IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Claim No HC 07 C0 2104

B e f o r e: HIS HONOUR JUDGE FYSH QC
(Sitting as a Judge of the High Court)

B e t w e e n:

LABORATORIOS ALMIRALL S.A. Claimant

and

BOEHRINGER INGELHEIM INTERNATIONAL GmbH Defendant

JUDGMENT

Andrew Waugh QC and *Piers Acland* instructed by Bristows appeared for the Claimant
Simon Thorley QC and *Andrew Lykiardopoulos* instructed by Powell Gilbert LLP, appeared for the Defendant.

Dates of hearing: 10-14, 17, 18 November 2008 and 23 January 2009

This judgment is in final form. I direct that pursuant to CPR, PD 39A para 6.1, no official shorthand note shall be taken of this judgment and that copies of this version as handed down may be treated as authentic.

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JUDGMENT

I Introduction[1]

1. This is a patent revocation dispute within the pharmaceutical industry involving a substance called aclidinium. Aclidinium is an anticholinergic which is used in combination with a β_2-agonist in the treatment of respiratory disorders, particularly asthma and Chronic Obstructive Pulmonary Disease ('COPD'). Aclidinium is currently in Phase III clinical trials.

2. The issues involved are familiar enough in cases of this kind and to my mind would not be particularly difficult to resolve were it not for the experiments undertaken by both sides and the extensive evidence which they have generated. One of the parties' counsel suggested in closing that the case had in fact been 'hijacked' by these experiments. I agree; they have not proved to be as useful as the parties had no doubt intended.

The proceedings

3. In this action, the claimant, Laboratorios Almirall SA of Barcelona ('Almirall'), were represented by Mr Andrew Waugh QC and Mr Piers Acland. Almirall seek the revocation of European Patent (UK) № 1 651 270 (''270')[2] which stands in the name of the defendant, Boehringer Ingelheim International GmbH of Ingelheim am Rhein, Germany ('Boehringer'). The priority date of '270 is 29 July 2003, to which there is no challenge.

4. Mr Simon Thorley QC and Mr Andrew Lykiardopoulos appeared for Boehringer. I understand that the anticholinergic field had been strongly represented for some time by Boehringer with a number of classic offerings, including ipratropium bromide (Atrovent®), oxitropium bromide (Oxivent®) and tiotropium bromide (Spiriva®). By 2002, Boehringer was also selling a *combination* treatment for respiratory disorders (primarily for COPD) called Combivent® containing an anticholinergic (ipratropium bromide) combined with a β_2-agonist (salbutamol (referred to

[1] Reference to the trial bundles are by bundle number, tab, page and paragraph/or, thus:B/20/27/§5. References to the transcripts is by day and page number, thus:T2/55. 'ISC' is inter-solicitor correspondence.

.[2] 1/1

as albuterol in the US) sulphate) within a single inhaler. The latter has been sold under the slogan '*The Power of Two'* and soon became a market leader.

5. The title of '270 is '*Medicaments for inhalation comprising betamimetics and an anticholinergic'*. The claims are thus directed to a *combination* of a particular anticholinergic with one (or more) betamimetics, the latter being better known as β-agonists (or in the present context, β_2-agonists). In '270, the combination is said to possess an '*unexpectedly beneficial therapeutic effect'* in the treatment of respiratory illnesses but, I should say at the outset, the message conveyed to the addressee of '270 by this optimistic sentiment and its implications, were the subject of considerable debate.

6. The sole anticholinergic mentioned in'270 is a quinuclidine derivative. It is a *chiral, ionic* molecule, whose 'flat' structure is shown as formula 1 in '270. Its use, always in combination, is claimed whether in its racemic or enantiomeric forms. The R-enantiomer became known as aclidinium[3], and a sub-dispute in the case is whether (or to what extent) the S-enantiomer has any relevant therapeutic benefit whatever.

Almirall's Forner patent

7. Another important twist to the history of the dispute is this: that before the priority date of '270, Almirall had specifically disclosed the substance represented by formula 1- and its racemates and enantiomers (among other quinuclidine derivatives) in a published patent application (№ WO 01/04118 – hereafter 'Forner'[4]). Forner had stated that the new quinculidines were therapeutically useful in the treatment of *inter alia*, asthma and COPD. Moreover, for this application, Forner also taught that they could be used in combination with inter alia β_2-agonists. Perhaps not surprisingly, Forner features as prior art in this case. Mr Thorley in fact referred to Forner as a 'spoiling' patent but I

[3] Almirall's and Boehringer's use of the word 'aclidinium' is sometimes inconsistent. The former uses it in relation to the R-enantiomer alone, the latter in relation to both the racemic mixture and its two enantiomers. In this judgment, I have used the word 'aclidinium' to refer to the R-enantiomer alone. Aclidinium is not referred to as such in '270.
[4] Applied for 7/7/00, published 18/1/01

think that this is a harsh description. What followed (such as the patents in suit) could well be regarded as the first buds of a customary 'evergreening' – which in the context of the pharma industry, may (or may not) be patentable.

8. A little later, after the priority date of '270, Almirall itself applied for a patent covering a *combination* of the R-enantiomer (only[5]) of the substance represented by formula 1, with long-acting β_2-agonists. This UK patent, GB № 2 419 819 (''819')[6], was filed in May 2005 claiming priority from 31 May 2004 and is the subject of a counterclaim by Boehringer for revocation. There is also no challenge to that priority date. '819 is entitled '*Combinations comprising antimuscarinic agents and beta-adrenergic agonists'*. Almirall contends that this combination is novel and inventive, pointing to a particular advantage of the aclidinium in that, when combined with long-acting β_2-agonists, it is said to give rise to fewer cardiac side effects than in existing combinations of anticholinergics with β_2-agonists.

9. I should say that in the period between the two applications there was no material change in the 'common general knowledge' of the art. This was common ground. Therefore, when counsel and the witnesses referred to events in '2003/04' (as they often did), they were in fact referring to about the same time. I shall do likewise unless the context otherwise requires.

10. In May 2008, Boehringer counterclaimed in this action for the revocation of '819[7] contending that if their '270 patent is invalid on the ground of obviousness (as Almirall allege), then so too is Almirall's '819 patent invalid. As regards the prior art material relied on, the Boehringer pleading mirrors Almirall's in this respect. The dispute thus contains sundry two-edged swords – as the pleadings show.

