have to be done. The excipient would be mixed in with the carrier over one to two months in order to determine compatibility. The usual dry powder inhaler carrier would be lactose, and the evidence indicates that this is what was common at that time. For the liquid to gas inhaler, as I have called it, the compatibility of the two compounds would be tested with a range of surfactants, for example oleic acid or polysorbate or lecithin. When these were done, there would be an analysis on the compounds, the impurities and, in addition, particle size would be analysed.

67. On the issue of testing, I believe that Professor Martyn Davies is probably not in error in saying that all of the tests that he has mentioned would be done. I do not think that he differs from the evidence of Professor Graham Buckton in that regard; rather, where they differ is as to the timing of the test, the cost of the tests, which test would be done first, and the level of reporting back to the team. In this respect, I prefer the evidence of Professor Buckton. I find as a fact that there is nothing in the full range of tests that would intimidate the team from attempting some level of testing. I consider it probable that a stress test would be done first and if nothing was discovered in terms of reactivity between the compounds, that this would be very good news that would be reported back to the team.

68. I believe it probable that, following this, a light test, an exposure to acid and base test and an oxidisation test would be performed. The most crucial test, however, would be the stress test. In reality, both witnesses are in effect agreed, this would be the first test, though Professor Martyn Davies would have other tests run as well at the same time. I think Professor Buckton is right on this point. The team would probably choose the stress test first. They would have very good reason to do so as this is the core test as to chemical stability. Light, water and acid can be coped with at the state of the art at the time by choosing appropriate blister packs or dark bottles or canisters; all matters of relatively small expense should there be a problem. These other conditions can, as to water, light and solvents, as Professor Martyn Davies told me, be overcome in terms of packaging. As of the state of the art of the formulation chemist in 1989, medicines could be kept away from light, could be kept relatively water free and this did not involve any new invention. Furthermore, I believe that the full range of testing on the two compounds together, as detailed by Professor Martyn Davies, would involve a reporting back to the team at the latest at the halfway stage before excipient compatibility was tested. As regards the cost in consequence, it would be very much less than the $200,000 mentioned by Professor Davies. Furthermore, I find as a fact that a team considering marketing a combination of salmeterol xinafoate and fluticasone propionate would, as a matter of probability, try this stress test initially and then use chromatography to discover peaks and molecular weights. They would then go on to spend more money on doing the photolysis, hydrolysis, and oxidation tests if the results were acceptable. Excipient compatibility would then be tried. This, it seems to me, is far less important on the evidence as I analyse it here. So, overall, the team would not be at all intimated by the cost of testing or the time needed to do it.

69. Professor Klibanov told me that, in general, pharmaceutical companies have a reluctance to use a combination of two active ingredients since the possibility exists of them reacting within the body or in storage. On a pharmaceutical level, the risk always exists that two apparently stable compounds might react together. Drugs can, I accept, react with an excipient, like lactose or glucose or sucrose, whatever the delivery medium is, solid or liquid, or with atmospheric oxygen, atmospheric moisture or light. There is always a real concern that even if an active ingredient is stable separately, by reason of inherent reactivity between compounds they may be unstable when put in combination. An excipient can assist or hinder this. Since water typically accelerates all deleterious reactions, accepting what Professor Klibanov told me, absorbed water on the surface of a particle and absorbed water through the particle can be an added problem. To deliver a solid substance to the lung, it also needs to be ground up or, as it is put, micronised.

70. Part of the case for Glaxo is that the micronisation of the particles even in the solid state would tend to break up their inherent crystalline structure, in the case of salmeterol in its salt form of salmeterol xinafoate, and of the crystalline structure of fluticasone propionate, thus leaving amorphous quantities of the substance likely to be shaken together, brought together by gravity, pulled together in the preparation or pushed together by their inherently hydrophobic quality within an aqueous solution, thus agglomerated, if such was chosen as an excipient or, as in lactose, when prepared within an apparently neutral carrier that is, to a degree, hydrophilic. So, it is argued, the solid state would give little comfort. I do not accept this. As a fact, however, I accept Professor Buckton's evidence that lactose is much less hydrophilic than theory might suggest. Also, even when ground up, I find it hard to see that in 1989 packaging could not keep water content to a minimum. That, after all, is what is done with aspirin which rapidly degrades in water. Micronisation involves making particles very small; in this case as low as 1 and as high as 5 microns. That is what the team would have thought of here.

71. I accept as well, that crystals of a substance tend to be less reactive, even when micronised, then amorphous substances. In grinding them down, however, crystalline substances become in some small part more like amorphous substances, sometimes have glassy surfaces, depending in part on the glass conversion temperature, and that therefore, in theory, they would be more susceptible to reaction even while in the solid state. The problem for the team at discussion stage would be, in theory, that particular sections of the molecule are exposed through the structure of the crystal being thus broken down and thus made more open to interactive chemical influences that might occur in the presence of a reagent; by this I mean the other molecule. While I accept the evidence of Professor Graham Buckton, and I prefer his evidence in this regard to that of Professor Martyn Davies, that the precise nature of crystal to amorphous degradation by micronisation may not have been measurably defined in 1989, it stands to reason that the micronisation of particles gives an increased risk of making them more reactive due, at a minimum, to their small size. Measuring or predicting that risk is what, it seems to me, would have been a crucial question for the team. Furthermore, I fully accept Professor Buckton's evidence that the particles of each substance in this preparation are in a solid state. I regard this fact as crucial to the scientific view which a drug development team would have taken in 1989. When considering a proposal for combining two molecules in a preparation, the team would know that solid state molecules move less than in

solution. This is particularly important in considering how they might be brought together, and how they might be kept apart. Some small amorphous quantity would also remain from the salt form. However, I am not convinced that this is a serious problem, on the basis of the evidence. These are among the dangers that the team would be aware of in 1989 and the question is the reaction of that team, when the idea was discussed, as to whether a preparation of salmeterol and fluticasone propionate should be tried out in tests.

72. My view is that these two new compounds, with the very good initial results quoted to back them up, would be the ones the team would think of developing, and with a good expectation of success, and not any alternative drugs. I cannot, on the evidence see the alternatives as being as attractive. I cannot see developing new molecules as being practical at all. In my view, the practicalities of costs and time would be major factors in the collective mind of the team. They would also be aware of the results that those skilled in formulating two compounds in a stable preparation can potentially achieve. In this regard, I accept the evidence of Professor Graham Buckton, and I accept his expertise as a formulation chemist. I prefer his evidence to that of Professor Klibanov and Professor Stephen Davies and Professor Martyn Davies on these issues, insofar as they were in conflict. I do not accept the view of Professor Klibanov that in 1989 that there was an inherent prejudice in the pharmaceutical industry against combination products for treating the elements of different illnesses. I accept the evidence of Professor Buckton that many pharmaceuticals contain a number of active ingredients. The evidence of Professor Graham Buckton seems to me to be very sensible; especially to the effect that some stability testing would have to be done anyway, whether the preparation was a combination of two active ingredients or active ingredient and an excipient. It also seems to me to be likely that, compared to starting from scratch and developing a new product, it would be inherently likely to consider a combination. The evidence points to these drugs as a combination.

73. I accept the evidence of Professor Buckton that there are methodologies in formulation of a medicine whereby particles in solid state could be held so they are likely to be apart from each other. The issue for the formulation chemist would be as to whether these two apparently reactive compounds could be formulated in a solid state. It seems to be more than likely that during the team discussion, at the stage of theoretical development in terms of combining these two compounds, the formulation chemist would have something positive to say as to the manner in which reactions could be avoided through the careful devising of an appropriate medium in which to hold them.

74. As between Professor Stephen Davies and Dr. David Widdowson, it is clear that Professor Buckton prefers the opinion of the latter on the likelihood of being able to make a stable preparation. I accept Dr. Widdowson's evidence as being highly reliable. In addition, it seems to me that, of all the witnesses, Professor Buckton has the highest degree of expertise with the physical form of pharmaceutical molecules and formulation issues. I prefer his evidence to that of Professor Martyn Davies on the issues now discussed.

75. Among the portions of Professor Buckton's evidence which influences me the most is that which is best reproduced in its most understandable form in his witness statement as follows:-

> "Whilst I am not an organic chemist, as a pharmaceutical formulator I do have sufficient understanding of chemistry to form a view as to the likelihood of an interaction occurring. I agree with Dr. Widdowson in his conclusions that the reactive sites of the fluticasone propionate will be very hard to access by a large molecule such as salmeterol xinafoate. More importantly however, I do not accept that the theoretical reactivity, or absence of, is the subject at issue here. The behaviour of molecules in the solution state is very different to the properties of particles in which molecules are held indiscreet conformation in a crystalline lattice […] In my experience, and as I have stated above, given the state of knowledge in September, 1989 concerning the individual active compounds, a medicinal chemist would not be involved at the stage in a team seeking to develop a pharmaceutical composition in which they were combined. In my opinion, he would not be asked whether conceptually there could be an interaction between the free molecules of fluticasone propionate and the nucleophilic groups… Rather than consult with a medicinal chemist in a situation such as this, the formulator would simply carry out the routine pre-formulation tests of drug – drug and drug – excipient compatibility. These tests, which would inevitably be undertaken, would determine precisely whether such interactions would occur in the solid state. The formulator would build upon knowledge he gained from the literature, for example the 80877 Patents) relating to the formulation of the two active substances as single component formulations when taking forward the development of the combination product.
>
> Despite the fact that, in my experience, a medicinal chemist would not have been asked to provide his thoughts as to whether conceptually there could be an interaction between the molecules of fluticasone propionate and nucleophilic groups on salmeterol, if such a hypothetical question, had been asked of him, and he had expressed such theoretical concerns, in response (whether correct or incorrect), I would have pointed out that:-
>
> (a) It is not possible to predict solid state reactivity of compounds in any reliable manner from solution state properties so the combination should proceed to testing.
>
> (b) If concerns were expressed that the amine in salmeterol may interact with fluticasone propionate, I would assume that the salt formulation on salmeterol would most likely make this region inaccessible for chemical reaction, especially in the solid state, even if there were some unreacted freeform (unless proved otherwise by routine testing).
>
> (c) If concerns were expressed about the hydroxyl groups in salmeterol reacting with fluticasone propionate, I would take comfort from the fact that formulations comprises fluticasone propionate mixed with large quantities of lactose, a compound with many hydroxyl groups had been disclosed in the original fluticasone patent (the 877 patent) and DPI and PMDI formulations were being developed (Scrip 20, April, 1998). I would have assumed that the extent of fluticasone propionate exposure to hydroxyl groups in salmeterol (which is present in very small quantities) would be small in comparison with the contact between fluticasone propionate and lactose and as such the formulations should be prepared for routine testing.
>
> (d) If water were present in sufficient quantity, it would seem to me to be the smallest and most likely substance to be able to access fluticasone propionate, such that it would be more likely to react with

fluticasone propionate then to facilitate any hypothetical interaction between the two actives. The understanding from the 877 Patent of the single component fluticasone propionate formulation (disclosed as being suitable to formulate as a dry powder inhaler with lactose without any mention of concerns with water vapour (would be that with water, would not create any instability) this is what I would suspect, as fluticasone propionate is hydrophobic and has poor water solubility.