11. But there is an important addendum to Boehringer's counterclaim which concerns claim 20, the last claim, of '819.

[5] ie aclidinium.
[6] 1/3
[7] 2/5

12. Save only in relation to claim 20, Mr Waugh said that Almirall was not proposing to gainsay Boehringer's contention concerning the validity of '819 in this litigation[8] (though he was not conceding it). This led Boehringer to add an alternative attack directed specifically to this claim. In the event that 'claim 20 is not held to be obvious' it was unpatentable as it was directed to '*a method of treatment of the human ...body by therapy'*, using the 'medicament of claims 10, 18 and 19' and was thus contrary to the Patents Act 1977 (PA '77'), s 4A (1). Almirall's riposte was that claim 20 was a legitimate 'Swiss type' claim.

13. Almirall alleges that the '270 patent is:

> (a) Anticipated and/or rendered obvious by the earlier Forner application – to which I have briefly referred. This had been published in January 2001.
>
> (b) Obvious in the light of the contents of two so-called 'posters' dated 18 and 19 May 2003 relating to a trial undertaken by a team comprising inter alia a Dr V Schelfhout, who was working on anticholinergics at the University of Ghent in Belgium with Almirall's support, and
>
> (c) Insufficient.

14. 'Posters' in this context are typically notices of research work which are deliberately displayed by their authors (and/or sponsors) for general viewing whilst a medical conference is in progress – in this case at that of The American Thoracic Society in Seattle on the two following days in May 2003. In this case there is no dispute that the two 'Schelfhout' posters (**Schelfhout I** and **Schelfhout II** as they came to be called), were 'made available to the public' in this way.

15. Then, in August 2008, Boehringer decided to apply to amend the '270 patent, restricting the claims to four particularly preferred β-agonists[9] The Comptroller has indicated that in his view, this proposed amendment is unobjectionable.

[8] I was told that examination proceedings in the EPO regarding '819 are ongoing.
[9] The amendment proceedings are all in Bundle 3

Almirall on the other hand, oppose the amendment on the ground that it adds subject matter. Mr Thorley said that if the proposed amendment is allowable, then there was no need for Boehringer to defend the unamended claims. However, if the amendments are not allowable, then, subject to some selection among the sub-claims, Boehringer seeks to defend various claims as granted.

16. In respect of the sub-claims of '270, Boehringer's position was I think, as follows:

(a) In respect of novelty of the claims as granted, Boehringer say that claims 1 and 6 are independently valid.

(b) In respect of obviousness, (as regards '270 both as granted and as proposed to be amended) independent validity is asserted for claims 1 and 2, and

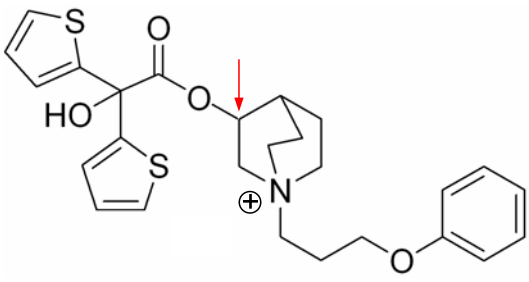
(c) in respect of sufficiency, independent validity is claimed for claims 1, 6 and 7 as granted and claims 1 and 6 as proposed to be amended.

The Aclidinium Story

17. I should first offer a short explanation of **chirality** since this phenomenon features a good deal in this case. I do not think this explanation is in any way controversial.

18. A compound is said to be *chiral* if it can exist in the form of *stereoisomers*. Stereoisomers of a chirally active compound are mirror images of each other and are called *enantiomers*, the designations R- and S- being used to designate the differences in absolute configuration around the chiral atom of the stereoisomer. A *racemate* is a 50:50 mixture of the R- and S- enantiomers.

19. Aclidinium was being studied for use in the treatment of respiratory illness with Almirall's support at Ghent - and was the subject of the posters to which I have referred – though it should be noted, it was not identified as such in the posters. Aclidinium is the R-enantiomer of an ionic molecule having the following chemical structure:



20. The above molecule, (which is chemically equivalent to the compound designated as 'formula 1' in '270), is 3-(2-hydroxy-2-dithiophen-2-yl-acetoxy)-1-3-phenoxypropyl) -1-azonia bicyclo [2.2.2]octane bromide. It has a **chiral centre** (indicated by the arrow) and can thus exist as R- and the S-enantiomers. I shall refer to the 'flat' (or non-stereospecific) chemical structure depicted above simply as "the Almirall Compound" (i.e. a nomenclature which embraces both enantiomers, the racemate and mixtures thereof).

21. However, neither the Almirall Compound nor aclidinium were new compounds in 2003/04 since their existence had been published in Almirall's Forner patent (see above). As Mr Thorley pointed out, the Forner application disclosed a large number of other things as well but there is no doubt that its example 44 was for the preparation of the R-enantiomer, aclidinium, alone.

22. In May 2003, Schelfhout et al presented the two poster presentations of their preliminary *clinical* data for aclidinium at the American Thoracic Society conference in Seattle, to which I have referred. The first poster [Schelfhout I, 4/ 2] included the Almirall Compound by reference to an Almirall reference number (LAS 34273) and chemical name of the molecule depicted above[10] but without any indication of its stereochemistry or mention of which (if any) enantiomer they were working on. The first poster caught the eye of a passing Boehringer scientist, a Dr Thomas Flüge, who took four photographs of the poster [8/ 1 and 2]. The photographs were then sent to Boehringer's International Project Management

[10] The First Poster ("Schelfhout 1") was headed *"Activity of LAS 34273, a new long acting anticholinergic antagonist"* and stated, at numbered paragraph 7 of the introduction of the poster that "*LAS 34273 is a new selective M_3 anti-muscarinic drug from Almirall SA"*. Its chemical name was also given.

team in Germany for what was referred to as a "Competitive Assessment Update" on anticholinergics [8/3 and 4]. And thence, one supposes, they in due course found their way into the Boehringer patent department.

Boehringer's '270 patent: a history

23. Less than three months later, on 29 July 2003, Boehringer filed *three* patent applications, for the Almirall Compound ('formula 1'), its 'racemates, enantiomers or mixtures thereof' in combination with numerous conventional therapeutic agents used in the treatment of respiratory diseases. These three applications were collected in a single volume for use at trial. A glance at this bundle shows that the same three inventors were named in the applications: Messrs Meade, Pairet and Pieper. The specifications contain extensive lists of (for example) possible salts of formula 1, propellants, powders, excipients, combination ingredients, atomisers, dosage variants etc all of which are such as one sees often enough in patents relating to pharmaceutical products. The enantiomers[11] of the formula 1 structure (called simply '1-en') are said to be 'of particular interest according to the invention'.