(e) The obvious thing to do would to undertake the standard formulations studies and to see if any issues did indeed arise."

76. A formulation chemist would exercise considerable influence in the team. Although I am prepared to accept a leading role for the medicinal chemist on that team, in accordance with the submissions of Glaxo, I do not accept that he or she would have led the team away from this proposed combination, as Glaxo have submitted. I cannot accept the evidence for that proposition at all.

77. Although the example Alka Seltzer may be regarded as trite, its very obviousness undermines, in a real way, the case put forward by Professor Stephen Davies and by Professor Martyn Davies. The fact that the evidence, given on day 10 of the trial, by Dr. John Cavalla is readily understandable does not make it any less apparently correct. I accept it. He said:-

> "I am not a formulation scientist, but it is really common sense, everyone knows that if you freeze things they decay at a much slower rate. We heard in the evidence of Professor Klibanov, who was referring to a question [on] Alka Seltzer, despite extending his unsureness about the shelf line of Alka Seltzer, in fact it is a stable pharmaceutical product and has been on the market for many years and has a shelf life of over three years, yet the ingredients which caused the effervescent are citric acid and sodium bicarbonate and if there is such a thing as a facile chemical reaction, then the reaction between citric acid and sodium bicarbonate is a facile chemical reaction. Yet, with the wonders of formulation technology they have been able to create a solid form that is sufficiently stable to be marketed for decades as a stable and useful and remunerative product. Whilst there may be imperfections in the formulation that need or can be solved from an academic point of view, as an industrialist I would say that one really needs to work with the technology that one has at a given time and try to put products on the market as soon as possible in order that they are able to return their revenue back to the R. and D. for the next stage of development. So, as an industrialist I would have no concerns about the stability of fluticasone propionate and salmeterol, and I would need to do what I can to advance projects, rather than consider negative reasons to discontinue them… Can I put it this way; as a medicinal chemist in industrial context, then what I am trying to do is to advance my projects so that they become commercialised and it is through that commercialisation process that the money is then deferred back to the next stage of R. and D… [the compounds in Alka Seltzer], they don't react with the water, they react with each other in water, in other words, what is happening is the reaction is slowed down so much by virtue of being in a solid state that you are able to have a pharmaceutical product. When you admit it into the liquid state, the reaction is enhanced so dramatically that you have an immediate and visible reaction with the production of CO^2 as bubbles […] [This] evidences the difference in rate between the solid stage and the liquid state. Much of the chemistry we have heard is in reference to the liquid state or solution stage, and I am just making the point, not as pharmaceutical formulation specialist but as someone who is trying to deploy a little bit of external reality to this of what is actually possible in the real world […] [In] Alka Seltzer you had this additional unstable pharmaceutical aspirin itself which degrades fairly easily in water and certainly would degrade under the conditions that I am referring here to the conditions of Dr. Zale's experiments which involve 100º Celsius in DMSO."

78. In addition to that example, in the evidence, the instance of aspirin was mentioned on a number of occasions. It is illustrative of the point made by Dr. Cavalla and I accept it as such. Aspirin degrades rapidly in water. Since water is present in the atmosphere, a compound of aspirin needs to be kept away from water in foil packs, or through some other means. Yet, this is done, and has been done for many years.

79. The following passage from the cross examination by Mr. Tappin Q.C. of Professor Stephen Davies influenced me towards the views of Professor Buckton and Dr. Widdowson on these issues. Professor Davies was asked whether it was reasonable to spend a few thousand pounds investigating a stability issue in relation to these two drugs mixed together in the solid state, especially when both of these molecules were in advanced development and, as I have quoted from 'Scrip', already in Phase III clinical trials. The cross examination continued in consequence of Professor Davies's answer that the team would not enter the realm of testing unless there was "no risk". It continued:-

> "Q. So why does anyone ever do these tests?
>
> A. They would presumably do them when they don't have a real concern of reactivity, you are de-risking the process. It is when there is a real risk of reactivity that it is not going to help you to make an absolute decision that it is not all going to go wrong in to the future, that they will react. So you would have to go and do a lot more deeper studies, which you would do anyway.
>
> Q. I am not sure I am understanding this, Professor, because you are saying when there is a real risk of reaction, it is when there isn't a real risk of reaction or serious risk of reaction, that you do an accelerated stability study but you are saying it is unlikely to pick up the problem, so what is the point of doing them at all?
>
> A. The risk does not go away if you have the done accelerated stability test, the rough and dirty one, the risk does not go away. If it was a big risk to start with, it is still a big risk afterwards, if nothing happens. If it was a small risk to start with, it is a small risk. You are still making a choice over which set to go to. It is unlikely that the scientist would come forward and say, "here is only one option". They are going to a range of options and, as I have said before, you are going to class them according to risk and you will do the ones that don't have the big risks.
>
> Q. I will come on to look after the other options, but what I am not understanding at the moment is why these studies are routinely done. In all formulation programmes people do these accelerated stability studies don't they?
>
> A. Yes.

Q. That is because they think the accelerated stability studies will give them useful information, presumably?

A. They won't just do the quick and dirty one, they have to do long term ones and spend a lot of money. What I am saying is it doesn't de-risk the process. It is back to the point that you can't do every single experiment. If you could do every single experiment you could possibly dream of, you would obviously do the quick and dirty test on everything, but you can't, you have to prioritise the options.

Q. I understand, Professor, that these things are iterative. In order to get a drug on the market, you have to go through the full battery of regulatory approved stability studies, just like you have to go through the full battery of regulatory approved clinical studies?

A. Yes.

Q. Let us look at the clinical studies and drug companies don't say, do they "I'm not going to bother to do Phase I, clinical studies because I will only have to do Phase III anyway and that is going to be lengthy and expensive?"

A. That wasn't what I was saying. What I was saying is that if you have a high risk adverse reactivity at the start, doing a quick and dirty one doesn't remove that high risk, it is still high risk. It has lowered it a bit, but it is still, [a] much higher risk than it would be if you had a low risk one that has gone through that same test.

Q. The purpose of these accelerated stability studies is to give you information about what is likely to happen over a longer period of time, yes?

A. It gives you that information.

Q. Yes?

A. It gives you some information towards that goal, yes.

Q. That is why people do them?

A. Yes.

Q. Because they are indicative of likely longer terms stability?

A. Yes, but they are not infallible."

80. It seems to me to be difficult to justify that opinion of Professor Stephen Davies in the light of all of the evidence taken as a whole. I do not regard it as the most correct view that can be taken on these issues.

81. I turn now to the issue as to whether the inherent chemical reactivity as between salmeterol, even using an appropriate salt of that molecule, and fluticasone propionate would cause the skilled team to drop the idea of testing at the discussion stage.

Reactivity

82. Fluticasone propionate is a fluorinated thioester. The ester group contains an electrophile grouping. In other words, to use very basic chemistry, it wants a pair of electrons. Salmeterol is an amine. Because of the lone pair of electrons on the HN section of the molecule it, to again use fundamental theory, wants to donate the pair of electrons. By making salmeterol into a salt as salmeterol xinafoate, it becomes protonated, though, it is argued, particularly by Professor Stephen Davies, the reactive site moves elsewhere on to the HO CH2 and HO groups. The potential difficulty is well described in Professor Anthony Hegarty's admirably clear statement of evidence at para. 14. I do not treat this as other than a concise statement of a potential problem for the team. He states:-

> "Since the 1940s there has been considerable work reported in the chemical literature on the reactivity of esters and thioesters. The key results were available to chemists by the 1980s and can be summarised as follows:-
>
> > "Thioesters and oxygen esters react at about the same rates with oxygen nucleophiles while thioesters react somewhat more rapidly than oxygen esters with amines (nitrogen in nucleophiles). The reaction of thioesters with amines generally also requires the presence of another base which acts as a catalyst … It is incorrect, in my view, therefore to refer to thioesters as "high energy" compounds or very highly reactive compounds."

83. The state of knowledge of the drug development team in 1989 would be dependant upon what they had been taught as undergraduates and postgraduates. It can be expected that they would have relied on standard textbooks on this issue. On that, I accept the evidence of Dr. Widdowson that textbooks can be unreliable and that a chemist at this level can be expected to do a relevant literature search for footnote citations and for original articles, not necessarily footnoted in a standard textbook, on this issue. What would the textbooks say about thioesters as acylating agents, back in 1989? There are a few textbooks and they do say something that might warn scientists relative to thioesters as acylating agents. I do not propose to detail these, beyond recording that I have considered those texts in some detail with Dr. John Stephens, the court's assessor. There would be some degree of wariness in the team. This would not necessarily stop people going back to the primary material. Chemistry is theoretical, but that theory is based on how substances behave in test. I would expect scientists, working as part of a team in a pharmaceutical company, to have more than average undergraduate grounding in chemistry and one would expect them, in addition, to be chary of general statements in text books and to look, in addition, at basic sources before offering a view. It should be noted, that doing a paper search for relevant references, or to a lesser degree than is the case today, on a computer, is not described by anyone as expensive. It is what the court would expect of this team.

84. Furthermore, there is another aspect of the evidence on which I regard Dr. Widdowson as a sure guide. The principal that thioesters act as acylating agents cannot be seen as an isolated theoretical question that is to be answered only by looking at the chemical structure of the molecules. Substances react with each other depending upon the positioning of

the site of reactivity within the molecule. This principal is called steric hindrance. It applies more particularly to complex molecules like steroids, with their four rigid rings, than it does to simple molecules like water. Professor Klibanov put it to me in evidence that steric hindrance was like driving home to one's house on a very wet and dark afternoon in which many people had chosen to use their cars, rather than walk, cycle or go on public transport. It might take you hours to get there, but you would get there in the end in the ordinary course of traffic eventually moving. This may be very true about traffic problems, but the question arises as to when one will actually arrive? Professor Stephen Davies said something a bit similar; emphasizing that steric hindrance in the high preponderance of cases merely delays a reaction but does not prevent it from ever happening.

85. Time, however, is most important in a pharmaceutical context. What the team would be looking for would be a practical shelf life of two years where they would be satisfied that the compounds in the preparation would not react with each other over that time frame or with the excipient through which they would be delivered. To overcome steric hindrance requires energy. Chance interaction at the right sites in the molecules may also occur through positioning and agglomerations. What is the risk, however, and what is the percentage of reaction? Professor Widdowson's analogy was of the traffic jam mentioned by Professor Klibanov being overcome through a larger vehicle barging the homeward bound driver through the traffic. This is a more likely analogy, although it is not perfect; anyway, no analogy is in this context. In any event, analogy or not, I very much prefer the evidence of Dr. Widdowson to that of any witness testifying in opposition to him on this issue.

86. The material given in evidence on steric hindrance has to be seen in the light of the fact that steroids were identified well before 1989 as having the potential for steric effects. I accept the evidence of Dr. Widdowson that both he and Professor Stephen Davies had worked with Sir Derek Barton, who won the Nobel Prize in chemistry for conformational analysis. Anyone coming to study chemistry in Imperial College London in 1981 would have been taught about conformational analysis directly by Sir Derek Barton. Anyone studying chemistry in a good university in the 1980s would be taught about it too. This concerned the study of the effects of shapes of molecules on their reactivity with any particular substance. Anyone who purported to be a chemist in 1989 would also know about it as well. Steric hindrance is not an obscure branch of chemistry. It is part of common general knowledge. It countervails the argued-for prejudice based on chemical reactivity. Any chemist worth their salt would have serious regard to it.

87. In fluticasone propionate the four rings are rigid. Steric effect considerations were part of general knowledge as of the priority date of this patent. A skilled team led by, or highly influenced by a medicinal chemist, would be incompetent if they did not consider it, and relevant material would be found in standard literature like textbooks. In addition, the paper published by *Idoux* [1973] is important to this issue. In part, this states:-

> "However, in contrast to the thiolacetates, the methyl thiolesters all undergo the alkaline-hydrolysis reaction more slowly than the corresponding methyl acetates under the same experimental conditions. This is probably due in part to the slightly greater influence of steric effects in the acyl portion of a methyl thiolacetate relevant to that in a methyl acetate… In general steric effects are of preponderant influence in controlling the alkaline-hydrolysis of any thiol ester (RCOSR'). This is confirmed by the correlation provided by equation 11 which is the multiple regression of log *k* for all the thiol esters in Table I on the appropriate steric substituent constants."

88. To this must be added the work of *Bürgi and Dunitz* [1974] showing the results of recent experimental and theoretical studies of nucleophilic addition to carbonyl groups. Their paper shows reaction paths by different methods for different nucleophiles and demonstrates striking similarities that appear to be characteristic for the reaction type. Their paper proposes that the hindrance through steric effects as between these compounds could be overcome but that it would require a particular angle for interaction. That principle is clearly relevant here. It would be considered by the team considering the development of the product. With proper formulation, and given that it is known that steric effects rarely stop a reaction but hinder it, a considerable degree of comfort for a two year shelf life at room temperature, that is as to the possibility of slowing reactivity, especially in a solid state and at relatively low energy temperatures, might be obtained. In part, *Bürgi and Dunitz* state:-

> "Interpretation of kinetic data by Storm and Koshland indicates that molecules with an intramolecular O… C = O angles alpha of about 98º show the highest rate of intramolecular lactonization, whereas both the calculations (Part C) and experimental results show that the N… C = O or O… C = O angles alpha are about 105 plus/minus 5º for all distances between nucleophile and electrophile smaller than about 2.5A[ngstroms]… The kinetic and structural evidence taken together suggest that the transition state of a nucleophilic addition reaction will also show an angle alpha between a 100 and 110º."

89. In quoting this I am not ignoring the work of *Hawkins and Tarbel* [1953] on thioester and amine reaction and in particular the table which shows base catalysis of the second step. Dr. Widdowson makes the point that there is a need for a base, a second molecule of salmeterol in this case, to catalyse the second step and that this would increase the steric hindrance of the second step and hence the energy barrier to reaction. While this is an interesting point it did not overly influence the court as a water molecule could conceivably fulfil this role, as indeed was pointed out by Professor Stephen Davies. On the paper by *Connors and Bender* [1961], Dr. Widdowson makes the point that while the susceptibility of the thioester to aminolysis is consistent with the behaviour observed with other thioesters, and with phenyl acetate, the absence of detectible aminolysis of ethyl *p* – nitrobenzoate – was unexpected. This is a good point.

90. In addition, I need to remind myself at this point that a prior combination was available as of the priority date. Ventide was, as I have said, the brand name of the preparation available, as the evidence tells me, from 1983 onwards. I have previously indicated the figures in respect of sales of this drug which were small in comparison to Ventolin and Becotide. The active ingredients of these, however, were combined in Ventide so that it was delivering the four hour long acting â 2 -agonist salbutamol together with the earlier and less satisfactory form of corticosteroid beclomethasone dipropionate. Some of the things which, it seems to me, the team were very likely to take account of, in the possible reaction between salmeterol and fluticasone propionate, were these two molecules and how this lesser reactivity potential had not been manifested or had been overcome in the pharmaceutical preparation Ventide. It seems to me to be fair to say that in fluticasone propionate, the thioester is a better leaving group but is more sterically hindered. It would cause concern that it could react with an amine nucleophile like salmeterol but beclomethasone dipropionate had an oxyester, yet it was less sterically hindered. Why, therefore, would beclomethasone dipropionate not react with salbutamol in a preparation? This had been shown to be stable to the degree that the product could be marketed safely for about six years prior to the priority date of Seretide in 1989. This has nothing to do with hindsight: it is ordinary good sense adjudged at that time.

91. I turn to the cross-examination of Professor Stephen Davies by Mr. Tappin Q.C. My comment on it is that a drug development team would always bear in mind the practicality of a combination. I believe they would have been influenced,

probably through the medicinal chemist, by what had been achieved in Ventide. I quote part of the cross-examination:-

> "Q. Now both these Ventide products were obviously being marketed in 1989 and so, obviously, these combinations were sufficiently chemically stabled to be marketed?
>
> A. Presumably, yes.
>
> Q. That is what the skill[ed] team would assume?
>
> A. Yes.
>
> Q. Now, salbutamol has a number of nucleophilic sites, doesn't it?
>
> A. Yes.
>
> Q. In fact, they are exactly the same as the nucleophilic sites in salmeterol; isn't that the case?
>
> A. Well, as a hydroxy and a nitrogen.
>
> Q. Well, perhaps I should show you… You should find the Ullman and Svedmyr paper and, on the first page, the bottom right-hand corner, you should see the chemical structures of salbutamol and salmeterol, and they share exactly the same nucleophilic groups in exactly the same locations, don't they?
>
> A. Well, they are different groups next to the nitrogen. But relative to one another, they are the same, yes.
>
> Q. It's got the primary alcohol, it's got the secondary alcohol, it's got the secondary amine and they are all in the same location. The difference is that there is a tail on salmeterol on the amine?
>
> A. Well, then there's the t-butyl group, yes.
>
> Q. Now, if you look at BDP… there you will see the same coloured structures or partial structures of the various molecules?
>
> A. Yes.
>
> Q. On the top left we see fluticasone propionate… and at the bottom we have BDP. Now, here we see the BDP, they both have the green oxyester group in the same location – that's the first point – correct, Professor?
>
> A. Yes, yes.
>
> Q. The difference lies in the group at the top. We see that in BDP, there is an oxyester group at the top of the molecule?
>
> A. It is somewhat removed from the molecule as well but there is an oxygen ester group, yes.
>
> Q. Whereas, of course, we know in FP there is the fluorothioester group and the oxyester group that we see at the top of BDP is going to be less sterically hindered, isn't it, then the thiosester group in the fluticasone propionate?
>
> A. I would think so, yes.
>
> Q. So the difference between the known stable Ventide combinations and the proposed fluticasone combination with salmeterol or a salmeterol salt is that we have the fluorothioester in the fluticasone propionate rather than the oxyester, but it is more sterically hindered that the oxyester in BDP?
>
> A. You have a thioester that is in a more hindered position in fluticasone propionate yes.
>
> Q. But that is the difference, isn't it, between the known stable combinations of the Ventide and these proposed combinations?
>
> A. That's not the only difference. BDP has a different steric chemistry where… well, that could change the shape, that could do lots of things. It is certainly more hindering up to the carbonyl on 17. It probably doesn't extend out to the propionate, I can agree with that, but it is not exactly the same. You can't say they are they same apart from these two when the steric chemistry of that position is changed and could change the geometry.
>
> Q. But the oxyester group in BDP that I am concerned about is the one right at the top of the molecule?
>
> A. Yes I understand that.
>
> Q. That is not going to be affected by that 16 methyl group, is it?
>
> A. It is unlikely to be."

92. The example put forward by Dr. Cavalla, that would give comfort to the team and the answer to it by Professor Davies on the United States patent 4,335,121 of 1982 for fluticasone propionate, it seems to me, brings the matter no further. The analysis given by Dr. Cavalla on examples 17, 19 and 27 in the U.S. patent might provide some comfort to the team considering this issue. At the same time, it might, and should, act as a spur for them to look into the matter a bit more closely. If they did, and in my view they would, then steric hindrance would be a real incentive for them to be optimistic that a formulator like Professor Buckton could readily overcome any theoretical problems of reactivity. In any

event, these are practical as well as scientific people on this team and they would well predict that they could achieve the two year stability at room temperature which they required.

93. I have taken into account, as well, the rest of the cross-examination on this issue and I have attempted to judge it in the context of the evidence as a whole. The last piece of evidence proffered to support this aspect of prejudice was the Zale experiment. This was a series of experiments carried out by Dr. Steven Zale at the behest of Professor Klibanov. That series of experiments was shown to be of no assistance at all to Glaxo's case.

The Zale Experiment

94. The purpose of Dr. Zale's experiments was "to answer the question as to whether the fluoromethyl thioester group was more labile in the presence of salmeterol [xinafoate] than the corresponding methyl oxygen ester". Dr. Zale was not asked specifically to focus on the stability of the combination of fluticasone propionate and salmeterol xinafoate.

95. Dr. Zale designed the experiments that were to be carried out after discussions with Professor Kilbanov. The entire origin of the experiments was in the suggestion of Professor Klibanov. In actual fact, the experiments were carried out by a contract laboratory, Chemic Laboratories of Canton, Massachusetts, under the direction of Dr. Zale: "The exact conditions were determined after I [Dr. Zale] had retained the contract laboratory to perform the experiments". Dr. Zale did not personally witness the experiments being performed. The hearsay rule was invoked by Glaxo in order to prevent the admission of documents apparently having their origin in their head office. Notwithstanding that I ruled in favour of that objection, no point was taken on this more obvious hearsay issue. An attorney in New York that worked for Glaxo supplied Chemic Laboratories with fluticasone propionate, fluticasone furoate, salmeterol xinafoate and fluticasone.

96. The Zale experiment was severely criticised in evidence by Professor Buckton. He called it a "very, very strange test". He suggested that it was of little scientific use, or none: because it did not look at the interaction of the precise compounds in question, namely salmeterol xinafoate and fluticasone propionate; because as a formulation chemist he could not imagine using such a high temperature; because an extreme solvent was used which unlike water is not at all prevalent in the domestic circumstances where drugs may be stored after purchase; and finally because a solution was chosen in order for the molecules to come more closely into contact in contrast to their formulation state which would be solid and relatively less movable. All these criticisms were valid. In addition, the cross examination by Mr Tappin Q.C. brought out the basic problem that as salmaterol xinafoate degraded in this solution at this temperature, the result of the interaction was not with that substance at all but with some component part of the molecule, which is not the same thing at all.