24. The *first* application concerned the combination of the Almirall Compound with PDE IV inhibitors, the *second* application concerned its combination with steroids and the third application concerned the combination with betamimetics (i.e. β_2-agonists). '270 is the result of this *third* application.

25. By this strategy, within about 3 months of Dr Flüge's photographs of Schelfhout I being sent to Germany, Boehringer had planned to establish monopolies over *combinations* of the Almirall Compound with three other drugs (whether in the form of the racemate or as either of its enantiomers) and when offered in all commonly used presentations.

26. Each of the three applications included an introductory statement in virtually identical terms. The first application stated that:

[11] In the plural. The isomeric structure of one of the enantiomers (the S-enantiomer, in fact) is set out.

> "Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if the anticholinergic of formula 1 is used with one or more PDE IV inhibitors (2)."

Extensive lists of PDE IV inhibitors (with graded preferences) are set out but no pharmacological or clinical data to support any beneficial combination of the Almirall Compound with any PDE IV inhibitor is given. The second application contained a paragraph in the same terms, ending with the words:

> "is used with one or more steroids (2)."

Extensive lists of steroids (with graded preferences) are given, again with no data to support any beneficial combination of the Almirall Compound with any steroid.

27. The third application (with which this case is concerned) used similar words:

> "Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if the anticholinergic of formula 1 is used with one or more betamimetics[12] (2)."

Extensive lists of betamimetics (with graded preferences) are given. As with the other applications, there is no data to support any beneficial therapeutic effect of the combination of the Almirall Compound with any betamimetic. The statement which I have quoted from the third application, was to become paragraph [0008] in '270 as granted.

28. As with the other applications, the specification of '270 is also silent as to the *nature* of this "unexpectedly beneficial therapeutic effect" which it says, 'can be observed' [*sic*]. This omission is important as this therapeutic benefit is, apparently, the sole contribution to the art said to have been made by the inventions subject of these parallel applications.

[12] The term "**betamimetic**" is generally synonymous with "**β_2 receptor agonist**" or **β_2-agonist** (although the Boehringer patent includes compounds which are not β_2 receptor specific).

29. In the workup to trial, Almirall became increasingly curious about the circumstances in which Boehringer came to make these inventions and began to make enquiries.

30. What emerged was this: no disclosure of any experimental work was given. Boehringer confirmed that they indeed had no disclosable documentation or laboratory records relating to experiments and/or tests with the anticholinergic compounds described as formula 1 (or formula 1-en) in combination with β_2-agonists. Neither did they have any disclosable documents relating to the recorded *observation* of any 'unexpectedly beneficial therapeutic effect' [ISC/Tab 2/65]. Then, a little later, when disclosure was given of Dr Flüge's photographs, the unusual genesis of these patents became clear. All these patents were based, said Mr Waugh, upon an adroit use of photographs, scissors and paste rather than by work in either laboratory or clinic.

31. Mr Thorley dismissed this as play to the gallery. He submitted that my immediate task involved an objective assessment insisting that the sequence of events which led to the making of the invention was irrelevant to any issues I had to adjudicate. Dr Flüge's photographs were, he suggested, being noisily paraded by Mr Waugh simply to generate prejudice against Boehringer. Many sound patents had been granted for inventions made entirely 'on paper' as a result of the ingenuity of an inventor who *in his mind*, had perceived or with wisdom born of experience had predicted, the possibility of a beneficial technical contribution to the art. That could be patentable.

32. I agree with Mr Thorley- but the proposition has two riders, in my judgment. The benefit must be specified and not just recorded in general, adjectival terms. Moreover, if (as with '270) the insight or prediction in question is the *raison d'être* of the patent, a paper prediction had better get it right. If it is not right, it is really no more than soothsaying. I also think that the burden must be on the patentee in such circumstances to reveal the benefit and if required, show that the benefit really exists.

33. Mr Thorley also drew my attention to the fact that Boehringer had laid stress on the fact that they were market leaders in the

treatment of bronchial diseases, possessing '*formidable in-house expertise'*[13] –and were thus particularly well equipped to make predictions in this field. I have borne this in mind.

34. On this issue Mr Waugh now moved to the attack. This was more than a matter of mere prejudice: it was relevant to their case at large, he submitted, for a number of reasons.

35. First, Boehringer's alleged unexpected benefit which was said to be associated with the claimed combination, had not been identified. There had in truth been no discovery of *any* beneficial property, unexpected or otherwise. Indeed no work had been done at all by Boehringer and this was why para [0008] of '270, had to be drafted in such a meretricious and uninformative way.

36. Mr Waugh also drew my attention to a number of other matters regarding '270, the most significant of which is the following. Because of the chiral centre in the Almirall Compound, Boehringer included reference to both the enantiomers (see e.g. claim 1 "*optionally in the form of enantiomers"*). The Schelfhout posters (which were silent on which enantiomer was the subject of the Ghent trials), were of no help; Boehringer had therefore been forced to do some guessing. Ironically, when the three named inventors made their 'guess' (as Almirall see it), they got it wrong: the formula shown at the bottom of page 2 of '270 which is said to be *'of particular interest',* is that of the substantially *inactive* S-form, rather than the active R-form. It was not aclidinium. This was referred to thereafter (and structurally claimed in claim 7) as compound '1-en'[14].

Boehringer's '270 patent: Body and claims

37. In pharmaceutical cases such as this, it is not usually necessary to set out details of the patent in suit *in extenso* because most of its content consists of lists of substituents, additives, excipients, propellants, presentations and so forth. Both patents in issue in this case are no exception, since both

[13] Supplementary opening skeleton §§2 and 4

[14] Instead of referring to the enantiomer in a proper scientific manner. This said, Mr Waugh, is further proof that at the time, Boehringer had not a clue as to which enantiomer was the more effective clinically.

contain long lists of such 'trimmings'. The latter, so one would guess, are likely to be available by archival (or electronic) trawl through patent attorney's lists.

38. The '270 patent first refers to an anticholinergic of 'formula 1' (that is the compound whose 'flat' structure I have set out from a different view in para 19 above). The invention is said to consist of its combination with 'a beta$_2$-agonist' as a pharmaceutical composition having use in the treatment of respiratory complaints. The anticholinergic is ionic and 17 anions of it are proposed, all of them I think, being conventional in such substances. Later [0006] we are told that the bromide is particularly preferred[15]. This is the first of a number of potential choices (some of them massive, occupying several paragraphs).

39. More importantly, formula 1 is '*optionally in the form of the racemates, the enantiomers and the hydrates thereof*'. Para [0007] states '*Of particular interest according to the invention are enantiomers of the formula '1-en'*[16] and a stereospecific structure is printed at the bottom of page 1. This is what Mr Waugh called Boehringer's 'bad guess': the structure is for the S- enantiomer which (as I shall hold –see below) is in fact substantially inactive in the treatment of respiratory disorders. Since Boehringer would never fully admit that this was so prior to trial, proving that this was so was the purpose of Almirall's experiment in reply.

40. Paragraphs [0008] and [0009] are key paragraphs (particularly the former) in this litigation. I have already set out §[0008] but for convenience I shall do so again. The paragraphs read as follows:

> [0008]'Surprisingly, an unexpectedly beneficial therapeutic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if the anticholinergic of Formula 1 is used with one or more betamimetics 2.
>
> [0009] This effect may be observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate

[15] This was also the salt identified and used by Schelfhout and her team in the 'posters'.
[16] I need not set this out as it differs from formula I only in showing by conventional means, the location of the structural isomerism.

formulations. According to the invention, it is preferable to administer the two active substance ingredients simultaneously in a single formulation.'

41. Extensive lists of β_2-agonists follow in the usual progressive sequence: preferred, more preferred, most preferably, particularly preferred. I note that some well-known β_2-agonists are included in this list – such as, salbutamol, fenoterol and so on. After ringing the changes around the salts of various β_2 -agonists, para [0022] states that the anticholinergic compound and the β_2-agonist "may be administered simultaneously or successively", using known devices. It is stated that the inflammatory and/or obstructive respiratory complaints which are targeted are 'particularly asthma or COPD' [0023].

42. After this reference to asthma and COPD, the draftsman has set out pages of alternative dosages of each component (see §§ [0026] - [0035]). Known methods of administration are then covered, including dry powder formulations, propellant gas-driven aerosols, propellant free inhalable solutions and suspensions (including nebulisers). "Examples of Formulations" are then given by reference to the (inactive) enantiomer "1-en".

43. The claims then follow at page 13, claims 1, 2, 6 and 7 being asserted to have independent validity. I therefore need consider only these claims. For reasons which will become apparent later, it should be noted that none of the claims are confined to the treatment of any particular respiratory ailment, the claimed compositions therefore being 'unexpectedly' efficacious with both asthma *and* COPD sufferers.

44. *Claim1* is directed to 'pharmaceutical compositions' containing the combination of one or more salts of the formula 1 compound with one or more β-mimetics –identified for the purposes of later claims by '(2)'. The claim is not stereospecific as regards the formula 1 compound, since, as noted, the salts of formula 1 may be '*optionally in the form of the enantiomers or in the form of mixtures of enantiomers or in the form of the racemates thereof...'*

45. *Claim 2* is a two-part claim to pharmaceutical compositions which covers (a) the substances of claim 1 together in a single

formulation or (b) in two separate formulations. Later claims are directed to inhalable powders and solutions but beyond such general indications of pharmaceutical utility, the claims are not concerned with any particular therapeutic application.

46. *Claim 6* is directed to 'pharmaceutical compositions' in which some 12 variants on the β2-agonists (2) 'optionally in the form of racemates' etc are set out.

47. *Claim 7*, as already noted, is directed to formula 1 compounds having the '1-en' structure – which is drawn out. This is the enantiomer which Mr Waugh says that the Boehringer team 'got wrong'.

48. No points of construction arise in respect of claim 1 and a minor point of construction (which in my view, merits no further consideration) arose on claim 2. The only dispute on construction was in the meaning of the teaching of § [0008] above.

Almirall's '819 Patent: Body and claims

49. The '819 Patent is entitled '*Combinations comprising antimuscarinic agents and beta-adrenergic agonists'* and like '270, its products are aimed at the alleviation of 'respiratory disorders'. As before, I have taken this primarily to refer to asthma and COPD - without distinction. However, unlike '270, this patent sets out a useful 'Background' section (pp. 1-2) which I regard as having some general relevance to the important issue of common general knowledge (see below). The 'Background' section begins thus:

> 'β-adrenergic agonists in particular β2-adrenergic agonists, and antimuscarinic agents, in particular antagonists of M3 muscarinic receptors, are two classes of bronchodilating drugs useful in the treatment of respiratory disorders such as asthma or [COPD].
>
> It is known that both classes of drug can be used in combination [*and examples are given from the patent literature]*.
>
> Combinations of drugs in which the active ingredients operate via different physiological pathways are known to be

> therapeutically useful. Frequently, the therapeutic advantage arises because the combination can achieve a therapeutically useful effect using lower concentrations of each active component. This enables the side effects of the medication to be minimised. Thus the combination can be formulated so that each active ingredient is present at a concentration which is sub-clinical in cells other than the target disease cells. The combination is nevertheless therapeutically effective in target cells which respond to both ingredients.
>
> Notwithstanding the above discussion, combinations of known M3 muscarinic receptors and β-adrenergic agonists which are used in combination to treat respiratory disorders, are known to have an unwanted effect in the heart…..Thus the use of combinations of known antimuscarinic agents and β-adrenergic agonists involve undesirable cardiac side-effects e.g. tachycardia, palpitations, …limiting thus the therapeutic value of the combination, especially in patients with an underlying heart disease.'

50. I have reproduced this 'Background' passage *in extenso* because it chimes well with some of my own findings on the relevant common general knowledge. These passages from '819 were put to the experts in cross-examination, but their responses have not caused me to revise my view that the foregoing is a fair epitome of an aspect of the common general knowledge as of 2003/04.

51. The 'Description of the Invention' says this (p2, lines 10 -15):

> 'Surprisingly, it has now been found that a combination of certain specific antagonists of M3 muscarinic receptors (further on referred to as the M3 antagonists of the invention) with long-acting β2 adrenergic agonists (hereinafter referred to as long acting β2-agonists) produce significantly less heart side-effects such as tachycardia than the combinations proposed in the art, yet retaining a robust activity in the respiratory tract.'

I would mention that tachycardia (or increased heart rate) is a condition which

> (a) is a known and undesirable *side effect* of the treatment of respiratory disease with the drugs in issue, and
> (b) is known and is well-recognised among a rather limited number of patients with respiratory problems as a pre-existing or *underlying* condition. There was

evidence about tachycardia (and other cardiac disorders) from the experts[17] and I shall come back to it.