97. Dr. Zale had five central experiments carried out, with each of the five experiments performed in triplicate. The experiments were not carried out in the solid state. Instead, D.M.S.O., the solvent dimethyl sulfoxide, was used so that the individual molecules were in a liquid state and were, in consequence, much more mobile than they would be if locked into a crystalline structure, even one slightly amorphous as a result of micronisation. These are the five central experiments:

1. Fluticasone plus salmeterol xinafoate were heated to 100oC in DMSO for 24 hours.

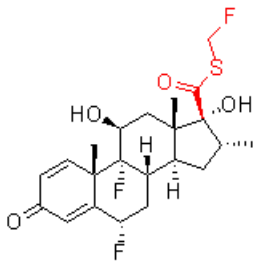
2. The methyl ester oxygen analogue of fluticasone + salmeterol xinafoate were heated to 100oC in DMSO for 24 hours.

3. Fluticasone on its own (with no salmeterol xinafoate present) was heated to 100oC in DMSO for 24 hours.

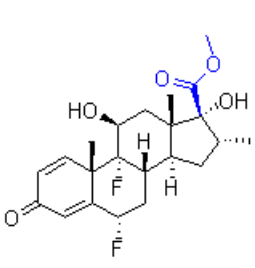
4. The methyl ester oxygen analogue of fluticasone on its own (with no salmeterol xinafoate present) was heated to 100oC in DMSO for 24 hours.

5. Salmeterol xinafoate on its own (with neither fluticasone nor its methyl ester oxygen analogue present) was heated to 100oC in DMSO for 24 hours.

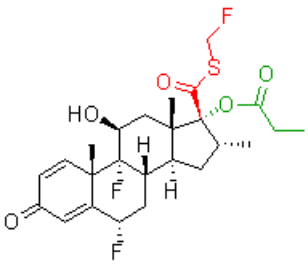
98. Fluticasone propionate and the methyl ester oxygen analogue of fluticasone propionate were not used. Dr. Zale indicated this would have been potentially "confounding", though I find it hard to see how. Despite this, a reaction to generate the methyl ester oxygen analogue was attempted by Chemic Laboratories. The structure in the middle of this diagram indicates the methyl ester oxygen analogue of fluticasone. In this judgment, the diagrammatic representations of salmeterol xinafoate and fluticasone have already appeared, but I repeat this now for clarity in the context of this analysis here.



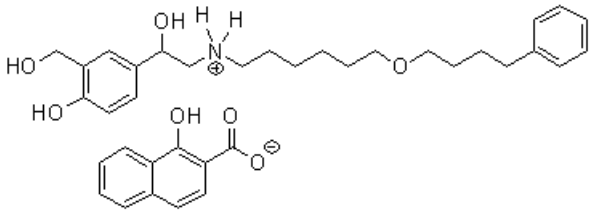
Fluticasone



Methyl ester oxygen analogue of fluticasone



Fluticasone propionate (propionate group in green)



Salmeterol xinafoate

99. A high performance liquid chromatography (or 'H.P.L.C.') machine attached to a mass spectrometer was used to analyse the reactions. The H.P.L.C. graphs show the degradation of the starting materials peaks and/or the appearance of new product peaks when this occurred. The mass spectrometer will generate a peak corresponding to the molecular weight of the compound that caused the peak. Analysis was performed after 0 hours, 3 hours, 6 hours, 15 or 16 hours and 24 hours.

100. Experiment 1 (fluticasone + salmeterol xinafoate) showed essentially complete degradation of fluticasone after 24 hours (0 to 0.5 % remaining) with the appearance of unidentified product peaks. Experiment 2 (methyl ester oxygen analogue of fluticasone plus salmeterol xinafoate) showed some/slight degradation of the methyl ester oxygen analogue of fluticasone after 24 hours (81 to 90 % remaining) with the appearance of unidentified product peaks. Experiment 3 (fluticasone on its own) showed no degradation of fluticasone after 24 hours and no new product peaks. Experiment 4 (methyl ester oxygen analogue of fluticasone on its own) showed no degradation of the methyl ester oxygen analogue of fluticasone after 24 hours and no new product peaks. Experiment 5 (salmeterol xinafoate on its own) showed degradation of salmeterol xinafoate and the appearance of a new unidentified product peak (peak labelled 4.1 minutes). The new unidentified product peak could be observed after 3 hours and grew over time, the peak was larger after 6 hours and larger still after 16 hours.

101. Experiment 1 and experiment 2 indicate that fluticasone in the presence of salmeterol xinafoate at 100oC in D.M.S.O. was less stable, therefore degrading faster, than its methyl ester oxygen analogue under identical conditions (experiment 2). The half-life of fluticasone under these conditions was 2.9 hours while the half-life for the methyl ester oxygen analogue of fluticasone was longer at 86 hours. This latter figure is based on the projected decay of the compound. Four new product peaks appeared in the H.P.L.C. graph for experiment 1, taken after 24 hours. One of which (peak labelled 4.1 minutes) appears to correspond to the degradation product from salmeterol xinafoate, also labelled 4.1 minutes (experiment 5). Experiments 3 and 4 indicate that fluticasone (experiment 3) and its methyl ester oxygen analogue (experiment 4) are stable at 100oC in D.M.S.O. over 24 hours.

102. However, it is crucial that experiment 5 indicates that salmeterol xinafoate is unstable at 100oC in D.M.S.O. over 24 hours. The new product peak that appeared (labelled 4.1 mins) also appeared in experiments 1 and 2. Any new products were not identified and there was no attempt to identify the mechanism of any reaction.

103. Dr. Zale's experiments show that, specifically under his reaction conditions, fluticasone with its fluorothio ester group is less stable than its methyl ester oxygen analogue. The Zale experiments, however, do not indicate whether salmeterol itself reacted with fluticasone or whether it was the degradation products of salmeterol xinafoate that reacted with fluticasone. To my mind this is very important, as salmeterol xinafoate was known to be a stable product/drug with regulatory approval. It therefore could be expected to last, in the solid state at least and outside of attack from any solvent not known in domestic circumstances, for an approved shelf life. Therefore one would not expect salmeterol xinafoate to degrade during its shelf life. It follows that a reaction between the degradation products of salmeterol xinafoate and fluticasone propionate would not have an opportunity to occur. It was not conclusively demonstrated, or even shown as a probability, that it was salmeterol itself, and not the degradation products, that reacted with fluticasone. In fact, no peaks were found in the tables of mass spectrometry analyses, which contained species that indicated molecules with the correct mass for the postulated reaction product between fluticasone and salmeterol. There is nothing to say as a probability that it was not the degradation products of salmeterol xinafoate that reacted in Zale's experiments, and not salmeterol itself. It follows that a combination of salmeterol xinafoate and fluticasone propionate would not have been expected to be problematic as salmeterol xinafoate is a stable product.

104. The methyl ester oxygen analogue of fluticasone was prepared by reacting the fluorothioester ester group on fluticasone with methoxide, which as I understand it is a transesterification reaction. It is clear to me that this reaction was successful. Fluticasone propionate was also reacted with methoxide but it is not clear to me on the evidence whether the fluorothioester group on fluticasone propionate was, or was not, able to react with the methoxide. In other words, it is not clear whether fluticasone propionate was easier or harder to transesterify than fluticasone, but only that the transesterification of fluticasone propionate was also attempted using methoxide.

105. As a result, I am not at all satisfied that the Zale experiment proved anything for Glaxo. I reject the notion of prejudice arising from reactivity. I turn now to the other prejudices ascribed to the skilled team in 1989 those allegedly against combination therapy and the regular ingestion of â-agonist use.

Regular â 2-agonist Controversy

106. The question that I am asked here is as previously set out concerning whether or not there existed a prejudice in the common general knowledge of the team in 1989 against the regular use of â-agonist therapy. I remind myself that, in this context, regular therapy is that which is prescribed to be taken maybe twice or three times a day. It may be described in those terms, namely regularly, or twice or three or more times per day. The conclusion that I have reached, having considered the entirety of the evidence and the scientific papers cited, is that as of the priority date there was a debate as to whether regular â 2-agonist therapy was appropriate in the treatment of asthma. The debate had not, by any means, reached the point where those clinicians who were in favour of regular â-agonist therapy had been so overwhelmed that their point of view was considered insignificant.

107. The nature of the controversy as it existed in the late 1980s is well put in an article by *Drazen and Others* [1996]. This examined inhaled â 2-agonists and concluded that in patients with mild asthma neither deleterious nor beneficial affects derived from the regular use of inhaled albuterol, which is the American name for salbutamol, beyond those derived from the use of the drug as

needed. This article is of historical interest as to the controversy. The debate was relatively settled by *Greening* [1994]. The *Drazen* article points up the two sides of the issue, remembering that the matter is to be looked at as of September 1989, the priority date The summary they give of the historical position is worth quoting:-

> "Before 1990, a number of standard referenced works recommended the use of inhaled â-agonist medications on a regular basis as a treatment for mild asthma. The recommendation, based on evidence that this approach resulted in better control of asthma than the use of â-agonists on an as-needed basis, has been reinforced by subsequent studies. In 1990 and in a follow up paper in 1993, *Sears and Co. Workers* reported that regular use of â-agonists was associated with diminished asthma control and suggested that the use of â-agonists could account for increasing worldwide asthma morbidity. Subsequent reports have also reinforced these observations. However, none of these studies, either in favour of or against the regular scheduled use of â-agonists have involved sufficiently large cohorts of patients with clinically uniform disease for a long enough period to be used in drafting recommendations for treatment. Indeed, the debate about the safety and efficacy of â-agonists as a class continues".

108. The controversy on asthma deaths was reported by *Mitchell* in an editorial in Thorax [1989]. I will quote selected parts of this paper:-

> "The cause of the epidemic of deaths from asthma seen in the mid-1960s in many countries was probably related to the introduction of a higher concentration isoprenaline inhaler, although this is still the subject of debate. In 1982 a further epidemic of asthma deaths in New Zealand was reported. Since then an increase in asthma mortality has been reported in England and Wales, Canada and the United States…
>
> The evidence suggests that any changes in the prevalence of asthma may have been relatively small, yet there has been a dramatic increase in the number of patients with severe episodes requiring hospital admission and a further increase in asthma mortality, particularly in adults. What might be causing these changes? Evidence of over reliance on sympathomimetic treatment has been seen in studies of both the epidemics of asthma deaths; such over reliance may have resulted in delays before more appropriate treatment was started and therefore indirectly increased the risk of death. Mortality reviews have disclosed errors in management and failure to recognise the severity of the episodes by the patients, their families and their medical practitioners. Similarly, over reliance on â-agonists and failure in medical management may be factors in hospital admissions. It seems unlikely, however, that management of asthma is now worse than a decade ago or that this deterioration occurred simultaneously in several countries.
>
> The correlation between increasing morbidity from asthma and sales of asthma drugs raises the possibility of a causal relation. Undoubtedly inhaled â-agonists have a beneficial affect in the treatment of acute asthmatic episodes. But could inhaled â-agonists given regularly make asthma worse or more "brittle" in the long term?
>
> Tolerance to the bronchodilating action of â-agonists (tachyphylaxis) has been shown to occur in vitro and in vivo in animals and man in several studies. Tachyphylaxis could lead to a worsening of the asthma in patients using â-agonists, though this hypothesis is not supported by most of the clinical data… Could drug induced changes in bronchial hyper responsiveness be responsible for the increase in asthma mortality and morbidity? The degree of bronchial hyper responsiveness can be measured by using inhalation tests with agonists… The degree of hyper responsiveness correlates well with severity of asthma, although there is a considerable range of asthma severity for any level of hyper responsiveness. Three recent studies have shown that regular long term inhaled â-agonists produce an increase in bronchial hyperresponsiveness within twenty-four hours of stopping the treatment… A very small change in bronchial hyperresponsiveness in the population results in a small increase in the number of patients with moderate asthma but a substantial increase in the proportion of patients in the severe category".