52. Page 2, lines 16-21 of '819 reveal the particular combination which is subject of the invention. The antagonist of M3 muscarinic receptors in this combination is the R-enantiomer of the Almirall Compound that is, aclidinium, the bromide salt of which is later called 'Compound 1'. Like '270, '819 contains extensive lists of long-acting β_2 agonists [18] together with detail concerning possible presentations i.e. doses, inhalers, dry powders, etc (pp 2-20).

53. Unlike '270 however, the specification identifies the therapeutic advantage claimed, namely the fact that they are[19]

> 'particularly suitable for the treatment of respiratory diseases in all kinds of patients, including those having an underlying heart condition.'

54. Moreover, it provides animal experiments to support the advantage stated: see the entire final section entitled 'Pharmacological activity', starting on page 21, line 1.

55. The combination to be tested is made up of therapeutically equivalent doses of aclidinium bromide and two known long-acting β_2-agonists: formoterol or salmeterol. The results (presented as comparative cardiac side-effect profiles between the two anticholinergics, compound 1 and the prior art anticholinergic, tiotropium bromide) are collected in Table 1 on page 23 and are graphically presented in Figs 1-4. Under test were the two β_2-agonists with Compound 1 at various dosages. The combinations were injected rather than being inhaled.

56. In all three experiments, the combination of anticholinergic plus β_2-agonist produces a rapid increase in heart rate. The key difference, I think, between the aclidinium and tiotropium results, is not so much the magnitude of the peak effects but

[17] Principally from Dr Costello who gave evidence for Almirall.
[18] Together with PDE4 inhibitors corticosteroids, and LTD4 antagonists which feature in the trio of Boehringer's applications previously referred to.
[19] p25, ll. 1-4

the speed at which they decline. The time taken for the heart rate to fall to 50% of the maximum value (referred to as t_{50}) is much shorter for the aclidinium combination than for the tiotropium combination. The difference in t_{50} is said to be 'statistically significant' (see page 24 lines 5-26)[20].

57. *Claims 10-11, 18* and *19* are in '*Swiss style'* form. Claim 10 for example is directed to the use of (a) a long-acting β_2-agonist as defined in a number of antecedent claims and (b) an antagonist of M3 muscarinic receptors as defined in claims 1 and 2 for the preparation of a medicament for simultaneous, concurrent, separate or sequential use in the treatment of respiratory disease which is asthma, acute or chronic bronchitis, emphysema, [COPD], bronchial hyperreactivity or rhinitis in a patient

58. *Claim 20*, which is alleged to be independently valid, is another 'Swiss style' or 'Quasi-Swiss style' claim and reads as follows:

> 'Use according to any one of claims 10, 18 and 19 wherein the patient is suffering from a pre-existing heart condition or condition that would be aggravated by tachycardia.'

59. In summary, '819 differs from '270 in being directed to:

> (a) a β_2-agonist combination with the active R-enantiomer of the Almirall Compound only;
>
> (b) an identified clinical advantage associated with that use;
>
> (c) the provision of data supporting that particular clinical advantage (viz 'significantly less side-effects such as of tachycardia yet retaining a robust activity in the respiratory tract'); and
>
> (d) claiming the application of such an advantage specifically in claim 20 via e.g. claim 10.

[20] I should mention at this stage a sub-dispute which developed regarding the experiment reported in '819. One of Boehringer's experts [Prof Zaagsma] considered it to be 'fundamentally flawed'. I have considered the evidence on this matter and believe the objection to be without foundation – and moreover irrelevant. I shall not therefore refer to it again.

Construction

60. The only point on construction related to the 'Swiss style' aspects (if I may so call them) of claim 20. This is the subject of a separate section later in this judgment.

61. Mr Waugh's position regarding the 'two edged sword' represented by Almirall's own case against '270 may be appreciated from the Re-amended Grounds of Invalidity [2/5]. Nonetheless, by his closing speech, Mr Waugh told me that if Almirall's attack on '270 succeeded, claims 1-19 of '819 could not survive *before this court*. I am not entirely sure about the scope of this *caveat* but I conceive my task as regards '819 to be confined to adjudicating the validity of claim 20 only.

Issues to be determined

Boehringer's '270 Patent

62. When it comes to assessing the validity issues, establishing the scope of the **common general knowledge** by the 2003/04 era has, I think, played a more important role in this case than in many others.

63. The following **validity** matters then fall to be determined:

Lack of novelty over WO 01/04118 ("Forner") [4/ 1].
Obviousness over Forner.
Obviousness over ("Schelfhout 1") [4/ 2].
Obviousness over Schelfhout 1 in combination with ("Schelfhout II") [4/ 3]
Insufficiency.
The independent validity of claim 2

64. **Amendment** The Amended Grounds of Invalidity are at [2/3]. Boehringer have made a conditional application to amend the '270 Patent in the form shown at [1/2]. The amendments are opposed on statutory grounds [3/5].

Almirall's '819 Patent

65. The Re-Amended Grounds of Invalidity at [2/5] raise the following issues against claim 20 only:

> Lack of novelty over Forner.
> Obviousness over Forner.
> Obviousness over Schelfhout 1.
> Obviousness over Schelfhout 1 in combination with Schelfhout II
> Is claim 20 directed to a method of treatment of the human body and thus unpatentable under PA '77, s. 4A (1)(a)?

II Background

Medical and pharmacological background

66. Because of the importance of the common general knowledge, this is in some ways an unusual case. In order to give this judgment narrative coherence, it will therefore be worthwhile first setting out some general medical and pharmacological facts (much of which I have unashamedly quarried from counsels' very clear skeletons of argument) to introduce my thinking on this topic.

67. The upshot is this: in view of the large amount of clear, contemporaneous documentary material which was before the court, all of what follows in this section, in my judgment, formed part of the common general knowledge possessed by the skilled addressee (see below) by the 2003/04 period. I should however say that not quite all of what follows was accepted as being so by Boehringer.

68. The relevant expert witnesses on this part of the case were Professor Page and Dr Costello for Almirall and Professor Barnes FRS for Boehringer. I shall consider their status and evidence in due course. In what follows however, I have made little reference to the expert evidence on the common general knowledge.

The lungs

69. Let me begin with the lungs. The lungs comprise a highly branched network of airways called bronchi and bronchioles which terminate in small air sacs (**alveoli**) where exchange of gasses takes place between air in the lungs and the bloodstream. The bronchi and bronchioles are surrounded by thin layers of **smooth muscle** whose contraction and relaxation controls the diameter of the airways and hence the ease with which air flows in and out of the alveoli. The airways are lined by mucosal membrane. There are two main regulatory pathways which affect the state of contraction and relaxation (or so-called **'tone'**) of the bronchial smooth muscle – the **parasympathetic** nervous system (which causes muscle contraction) and the **sympathetic** nervous system (which causes muscle relaxation). The existence of these two, separate mechanisms is of importance to this case.