109. The editorial reasons that it only with a large clinical study, which can overcome the inherent defects of the small size of the existing studies, has been conducted that an answer has been possible. *Mitchell* concludes:-

> "Until such a study has been reported it seems prudent to avoid using regular high doses of inhaled â-agonists and to reserve these for symptomatic treatment. Symptoms necessitating frequent use of inhaled â-agonists should be seen as indicating a need to start or increase prophylaxis with inhaled corticosteroids or cromoglycate.

110. Following on the controversy caused by the *Sears* paper, BBC2 television presented a documentary on asthma which was broadcast on 31st May, 1991. Among the range of views canvassed was whether using â-agonists, in effect as a splinting mechanism as Dr. Costello told me, was increasing asthma severity. Dr. Britton, of St. Peter's Hospital, Chertsey, gave the following view:-

> "I think there are a considerable number of variables resulting in an apparent increase in the frequency and severity of asthma. I do not personally think that â 2-agonist therapy on a regular basis has much part to play in that deterioration."

111. One of the documents which most convinced me that a serious debate on this issue was ongoing in 1989, and was not at all settled even into 1991, was the transcript from the Department of Health and Human Services in the United States of America recording a meeting held by the Food and Drug Administration on Thursday 12th December, 1991, in Maryland. Extracts from this were put to Dr. Costello, Professor Clive Page, and Dr. Conor Burke. I also have regard to their evidence on this document but not to some interesting hearsay that Professor Page and Dr. Burke added in about Dr. Barnes. It added to the colour of the hearing but it could not add to the evidence. A pulmonary-allergy drugs advisory committee had been set up. I am satisfied that the catalyst for this meeting was, as is stated at p. 23 of the first day, the *Sears* study [1990] which had been followed up by the *Saskatchewan* [1991] study. Indeed, Dr. Taylor was called over from New Zealand to present this point of view against regular â-agonist therapy and he described himself as having the "dubious honour to be cited as [among] the instigators of this gathering". He was a co-worker with Sears. This two day meeting was cited by each side, by Glaxo and by Ivax, in support of their arguments. It seems to be one of these documents out of which much can be taken. The transcript is the nature of a debate on this very issue. Summing up his view, with slides, on the regular use of â 2-agonists, Dr. Nelson stated:-

> "So, finally, then is there a role for regular â-agonist therapy in bronchial asthma? I would say yes, there is. However, in most patients this must be combined with long-acting broncho-dilator drugs in order to protect the patient during the evening when the effect of the inhaled drugs will be lost."

112. On regular use in children, Dr. Shapiro stated that "daily routine therapy is quite common". While this might be regarded as a reference to exercise, which often brings on asthma earlier it had been stated that in severe situations, as-needed therapy, as opposed to regular therapy, was not enough. Dr. Wilson referred to the *Horan* study in general practice in the United Kingdom, where patients had been taking high doses of salbutamol for a period of up to nine months. He said that what he regarded as important was "that regular, even high doses of â-agonists did not have a negative impact". Dr. Leonard came out in favour of combination products. Though, because this is after the priority date, it cannot be part of the cited prior art or alleged prejudice in the common general knowledge. He was not against it. Dr. Leonard also spoke about modifications to what he called "current standard use". This he referred to as "a change from regular to PRN [as needed by the patient]". He

described the matter as needing more data. During the committee discussion, Dr. Hendeles said this:-

> "There is no evidence that the regular use of inhaled salbuterol [that is the US name for salbutamol] suppressed chronic asthma to begin with. In fact, nocturnal asthma is not suppressed by chronic use. So I do not believe there is evidence that it is effective for that, and I recommend and make a motion that the Agency do whatever is necessary so that inhaled â-agonists be recommended for PRN use only."

113. The committee then wished to take the views of each member. Dr. Shapiro was of the view that the issue needed to be studied further. Dr. Nelson said this:-

> "First I would have to disagree with Les. I presented a study by VanderWalker which clearly showed that, in that particular group of patients on those particular ancillary medications, the addition of inhaled â-agonists on a regular basis improve a.m. and p.m. peak flows, decreased symptoms and decreased the use of PRN broncho dilators."

114. Dr. Blessing-Moore described two populations of patients; those who benefit from regular use versus intermittent and then, it seems to me, a milder asthmatic group. Dr. Platz-Mills effectively concluded the discussion by saying that more studies were needed, which meant that no recommendation was to be made on the motion. Dr. Page, who gave evidence in this case, indicated that the regular use of â-agonists could not be recommended as a first-line therapy. Dr. Leonard than repeated his opinions.

115. It seems to me that the view of Dr. Page represented one aspect of the conclusion of the meeting: regular â-agonists were not recommended as a first-line therapy. Indeed a preponderance of views was against that, but in the more severe degrees of asthma there was a debate as to their usefulness, with some against, and some in favour. I contrast this with the overall general views of the scientific community that by the time one reaches the more severe stages of asthma, that patients apart from needing â-agonists, should by that stage, also have been put on inhaled steroids. These are, of their nature, regular. Ventide, as we have seen, is a combination of these. I want to briefly look at some other views. My conclusion, however, remains the same.

116. *Svedmyr and Löfdahl* [1987] described the physiology and pharmacodynamics of â adrenergic agonists. In particular, they compared the affect of isoprenaline with salbutamol. The first is a non-selective â-agonist and the second is selective â 2-agonist. I do not take much out of the evidence on this paper beyond the desirability of targeting bronchodilation affects on the â 2-agonist receptors in the trachea.

117. It is fair to say that the debate on the regular use of â-agonists continued through the 1990s and examples of this are two articles by *Page* [1993/1994]. Dr. John Costello was the main witness testifying that in the late 1980s, and as of the priority date for this patent, two schools of thought existed on regular â-agonist therapy for asthma sufferers. His view was that a body of prescribing physicians considered it proper to prescribe the use of a â-agonist inhaler on a regular basis. Some small support for this can be had for the sales figures in the United Kingdom for Ventide. Since this medicine is a combination of a short term â-agonist and an anti-inflammatory steroid preparation, it follows that those who prescribed this drug considered it proper that while the patient was receiving regular inhaled steroid therapy that at the same time they were regularly taking a â-agonist into their airways. It is, as I noted earlier, of the essence of anti-inflammatory corticosteroid therapy that the medicine must be taken regularly. Although the sales figures for Ventide are small, compared to the much larger figures for Ventolin, and for Becotide users, those taking regular corticosteroid therapy, I cannot regard them as insignificant. Ventide was not on sale in Ireland in 1989. In addition, both Dr. Costello and Dr. Conor Burke (who testified for Glaxo against the use of regular â-agonist therapy at this time), are agreed that all physicians following the standard international guidelines in 1989 followed up the therapy of as needed â-agonist inhalation, when asthma became worse, with regular inhaled, or more rarely oral, steroid anti-inflammatory therapy. My preference is for the evidence of Dr. Costello, as I find it difficult to conclude that it is probable that Dr. Burke's recollection is completely accurate in the light of the scientific papers. I am also influenced into believing Dr. Burke is making a mistake of recollection by reason of the matters put to him by Mr. Newman in cross examination. I have no doubt about the honesty of Dr. Burke, nor do I take issue with the wonderful work he and Dr. Costello do. Even if Dr. Burke is right about what was happening in Ireland on regular â-agonist therapy, I have to look at the common general knowledge and the prejudices alleged to be inherent within it outside the confines of our island. That is what the reference in the 1992 Act, s. 11(2) requires of me. The views expressed by Dr. Peter Barnes in the literature assist Dr. Costello's evidence. His view seems to me to be an expression of what Dr. Costello testified to. It is correct that Dr. Costello has had a change of mind on this issue. At the same time, in evidence, and I believe honestly, he told the court that through the late 1980s and in to the 1990s, his views were changing. Nor do I believe that Dr. Costello has deliberately tailored his evidence to this court. In particular, reference was made to a symposium at which he spoke in 1992, where he said:-

> "The use of â-agonists for the treatment of asthma has steadily increased throughout the world, and in the U.K. in particular. The British Thoracic Society guidelines recommend their use, as do the guidelines of the United States National Institutions of Help. Both guidelines stress, however, that inhaled "anti-inflammatory therapy", such as the use of inhaled corticosteroids, should be the main stay of regular treatment, with â-agonists used on an as-required basis. The recent introduction of longer acting â-agonists, such as salmeterol and formeterol and claims for an inherent "anti-inflammatory action" of salmeterol in particular, have generated much discussion about where precisely these drugs fit into the therapeutic regimen clinicians might follow."

118. Dr. Costello's evidence was that, following the papers by *Crane* [1991] and *Sears* [1990], he turned against regular â-agonist therapy and wrote accordingly. He said that another view was presented and, in stating this, he referred to the twin articles in Respiratory Medicine [1992] "why â-agonists should not be used regularly" by *Page and Costello* and "â-agonists can be used safely and beneficially in asthma" by *Twentymen and Higginbotham*. The view of Dr. Costello and Professor Page as expressed in these twin 1992 articles was that there was an abundance of studies demonstrating that the regular use of â-agonists had adverse effects by leading to bronchial hyper-responsiveness. In that regard, he referred to the British Thoracic Society Guidelines for the treatment of chronic asthma and interpreted them as saying that â-agonists should be used as required rather than regularly. *Page and Costello* expressed the view that, in that regime, there was no place for regular inhaled â-agonists. *Twentymen and Higginbotham*, took an apparently opposite view on regular â-agonists therapy. They discussed the clinical and experimental discrepancies and suggested that salmeterol may be anti-inflammatory. This was a speculation that was around at the time but it is not necessary for me to express a view on it. Their conclusion was that the overall long-term benefit chooses that â-agonists prescribed intelligently and with understanding can be safely and beneficially used in asthma. They do not come down heavily, however, on their supposed side of the debate and their opinion is less than certain.

119. It is fair to say, reading these papers, and considering the evidence on the literature, that in 1992 there was serious concerns about the regular use of â-agonists therapy for asthma and that the tide was definitely running against it. That, however, was not the situation as of the priority date in 1989. The *Sears* [1990] and *Crane* [1991] papers were where the tide turns. The 1988 general medical textbook by Sounami and Moxham, authored by Costello as to the chapter on asthma, set out a cascade in which the regular use of â-agonists was recommended at the more extreme end of this sickness. I do not see how his evidence on this issue can be ignored.

120. Some anecdotal evidence has been given to me concerning conversations that people may have had with Dr. Peter Barnes. These are all hearsay and I cannot possibly rely on them. More pertinent to the evidence on this issue, however, are two papers written by Dr. Barnes. In a widely read paper in the New England Journal of Medicine [1989] he said the following:-

"It is common clinical practice to prescribe long-term treatment with â-adrenergic agonists (three to four times daily) but in the light of recent studies it may be preferable to give them as needed, so that increased usage will indicate the need for more intensive anti-inflammatory therapy".