Parasympathetic control

70. The vagus nerve is one of the principal components of the parasympathetic nervous system and makes synaptic contact with bronchial smooth muscle throughout the lungs. Stimulation of the vagus induces release of the neurotransmitter acetylcholine ("**ACh"**) and similar substances into these synapses. The target **receptors** for ACh are on the surface of the smooth muscle cells and are known as "**muscarinic**' **receptors'** (because they also bind a fungal toxin called muscarine). Muscarinic receptors have already been mentioned in connection with '819. There are a number of subtypes of muscarinic receptor throughout the body (labelled M_1 to M_5). The predominant subtype in the smooth muscle of the lung is M_3. Binding of ACh to M_3 receptors induces contraction of the smooth muscle and hence, a reduction in airflow throughout the lung.

71. Activation of M_3 receptors by ACh also stimulates the secretion of mucus into the airways of the bronchioles. Excessive secretion of mucus can also reduce the effective diameter of the airways and so further impede the flow of air.

72. The term "**cholinergic tone**" refers to the bronchoconstriction *caused by* the release of ACh from the vagus nerve and its subsequent action in the airways. The protection or rather, the

occlusion of the muscarinic receptors from ACh is often referred to as '**bronchoprotection'.**

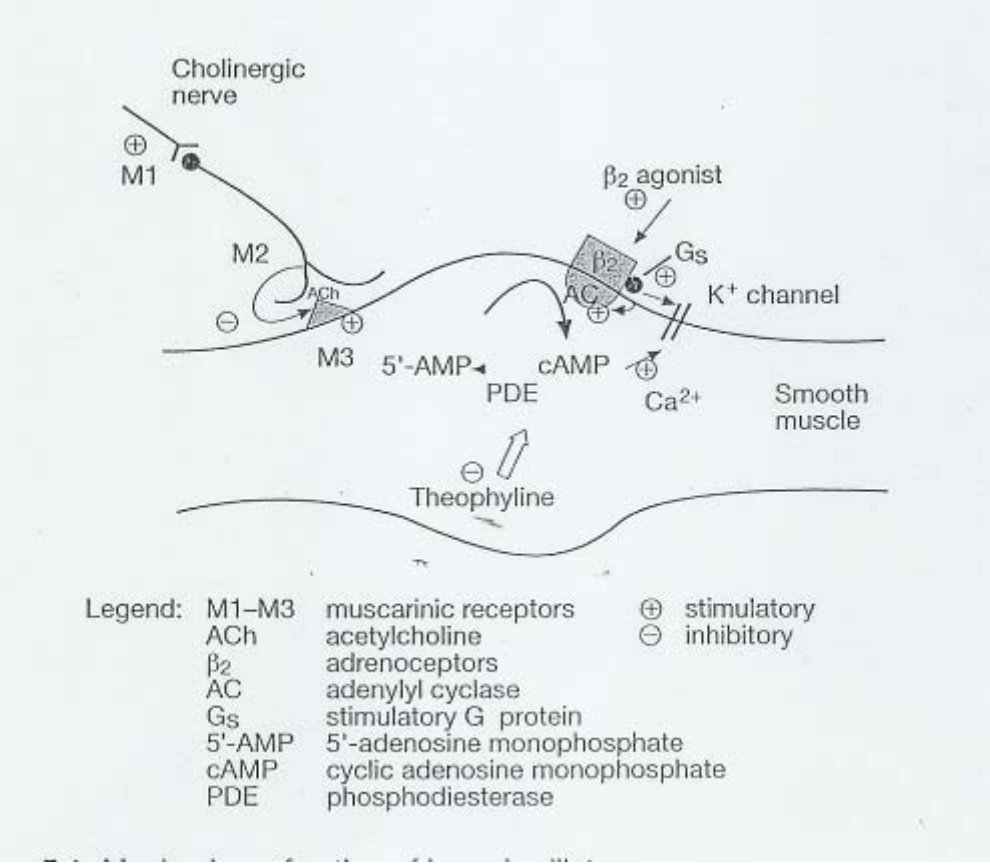
Sympathetic control

73. The sympathetic nervous system promotes the relaxation (referred to as '**bronchodilation**') of airways smooth muscle in two ways:

(a) The first is mediated by adrenaline released into the bloodstream by the adrenal medulla. Adrenaline binds to β-adrenergic receptors on the surface of smooth muscle cells (known as **β_2-receptors**) and induces dilation of the bronchioles.

(b) The second mechanism is indirect and involves the neurotransmitter, noradrenaline. This is released by sympathetic nerve terminals at junctions with the parasympathetic nerves of the vagus (known as ganglia). The noradrenaline binds to β_2-receptors on the parasympathetic nerves and inhibits their activity. The effect is to inhibit the release of ACh from the parasympathetic nerves and so bring about indirect relaxation of the smooth muscle.

74. In a standard textbook referred to a number of times at trial, 'The Effective Management of [COPD]' by Wedzicha et al (London, 2001), the authors have provided a useful diagram (Fig 5.1) to illustrate the mechanisms of bronchoprotection and bronchodilation - which I have reproduced below.



Respiratory complaints - Asthma and COPD

75. Both asthma and COPD involve the narrowing of the airways which results in the sufferer finding it difficult to breathe. They are both chronic inflammatory diseases where the airways become inflamed. The aetiology of the conditions are however different as may be the clinician's initial approach.

76. **Asthma** is a chronic inflammatory disorder which results in hyperresponsive airways. An individual with normal airways will respond to an irritant such as smoke, cold air or pollen with a minor degree of bronchoconstriction. An asthmatic may respond to such environmental factors with a rapid and excessive bronchoconstrictor response (an 'exacerbation' or 'asthma attack') leading to breathlessness, wheezing and coughing. The symptoms are episodic and are usually reversible by administration of bronchodilators. With late onset asthmatics, the inflammatory symptoms become more progressive and airflow obstruction becomes persistent and harder to treat.

77. In asthma, bronchoconstriction may therefore have a number of different causes, one of which is change in cholinergic tone.

78. **COPD** is a multi-faceted condition, with symptoms that vary between patients. COPD patients are mostly elderly but COPD may also be manifest in persons as relatively young as forty. Its symptoms are never entirely absent.

79. The disease is usually caused by smoking and has two main manifestations: **chronic bronchitis** and **emphysema**. The former is characterised by **excessive mucus production** and thickening of the bronchial wall leading to an increase in airways resistance. Emphysema is associated with a **destruction of the alveoli** together with a narrowing and collapse of the airways during expiration. Scar tissue forms which is permanent. In COPD the reduction in airflow is *primarily* a function of cholinergic tone[21]. In addition, airway obstruction is affected by collateral processes such as mucosal congestion/oedema, mucus hypersecretion, inflammation or cellular infiltration, lung hyperinflation and bronchial hyperresponsiveness.

80. By the 2003/04 era, increased cholinergic tone was considered to be the principal *reversible* component of airway obstruction in COPD. However, the other processes referred to in the previous paragraph are also partially reversible[22]. To day, the thinking on reversibility may be different.

Overlap between asthma and COPD

81. There are typical asthma symptoms and typical COPD symptoms and in addition, there is a degree of overlap between these conditions. Some asthmatics present with COPD-like symptoms, for example a *progressive* (i.e. irreversible) narrowing of the airways with relatively little reversibility. Conversely, the inflammation in some COPD sufferers has features of asthma (such patients may in fact be suffering from both asthma and COPD).

[21] This was not accepted by Prof Barnes without qualification (see later).
[22] See previous footnote.

The treatment of asthma and COPD in 2003/4

82. At the time, a number of different classes of drugs were used in the treatment of asthma and COPD. For present purposes it is sufficient to concentrate on the following: (1) steroids; (2) anticholinergics (3) β_2-agonists and (4) Methylxanthines. Treatment of both disorders was (and as far as I know, still is) undertaken in GP asthma/COPD clinics by a specialist nurse and in more severe cases, in hospital in specialist respiratory clinics[23].

Steroids.

83. Steroids (specifically corticosteroids or glucocorticoids) work by suppressing inflammation of the airways –usually with speed. They are widely used in the treatment of asthma and (to a lesser extent) in COPD. They are not however **bronchodilators**. As noted, bronchodilation involves the reduction of smooth muscle tone resulting in a dilation of the airways. Bronchodilators treat the symptoms of the bronchial condition but do not affect the progression of a disease such as COPD. There were three main types of bronchodilators at the time: β-agonists, anticholinergics and methylxanthines.

β_2-agonists

84. β_2-agonists mimic the effects of adrenaline and noradrenaline. They activate β_2-receptors on the smooth muscle of the lung and on the parasympathetic nerves of the vagus, thereby inducing bronchodilation by direct and indirect means: see the diagram in para 72 above. But, as noted, by the 2003/04 era side effects associated with β_2- agonists were well known. β-agonists are also capable of binding to a different class of receptor, known as the β_1-receptor which is distributed in many parts of the body, including the heart and in skeletal muscle. Activation of β_1-receptors can induce undesirable side effects, notably tachycardia and muscle tremor.

85. Most patients who use a β_2 inhaler will experience a sensation of increased heart rate and some will also experience palpitations. On the whole however, β_2-agonists are well-

[23] Dr Costello I, 6/2/12.

tolerated. There are however patients for whom treatment with β_2 agonists pose some risk, even on maintenance doses, namely those who already suffer from cardiac rhythm disturbances and those for whom the efficiency of the heart muscle becomes impaired at higher rates of contraction. Tremor may also arise with elderly patients. Different β-agonists have varying degrees of specificity for β_1- and β_2-receptors. The early β-agonists introduced in the 1960s were non-selective. They were superseded by compounds having improved β_2-selectivity and are exemplified by the compounds salbutamol (also known as albuterol in the US) and terbutaline, both of which have a relatively short-lived action and therefore need to be administered several times per day. Longer-acting β_2-agonists were introduced in the early 1990s and are exemplified by the compounds salmeterol and formoterol. Both of these drugs have a duration of action of around 12 hours. The practical benefit of longer-acting β-2 agonists is obvious.

86. β_2-agonists are one of the mainstay treatments of both asthma and COPD. Conventional, inhaled short-acting β_2-agonists are in fact, the most widely used bronchodilators. They produce rapid-onset relief of symptoms, particularly of breathlessness They are usually administered using a metered dose inhaler (MDI) or in hospital, by nebuliser[24].

87. One of the most important features of β_2-agonists for present purposes is that they will induce bronchodilation irrespective of the agent which causes the muscle to contract in the first place. They act by sympathetic control. This is to be contrasted with anticholinergics whose bronchodilatory activity is only in respect of ACh mediated symptoms of bronchoconstriction (i.e. they act by parasympathetic control).

Anticholinergics

88. As noted, these drugs are also called 'antimuscarinic agents'. They block muscarinic receptors and can therefore be used to block the effects of ACh on the smooth muscle of the lung (i.e. to suppress bronchoconstriction and mucus secretion). Anticholinergics may also block muscarinic receptors

[24] A nebuliser was produced at trial as Exhibit C1 and C2..

elsewhere in the body, for example the heart and the salivary glands, also leading to unwanted side-effects such as increased heart rate and dry mouth, the latter being common features of higher dosage with anticholinergics.

89. As I understand it, the risk of heart rate or rhythm disturbances is however greater with β_2 agonists than for anticholinergics. Nevertheless, in patients with more severe airflow obstruction taking higher doses of anticholinergics, there may also be concerns about cardiac rhythm disturbances – all the more so since patients with the worst lung disease have lower levels of oxygen in their blood - which can of course make the heart function more problematic.

90. The earliest anticholinergics used in the treatment of respiratory diseases were relatively short-acting drugs such as ipratropium bromide and oxitropium bromide. A longer-acting drug called tiotropium bromide was approved for use in the treatment of respiratory disease in the UK in 2002. The aclidinium bromide in this case is another long acting anticholinergic.

91. Inhaled anticholinergics have a slower onset of action than short-acting β_2-agonists, but their duration of action is generally longer. The anti-bronchoconstrictive effects of ipratropium bromide (ATROVENT®) and oxitropium persist for around 4 hours and 8 hours respectively. By 2003, the long - acting tiotropium bromide (SPRIVA®) had become available. It is effective for up to 24 hours.

92. Anticholinergics are one of the mainstay treatments of COPD. However, they are also used in the treatment of severe asthma, for example where the condition cannot be controlled by other therapies or in life-threatening exacerbations.

93. I should add that though various forms of inhalation is the favoured route of administration of both β-agonists and anticholinergics, oral and injectible administration is also available.

Methylxanthines (such as theophylline).