121. Barnes also recommends, and this is a point on which all physicians who were sensible seemed to have been agreed, that anti-inflammatory drugs were central to treating more serious grades of asthma. Later in the article he goes through a cascade and comes down in favour a â-agonists inhaler being used as required, rather than regularly. This is because the number of inhalations is an indication of the adequacy of the anti-inflammatory therapy with steroids. Part of his conclusion is worth quoting:-

"An overreliance on bronchodilators may therefore be potentially harmful and may have contributed to the recent upward trend in the rate of death from asthma. By contrast, anti-inflammatory therapy suppresses the inflammatory response and allows the airway to heal, thus reducing symptoms in the long-term as well as the need for bronchodilator therapy. Corticosteroids are the most effective anti-inflammatory agents currently available, and steroids given by inhalation produce few side effects. They are grossly under used, however, partly because patients have a fear of steroids based on the media coverage of the adverse effects of oral or topical use and partly because steroids do not produce an immediate bronchodilator response. It would now seem logical to introduce inhalant steroids at a much earlier stage in therapy, with the aim of normalising the airway and preventing the chronic progression of asthma."

122. Added to this, I note that a cascade for asthma treatment published in *'A Colour Atlas of Asthma'* by *Cochrane and Rees* [1989] contains advice for the treatment of asthma. Certainly, regularly inhaled â-agonists had no place, in the opinion of these authors, in intermittent mild asthma or intermittent severe asthma. However, when one comes to persistent mild asthma, the authors recommend both inhaled corticosteroid, which of its nature is to be taken regularly, and then say that the position is to "add regularly inhaled â-agonists". When it comes to childhood asthma, over four years of age, "regularly â-agonists by dry powder or globe spacer is recommended".

123. Then we have the British Thoracic Society Guidelines on asthma treatment which were published in the British Medical Journal [1990]. Dr. Burke interprets these as being against regular â-agonists therapy. Dr. Costello clearly expressed a similar view shortly after these were published. These guidelines are important in the context of the evidence on them. They first of all recommend avoidance, such as leaving the factory where the allergen is present, or putting out the cat. They then recommend that the first step as required, P.R.N., bronchodilators. Anti-inflammatory agents by inhalation are added as a second step. The third step is to increase the doses of inhaled anti-inflammatory steroids. The fourth step is additional bronchodilators. The issue here is whether these guidelines could have been interpreted as recommending regular â-agonists therapy. These would emerge only at this fourth step. I quote:-

"All â2-agonists and xanthines should not be used as first line drugs. The main indication is the presence of symptoms, often at night, which are not controlled by high doses of anti-inflammatory drugs and standard doses of inhaled â 2-agonists. The addition of a single nocturnal dose of slow release preparation may be adequate; a twice daily regimen may be necessary. Either treatment may be effective, and each may be tried."

124. I find it very difficult to see the words "a twice daily regimen may be necessary" as being anything other than it being possible that regular â-agonists therapy may be prescribed in the more extreme cases of asthma. I rely on Dr. Costello here too. That interpretation is strengthened by the article published by *Barnes and Chung* [1992]. Although this was in a relatively obscure journal, it was written by a very important physician with a distinguished colleague. This is what they say about the guidelines:-

"Asthma, even in its mildest form, is an inflammatory condition, and there has recently been increasing emphasis on the use of anti-inflammatory treatments, such as inhaled corticosteroids and inhaled sodium cromoglycate, early in the course of treatment. Indeed guidelines have been agreed and drawn up for the management of chronic asthma in several countries (including U.K., Australia, Canada and U.S.A.), recommending that inhaled â-2 agonists are used only in "as required" for symptom control and that regular anti-inflammatory treatment is started in any patient who needs to use a â-2 agonists on a daily basis. Regular use of a bronchodilator is only recommended for patients who continue to have symptoms after high dose-inhaled steroids".

125. Towards the end of the article Barnes, and Chung refer to the concerns about regular â-agonists therapy. They said:-

"In view of the concerns about regular â-agonists therapy they should be used initially with caution. They are certainly indicated in patients who continue to have symptoms despite high-dose inhaled steroids, and are useful in some patients with unstable asthma and continuing nocturnal attacks. What long-acting inhaled â 2- agonists should not be used alone and should always be used in combination with an inhaled steroid, since there is no convincing evidence yet that they have clinically useful anti-inflammatory effects in asthma (although studies to investigate their anti-inflammatory potential are underway). Perhaps fixed combination inhalers with long-acting â 2- agonists combined with high dose steroids may be the best way to supply these drugs in the future."

126 I find myself preferring the recollection of Dr. Costello over that of Dr. Burke. I do not regard any analysis of the guidelines as essential to my decision.

127. I accept the evidence given by Dr. Costello that he was not prejudiced against the regular use of â 2-agonist therapy in patients suffering from asthma. I accept that his views were developing through the late 1980s and in to the mid-1990s in consequence of new thinking. In particular, he was strongly influenced by the *Sears* [1990] article. As to the guidelines, it seems to me, that the manner in which Dr. Mitchell-Heggs expressed it in his statement is correct. That evidence, though in statement form and not cross-examined, accords in its sense with the evidence from Dr. Costello which I accept. I therefore quote it:-

"Certainly clinicians were aware of the discussions concerning the deaths in New Zealand. That debate primarily concerned the use of the â 2-agonists fenoterol and the suspected overuse of nebulisers in New Zealand. Fenoterol was known not to be particularly â 2 selective – and so would have been expected to produce more side effects, then, say, salbutamol, the most commonly used â 2-agonist in the U.K. at that time. Furthermore I understand that in New Zealand it was then possible to buy nebulisers "over the counter". It was thought that this might be leading to patients (and G.P.s) in New Zealand trying to treat severe or acute asthma at home – with the results that patients were receiving improper medication, leading to increased asthma deaths from treatment side effects – under treatment of the disease.

Accordingly whilst clinicians in the U.K. were aware of the question marks over the increased asthma deaths in New Zealand, I (and I think most practicing clinicians) were not unduly concerned over the safety of selected â 2-agonists – and in particular salbutamol. I was aware at the time that some (primarily academic) clinicians took a stricter, more worried, view on the use of the whole â 2-agonist class of drugs, but I would be surprised if even they in 1989 would not have prescribed a regular dose of â 2-agonists to patients with moderate to severe asthma (almost certainly in addition to a regularly inhaled corticosteroid). On the other hand, even by 1989 I was still relatively frequently seeing patients who are being prescribed â 2-agonist monotherapy by some (relatively not up-to-date) G.P.s [...]

In my opinion, the most that these practices and later Guidelines, can provide are suggestions – as any individual patient may find the proposals in these guidelines in appropriate for them and they will need to be tailored to the needs of that particular patient. But I believe that in approaching that "tailoring of need" one

must try to balance the two conflicting demands of producing a clinically ideal regimen and prescribing a treatment system with which the patient is able to comply. The guidelines are just that, they are not protocols.

During the years leading up to and including 1989, I prescribed to patients a regular dose â 2-agonist in the treatment of asthma (in conjunction with a regular dose of inhaled corticosteroid). I believe that many other clinicians were also prescribing such a treatment. Certainly, many G.P.s under my guidance did so."

128. Lest there be any doubt, I accept the evidence of Dr. Costello as to these issues. I would not have accepted the untested evidence of Dr. Michael-Heggs on its own. There is another matter which I want to add here which is relevant to this issue and the issue of combination which follows, the A.B.P.I. data sheet compendium for Ventide for 1988-1989. This is cited as part of the prior art. I accept it as such. In addition, during the evidence, a large number of advertisements were referred to that bear out the sense of this document. Ventide is a combination therapy and it was recommended as such for regular use as of the priority date. This data sheet would be included in a box of medicine. I doubt that very many people read it in the privacy of their bathroom who are not physicians or pharmacists. However, I am satisfied on the evidence that a data sheet has to be in conformity with the claims made for a medicine and the evidence presented to the regularity authority otherwise, at the least, a query would be raised. It contains the following:-

"*Uses*: This association of Salbutamol BP with Beclomethasone Dipropionate BP is specifically provided for those patients who require regular doses of both drugs for treatment of their obstructive airways disease. Ventide inhaler is not intended for use as a first-line treatment but is for use once the need for inhaled corticosteroid therapy has been established.
Dosage and Administration: Adults: two inhalations (200mcg salbutamol and 100mcg beclomethasone dipropionate) three or four times a day. Children: one or two inhalations (100mcg-200mcg salbutamol and 50-100mcg beclomethasone dipropionate) two, three, or four times a day. . . .
Dosage and Administration: Adults: for the relief of acute bronchospasm and for managing intermittent episodes of asthma, one or two inhalations may be administered as a single dose. The recommended dose for chronic maintenance or prophylactic therapy is two inhalations three or four times a day.
To prevent exercise-induced bronchospasm, two inhalations should be taken before exertion.
Children: one inhalation is the recommended dose for the relief of acute bronchospasm. In the management of episodic asthma or before exercise.
One inhalation should be administered three or four times a day for routine maintenance or prophylactic therapy. These doses may be increased to two inhalations, if necessary.
For optimum results, in most patients… should be used regularly."

I appreciate that in considering the team, this is an objective exercise. While this document has its origin in Glaxo, I do not take that into account beyond what it teaches as prior art.

Combination Therapy

129. I cannot accept that as of the priority date the drug discovery and development team would not have had any motivation to create a combined preparation of salmeterol and fluticasone propionate. I do not accept that there was a prejudice among clinicians against the use of combined therapy. Instead, I accept there was a debate. I regard as useful, and very helpful, the evidence of Dr. Conor Burke, that not combining drugs would allow the use of an inhaler for bronchodilation to titrate the variable nature of the disease in asthma. However, it is apparent to me that some, and not an insignificant body of, clinicians thought differently. In particular, I accept the evidence of Dr. Costello that while he would need to know the precise clinical effects of any new medication, that as regards Ventide on the priority date, those patients who were referred to him while on this combination therapy did not have their prescription altered by him. As will have been apparent to the reader of this judgment, throughout the late 1980s, and indeed up to the present time, physicians treating asthma are concerned to get an anti-inflammatory medication into their patients. If you have mild asthma by reason of an allergy, then you avoid the allergy. If you have intermittent wheeziness, then you take a bronchodilator, such as Ventolin, salbutamol, as you need it. Once you get into the next worse category, the medical orthodoxy would appear to be that you need to have the inflammation of the trachea dampened down with a steroid medication. This you need to take regularly. You then also take your bronchodilation as you require it. The problem, however, is that as I have said, patients will reach for bronchodilation naturally but are wary of taking their anti-inflammatory medication. This is because they cannot see the effects of it, possibly do not understand the importance of it and, as sensible human beings, do not want to take something on a long-term basis which they do not immediately consider as doing them any good. Dr. Conor Burke devoted much of his very helpful evidence to the issue of educating patients. That is, indeed, a desirable purpose for any physician. A combination therapy, on the other hand, has the advantage of ensuring that patients take their steroids while, at the same time, having, if necessary, a single drug bronchodilator such as Ventolin, salbutamol, at hand when it is needed. My assessment of the evidence is that, again, as of the priority date that there was no prejudice against combination therapy in the common general knowledge but, rather, a debate.

130. I accept that there were many combination products that were relevant in terms of these providing an example, if not as to chemistry, then as to usefulness, up to 1989. These included Duovent which was a combination of the â 2-agonist fenoterol and ipratropium bromide which is an anticholinergic. Dr. Mitchell-Heggs, for example, would have used and advised GPs to prescribe this drug in appropriate asthmatics. His evidence as to Ventide also struck me as being sensible, but again I have not relied on it without considering the oral testimony that was so well tested in cross examination. Here is the relevant portion:-

"Although some clinicians (particularly those at the academic end of the profession) might have felt that the use of combination drugs, in particular in asthma, was inappropriate, I personally found that some patients, with whom compliance was an issue, could be treated perfectly well using Ventide twice daily, morning and evening, with that patient carrying only a rescue salbutamol inhaler with them during the day. Without the use of Ventide in these patients, there was a very real risk of non-compliance and hence the patient suffering from improperly controlled asthma."

131. A paper by *McDonald and Others* [1988] concerned an evaluation of the combination inhaler salbutamol and beclomethasone dipropionate in the management of asthma, in others words Ventide. This involved an open parallel study lasting 24 weeks of 39 asthmatics in order to evaluate patient compliance and the clinical affects of regular inhalations of these two products used simultaneously from a combination inhaler as compared to the sequential use of these products from separate inhalers. No difference was found as between the two treatment groups with respect to clinical pulmonary

function tests (F.E.V.1) and (F.V.C.). The finding was that in 12 weeks the research assessed significantly more patients to have better symptom control on the combination inhaler than on separate inhalers. Unlike the usual problem of compliance with corticosteroid medication, here patients diligently took their medicine in respect of both trials, perhaps because they were being closely watched. The paper, in addition, makes reference to two studies which, in 1984, showed that combination inhalers were as effective as the same two agents in separate inhalers.

132. Dr. Peter Barnes is acknowledged to be one of the world's leading experts on asthma. People interested in this area would follow closely what he said. In a paper delivered in 1988 he went into considerable detail on the psychological aspects of asthma and the possible treatment compounds. I do not need to detail these. This is part of the state of the art that shows that this combination in Seretide was not inventive. What is important is, that having looked in detail at a wide range of medications, and having looked at the advances that had, up to then, been made in delivering drugs straight into the airways, he put forward the following conclusion:-

> "Many different therapeutic approaches to the treatment of asthma may be possible, yet there have been few new drugs. Beta 2 adrenoceptor agonists are by far the most effective bronchodilator drugs and lead to rapid symptomatic relief. It is difficult to imagine how these drugs could be improved, apart from a longer duration of action when given by inhalation, since they antagonise bronchoconstriction irrespective of cause, are virtually devoid of side-effects and over-dosage does not cause problems. Similarly, inhaled corticosteroids are extremely effective as chronic treatment in asthma and suppress the underlying inflammatory process. It follows that a combination of inhaled steroids and Beta adrenoceptor agonists is required and combined inhalers would seem to be a sensible development, since they will improve the compliance of inhaled steroids (which is poor because of the lack of immediate bronchodilator effect). Future developments in asthma therapy should be directed towards the inflammatory mechanisms and perhaps more specific therapy may one day be developed. The possibility of developing a "cure" for asthma seems remote, but when more is known about the genetic abnormalities of asthma, it may be possible to search for such a therapy."

133. A paper by *Ruffin* [1988] also made a case for fixed dose combination therapy in asthma. This was presented as a positive case as against the view expressed by *Shenfield* [1986] which suggested there was no place in this form of treatment for asthma. The argument by *Ruffin* was that new knowledge about the implications of airway hyperresponsiveness in patients and a possible change in attitude to asthma therapy provided reasons to re-examine the case for fixed dose combination treatment in asthma. A patient suffering from asthmatic symptoms was always likely to reach for their medication, usually the existing â 2-agonist preparations, particularly Ventolin, in other words salbutamol, which gave, as I have indicated, quick results. The inflammation of the trachea, however, remained a problem. If that inflammation could be reduced by inhaled corticosteroids, then the trachea muscle was less likely to go into spasm. Patients, however, showed a reluctance to comply with dosage prescribed in respect of medicine that they could not see the immediate benefit for. This was well expressed in the statement of Dr. Peter Mitchell-Heggs, which was read as evidence:-

> "In asthmatics there was the problem that compliance – in particular with the corticosteroid – was (and still is) a problem.
>
> In the 1980s, and still now, I frequently speak at meetings to advise G.P.s and hospital staff on how best to treat asthma. At these I will always stress the importance of patient education. I also educate my own patients in the proper treatment of their disease. It is however, still the case that many patients take their bronchodilator in preference to their anti-inflammatory drug, with the result that their asthma is imperfectly controlled.
>
> As such I was often faced with patients in clinic who would be prescribed a number of drugs (not necessarily all asthma related), VW, XYZ, but when questioned in clinic they would need only replacements for two or three of these. When asked why, it would usually be because they didn't think WRZ did anything, so they didn't bother to take them! In my experience, I have found that not only do the majority of patients prefer not to take drugs, but that each prescription costs, what is for many people an not insufficient amount of money. When patients are on regular medication, they will often not want to pay for medicines that they do not perceive to be having an effect."

134. *Ruffin* addressed the issue of how best to administer corticosteroid aerosols in order to achieve good compliance. He suggested that a fixed dose combination of inhaled â 2 adrenergic agonist and a corticosteroid combination in a single metered dose inhaler would provide the best treatment. His argument was that this combination fulfilled both treatment modalities and he also argued that the component dosage was safe and effective for a significant part of the population. Under-treatment was a feature of mortality and morbidity. He concluded:-

> "If we are to reduce morbidity and mortality of asthma, we must educate patients and doctors to aim to reduce airway hyperresponsiveness. A combined â 2 adrenergic agonist and corticosteroid aerosol will be appropriate for most asthmatics and we must think in terms of over treating symptoms to enable a reduction in airway responsiveness. Combination bronchodilator is indicated in those patients in which there is better than either drug alone or results in a significant promulgation of effect. The patients need to be identified or selected by a clinical trial."

I would accept that the paper by *Ruffin* would not have had as wide an impact as one by *Barnes*. I find it difficult, however, to fully accept the criticism of *Ruffin* given by Dr. Burke. It is fair to say that two of reasons in favour of a combined aerosol may be of little weight, but its argument in favour of compliance and of reduced airway responsiveness are, it seems to me, sound enough.

135. On this issue of combination, in the absence of any testing of Dr. Mitchell-Heggs' view, I would not accept it. I accept it, however, in the context of what was stated by Dr. Costello. In particular, I am influenced by the passage from Dr. Costello's evidence which follows. He was referred to Dr. Barnes's comments on the development of combined inhalers and was asked whether describing these as exploratory was a fair summary of the position. He had this to say about combined inhalers, and I accept it:-

> "Well, firstly, at the time, there was already a combined inhaler on the market in the form of Ventide. So this was not exploratory, there was an established precedent for it . . . since 1983. Secondly, Professor Barnes was expressing a view. This was not a suggestion of blue-sky research, shall I say. It was an expression that this was a concrete suggestion rather than an exploration that this is the way we should go forward . . . and once again we had precedent for it. In Ventide, which was a combination of salbutamol and beclomethasone, a logical extension of that would be when a better corticosteroid or an apparently better corticosteroid in the form of fluticasone arrived and a drug like salmeterol that offered this great benefit of a long duration of

> action, and therefore the combination of these two clearly offered a way forward for benefit for patients. This was another logical step in the way we think about the treatment of our patients . . . well, first of all, we had in a combination, and this would have offered us for the first time a drug that would be given just twice a day. So in terms of compliance or ease of use, which sometimes amounted to the same thing, this would have been of clinical benefit. Secondly, the inherent qualities of these two drugs, the fact the fluticasone had been demonstrated to be low on side effects and to be a potent inhaled corticosteroid and secondly, the longer duration of action of salmeterol, both in terms of the drugs and their combination together within the same inhaler was a step forward."

136. Finally, in the event that any analysis of the evidence concerning greater than additive effect as between salmeterol and fluticasone propionate is necessary, I do not think that it bears on the issue of obviousness. In the event that anyone were to decide that it does, however, I wish to record that I have analysed that evidence carefully and fully with the assistance of Dr Stephens, the court's assessor. Following on the paper by *Greening* [1994], much of the debate against regular â-agonist therapy fell away. Whether this paper was as earth-shattering as has been presented is, to my mind, beside the point. All of the later papers which refer to it do not definitively show any clinical benefit of greater than additive effect by reason of this combination. I am grateful to Professor Ian Adcock for his assistance in that regard. As regards the *in vitro* studies, these cannot, in my assessment, be summarised as showing a probability of greater than additive affect. Instead, in my view, they establish that this is possible.

Obvious or Inventive

137. I find the evidence of Professor Page as to what would have been known to the skilled drug discovery and development team to be correct. The Thorax article by *Ullmann and Svedmyr* on salmeterol would probably have been read by the notional skilled team. Had not salmeterol and fluticasone been announced in 'Scrip', the relevant patents could have been searched for and considered. As it is, they are not essential to my decision. I accept the evidence of Dr. Cavalla that in 1989 'Scrip' was an authoritative publication on the activities of drug companies and that it was used as a good source of information. It is apparent that fluticasone propionate and salmeterol were in Phase III clinical trials. Moreover, the article by *Ullmann and Svedmyr* indicates that seven of the eight patients tested were receiving beclomethasone dipropionate as well as salmeterol on regular twelve hourly intervals. I accept the 'Scrip' article on fluticasone propionate as being correctly pleaded as part of the prior art.

138. On combination therapy there is no need, in my view, to rely on *Ruffin* [1988]. Combination therapy was already obvious from the Ventide data sheet and I have quoted this already.

139. The team would have had no prejudice against combining these two molecules in the light of the opinion expressed by *Barnes* that combined inhalers would be a sensible development. If necessary, I would take *Ruffin* [1988] into account but I do not believe there is any need to. *Barnes* had advocated the development of combination therapy, and the number of alternative combinations is limited. The notion that the team might seek to develop a new molecule would be, in effect, to pursue the cure for asthma that *Barnes* regarded as remote. It is still remote. On the evidence and the literature as explained in the evidence, I would regard that proposition as far-fetched. It is possible that formoterol might have been chosen as a â-agonist in a combination medicine. However, again, Ventide looms large. Salmeterol is an analogue of salbutamol. Of the relevant steroids in the proposed combination, fluticasone propionate had documented advantages over beclomethasone dipropionate.

140. In any event, I do not believe that the drug development team were predicting the outcome of clinical trials. Rather, any prejudice in relation to clinical practice has been disposed of by my previous findings in this judgment. I regard the properties of salmeterol to have been common general knowledge to this team as of the date. Any steroid previously used for anti-inflammatory effect might, as a mere possibility, have been chosen, but fluticasone propionate was both apparently safe and efficacious. As a development of Ventide, the combination now present in Seretide was not inventive. Furthermore, combination therapy, in the light of a statement by *Barnes* was merely an application of prior art. As has been previously stated, patent protection is not available in respect of a part of the state of the art, or what is obvious in consequence of it. This development would have been obvious to a person skilled in the art.

141. I do not believe that in the light of these findings any further comment is required. If necessary, I approve the statement of Laddie J. in *Brugger v. Medicaide* [1996] R.P.C. 635 at 651, where he said:-

> "First a route may still be an obvious one to try even if it is not possible to be sure that taking it will produce success, or sufficient success to make it commercially worthwhile. The latter point is inherent in *Johns-Manville Corporation's Patent* [1967] R.P.C. 479, a decision of the Court of Appeal under the Patents Act, 1949 which is just as relevant to obviousness under the 1977 Act. Secondly, if a particular route is an obvious one to take or try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well. If a number of obvious routes exist it is more or less inevitable that a skilled worker will try some before others. The order in which he chooses to try them may depend on factors such as the ease and speed with which they can be tried, the availability of testing equipment, the costs involved and the commercial interests of his employer. There is no rule of law or logic which says that only the option which is likely to be tried first or second is to be treated as obvious for the purpose of patent legislation."

142. I also regard this as a case where any pleaded gap between the novel combination and the existing prior art is extremely small. There is no inventive gap. I accept the evidence of Professor Page as to what would have been known to the skilled team and as to what would have been done to supplement its existing general knowledge, unhindered by the prejudices argued for brilliantly but unsuccessfully by Glaxo. As I have said, the evidence of Dr. Cavalla on 'Scrip' is correct and, in any event, it seems to me to be uncontradicted in the evidence. But even it were disputed, I would accept Dr. Cavalla's evidence.

143. In the event, I have determined the closest prior art; it is difficult to see a technical problem to be solved other than choosing a particular drug, namely salmeterol instead of salbutamol or formoterol, and fluticasone propionate instead of beclomethasone dipropionate or another steroid; finally, the claimed inventive step would have been obvious to the skilled team. Using the traditional four step English test cited above at para. 29, the result is the same.

Amendment

144. The Controller of Patents may, under the 1992 Act, allow an application to amend an existing patent. However, where litigation has commenced concerning that patent, then the matter should be referred to the High Court for consideration within that context. The amendments were sought in May, 2008 but, shortly after that, this litigation commenced. Hence it falls to me to decide it.

145. It is as well to set out s. 38 of the 1992 Act as amended by s. 11 of the 2006 Act:-

> "(1) Subject to the following provisions of this section, the Controller may, on an application made in the prescribed manner by the proprietor of a patent, allow the specification of the patent to be amended, subject to such terms as to advertising the proposed amendment and such other conditions, if any, as he thinks fit; provided that no such amendment shall be allowed where there are pending before the Court or the Controller proceedings in which the validity of the patent has been or may be put in issue.
>
> (2) In any proceedings before the Court or the Controller in which the validity of a patent is put in issue, the Court or, as may be appropriate, the Controller may, subject to the following provisions of this section, allow the proprietor of the patent to amend the specification of the patent in such manner, and subject to such terms as to advertising the proposed amendment and as to costs, expenses or otherwise, as the Court or the Controller thinks fit.
>
> (3) An amendment of a specification under this section shall be invalid to the extent that it extends the subject matter disclosed in the application as filed or the protection conferred by the patent.
>
> (4) An amendment of a specification under this section shall have effect and be deemed always to have had effect from the date of the grant of the patent.
>
> (5) Where an application for leave to amend a specification has been advertised in accordance with subsection (1) or (2), any person may give within the prescribed period notice to the Court or the Controller, as may be appropriate, of his opposition to an amendment proposed by the proprietor of the patent, and if he does so shall notify the proprietor and the Court or the Controller shall consider the opposition in deciding whether the amendment, or any other amendment, should be allowed.
>
> (6) Where an application for an order under this section is made to the Court, the applicant shall notify the Controller who shall be entitled to appear and be heard on the hearing of the application and shall so appear if so directed by the Court.
>
> (7) In considering whether or not to allow an amendment proposed under this section, the court or the controller shall have regard to any relevant principles applicable under the European Patent Convention."

146. The crucial test , in the light of the above, is whether the proposed amendment extends the patent. What is proposed may be readily stated. Referring back to the claims in the patent, that are quoted above, the words "or sequential" are sought to be removed from claims 1 and 5 so that it would become clear that in taking the medication comprised of these two compounds, that both will be taken at the same time. So, the medicine is no longer, if the amendment is allowed "for simultaneous or sequential administration" of the two compounds: instead, it is only "for simultaneous administration".

147. I see no reason not to allow this amendment. I appreciate that, at this stage of the judgment, it makes no difference to the position either of Glaxo or of Ivax. However, in deference to the arguments of counsel and arising of my duty to make appropriate findings, pending an appeal, it should be disposed of here.

148. I do not propose to add to what Clarke J. said on the principals of construction of patents in *Rambaxy Laboratories Limited v. Warner – Lambert Company* [2007] I.E.H.C. 256. In particular, however, I note what he has to say about Article 69 of the European Patents Convention. A strict literal meaning of the wording used in the claims is not to be used, but neither should such claims be construed as if they are merely a guideline. In interpretation, a position between these extremes combines both fair protection for the patentee with a reasonable degree of certainty for third parties. I am reading this patent, as Clarke J. suggested, from the perspective of the type of person "likely to be involved with it and have a true interest in what it says". I am not interested in whether Glaxo have said something that they, as a corporation, might now regret in the patent. Rather, the only issue for me is what the patent means, what the amendment means, and what the result would be if an amendment is allowed. In the event that this involves an extension of protection, then it should be disallowed. With regard to s. 38(7), I note that Article 123(2) of the European Patent Convention provides:-

> "A European Patent application or European Patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed."

My approach is the same as that of Aldous J. in *Bonzel v. Intervention (No. 3)* [1991] R.P.C. 553 at 574. His three part test on the amendment of a patent required the court:-

> "1. To ascertain through the eyes of the skilled addressee what is disclosed, both explicitly and implicitly in the application.
>
> 2. To do the same in respect of the patent as granted.
>
> 3. To compare the two disclosures and decide whether any subject matter relevant to the invention has been added whether by deletion or addition. The comparison is strict in the sense that subject matter will be added unless such matter is clearly and unambiguously disclosed in the application either explicitly or implicitly."

149. In *Vector Corporation v. Glatta Air Techniques* [2007] E.W.C.A. Cif. 805, the Court of Appeal in England, through Jacob L.J., approved this formulation as being correct. I agree with that. In addition, the Court noted that in *Richardson-Vicks' Patent* [1995] R.P.C. 568 at 576, the rule had been summarised so that the test of added matter became "within the text whether a skilled man would, upon looking at the amended specification, learn anything about the invention which he could not learn from the un-amended specification".

150. Should an amendment be allowed where subject matter is added? Two serious disadvantages to the rights of third

parties would arise. The first is technical, but nonetheless important, which is that the first person to apply to patent an invention is entitled to that statutory intellectual property right. Secondly, it cannot be permitted that by an amendment a different monopoly would be achieved compared to that justified in the original patent. I approve the elaboration by Kitchen J. on the above, which he set out in *European Central Bank v. Documents Security Systems* [2007] E.W.H.C. 600 (PAT) (26th March, 2007):-

> "First, it requires the court to construe both the original application and specification to determine what they disclose. For this purpose the claims form part of the disclosure (section 130(3) of the Act), though clearly not everything which falls within the scope of the claims is necessarily disclosed.
>
> 98. Second, it is the court which must carry out the exercise and it must do so through the eyes of the skilled addressee. Such a person will approach the documents with the benefit of the common general knowledge.
>
> 99. Third, the two disclosures must be compared to see whether any subject matter relevant to the invention has been added. This comparison is a strict one. Subject matter will be added unless it is clearly and unambiguously disclosed in the application as filed.
>
> 100. Fourth, it is appropriate to consider what has been disclosed both expressly and implicitly. Thus the addition of a reference to that which the skilled person would take for granted does not matter: *D.S.M. N.V.'s Patent* [2001] RPC 25 at 195 - 202. On the other hand, it is to be emphasised that this is not an obviousness test. A patentee is not permitted to add matter by amendment which would have been obvious to the skilled person from the application.
>
> 101. Fifth, the issue is whether subject matter relevant to the invention has been added. In case G1/93, Advanced Semiconductor Products, the Enlarged Board of Appeal of the EPO stated (at paragraph 9 of its reasons) that the idea underlying art 123(2) is that that an Applicant should not be allowed to improve his position by adding subject matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application. At paragraph 16 it explained that whether an added feature which limits the scope of protection is contrary to art 123(2) must be determined from all the circumstances. If it provides a technical contribution to the subject matter of the claimed invention then it would give an unwarranted advantage to the patentee. If, on the other hand, the feature merely excludes protection for part of the subject matter of the claimed invention as covered by the application as filed, the adding of such a feature cannot reasonably be considered to give any unwarranted advantage to the Applicant. Nor does it adversely affect the interests of third parties.
>
> 102. Sixth, it is important to avoid hindsight. Care must be taken to consider the disclosure of the application through the eyes of a skilled person who has not seen the amended specification and consequently does not know what he is looking for. This is particularly important where the subject matter is said to be implicitly disclosed in the original specification."

I note that by far the most crucial issue is whether an individual who seeks an amendment is improving his position by the addition of subject matter not disclosed in the application as filed. I do not see that here.

151. On the case made by Ivax against the amendment it was very hard to ascertain the mechanism whereby a sequential administration of salmeterol and fluticasone propionate could be delivered. It seems that, in fact, double-barrelled inhalers do exist whereby one can get a dose of one drug delivered into one's airways, immediately followed by a dose of another. I was slightly concerned about whether the team might have thought about of chemical reactivity. The evidence has shown that on tests with the Anderson's Cascade, with simultaneous administration, the two compounds tend to agglomerate together at the bifurcation of the airways. I do not, however, know if analysis by means of the Anderson's Cascade was available back in 1989, and I rather doubt it. When a question was asked of Professor Buckton as to whether the team in 1989 would be concerned about whether a reaction would take place in the airways, upon sequential administration, he indicated that the time involved would be very short before the substances would be absorbed into the body. As in so much else, I am content that Professor Buckton is correct here. I am not sure that it has been shown by Ivax that there is anything added to this patent by the proposed amendment. I think, on the contrary, that the form of wording used has to be read in the context of the entire description in the document. This, it seems to me, makes it clear that what is involved in the patent document was the simultaneous administration of these two substances. In that regard, again, the precedent of Ventide, specifically mentioned in the description in the patent, looms large.

152. As such, were the matter to be important in terms of the decision, I would allow the amendment.

Result

153. In the result, I hold that the patent should be disallowed under s. 58 of the 1992 Act, as amended by the 2006 Act, because the subject matter of the patent was not patentable in that it did not involve an inventive step.