94. These were orally administered and were used to treat both asthma and COPD. I got the impression however that due to side-effects, these substances though readily available to the respiratory clinician, were slightly less prescribed.

Combination therapies

95. The patents in suit are directed to a combination therapy: an anticholinergic combined with a β_2-agonist used in the treatment of respiratory disease.

96. The deployment of two or more drugs in combination which work by different but complementary pharmacological mechanisms has been known for many years. Numerous commercial products which work in this way have been available for use in clinical practice for a long time. Even the patent law reports contain record cases involving such combinations and in years past, the terms of patents relating to combinations of active components in a single presentation[25], have been extended.

97. The motives for combining drugs into a single presentation were and still are, varied[26]. Sometimes the components attack a metabolic pathway at different points or by different mechanisms. Sometimes two drugs target different symptoms of the same disorder, which cannot properly be reached by one alone. A combination may then be important as a matter of convenience to the patient particularly when treatment is by inhaler (as in this case), so as to encourage patient compliance[27]. On other occasions the clinician will look to achieve a beneficial result with two components so as to avoid the unwanted side effects of high dosage with a single drug alone: thus the same effect overall is achieved but with diminished side-effects. This may happen for example with chemo-therapeutic agents in cancer treatments. Clinicians also

[25] As to the latter see for example, *Wellcome Foundation Ltd's Patent* [1974] FSR 244 ('Septrin')
[26] In fact, the 'Background' to '819 (see § 49 above) gives some examples.
[27] It emerged in evidence that these days, the possession of one (or worse) more, inhalers ('puffing billies') may be tainted with some social stigma. It is also worth recording Dr Costello's observation 6/2/§36): "Patient *compliance with the prescribed regime is critical*."

use a combination when there exists a disparity in the therapeutic profiles of the components on the basis of time. All this was well-known before 2003/04

98. During the course of this case, various words have been used in a more or less technical context to describe the effect of such coincident therapeutic activity: 'potentiation', 'synergy', 'add-on effect', 'super-additive effect' and suchlike. However, I have learned from the experts that though the use of such terms may be convenient to promote or describe a commercial product, in scientific parlance, such usage may be imprecise. If necessary, so it seems, there is no better way of investigating what really occurs with particular combinations of drugs than by means of setting up proper pharmaco-clinical assessment.

Combination therapies in the treatment of respiratory diseases

99. The treatment of asthma, COPD (and other respiratory complaints) has for long been no exception to the trend to combination, being a fruitful arena for the deployment of a number of complimentary treatments. I have no doubt on the evidence that in this field, the use of combinations of steroids and β_2-agonists and of anticholinergics and β_2-agonists had been well-known for quite some time before the 2003/04 era. Indeed a good deal of the case was (not surprisingly) taken up by the cross-examination of the experts using 'The Guidelines', textbooks and articles (often of their own authorship), about just such prior art combinations. I shall look at these classes of publication in the following sub-section before I consider the evidence in this case.

Steroids and β_2-agonists

100. Chronic asthma is treated in a step-wise manner depending on the severity of the condition. If the symptoms are mild and intermittent, the first line treatment is an inhaled short-acting β_2-agonist. Where the need arises for regular therapy, the conventional approach is to combine the β_2-agonist with an inhaled steroid, to be supplemented with additional drugs if necessary. Acute exacerbations are treated with high doses of β_2-agonist and steroids, administered by simple inhalation or in hospital, by use of a nebuliser.

101. A number of fixed combination β_2-agonist/steroid products have been on the market since the early 1990s. Examples are Seretide® (a combination of fluticasone and salmeterol[28]) and Symbicort® (a combination of budeonside and formoterol[29]). As well as providing the therapeutic convenience of a combined bronchodilator and anti-inflammatory agent, such products offer an obvious benefit in terms of ease of use and patient compliance.

Anticholinergics and β_2-agonists

102. Like chronic asthma, COPD is treated in a step-wise manner depending on the severity of the condition. For mild, stable COPD, the first line treatment is a short-acting β_2-agonist or an anticholinergic. In moderate to severe cases, the two agents are used together (and may be supplemented with additional drugs if necessary). Such combinations are also used in the treatment of life-threatening asthma.

103. Fixed combination products containing an anticholinergic and a β_2-agonist have also been on the market since the 1990s. In fact, Duovent® (ipratropium and fenoterol) was launched in 1982. Combivent® (ipratropium and salbutamol) was launched in 1993/94. These fixed combination products were available as both handheld inhalers and nebuliser solutions[30].

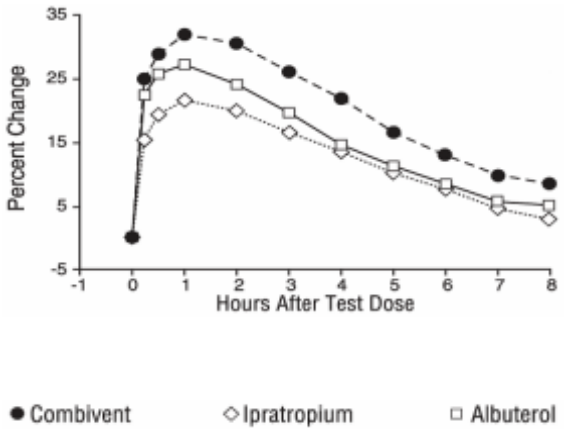
104. As indicated above, anticholinergics and β_2-agonists work by different mechanisms, the former by blocking the parasympathetic nervous system (i.e. maintaining bronchodilation via bronchoprotection) and the latter acting via the sympathetic system (i.e. by direct bronchodilation). The combined effect is greater (alternatively, better for the patient) than that of either agent alone. Furthermore, the rapid onset of the β_2-agonist with the greater duration of the anticholinergic provides another classic clinical benefit. The

[28] The patent of Glaxo for this combination GB 2,235,627 was revoked by Pumfrey J. in *Cipla Ltd v Glaxo Group Limited* [2004] EWHC 477 on 19th March 2004. Permission to appeal was refused by the judge and by the Court of Appeal.

[29] The patent of AstraZeneca for this combination was revoked by the Technical Board of Appeal in the EPO by decision T794/05 dated 18th October 2007. Revocation proceedings in the UK had been stayed pending the final decision of the EPO.

[30] In this connection I regard the 'Background' section to '819 as providing a fair epitome of the situation at the priority date (see above)

overall effect (i.e. greater and more prolonged bronchodilation than with either agent alone) is well illustrated in the following graph taken from Boehringer's Combivent® literature – to whichI shall return[31].



The 'Guidelines', textbooks and articles

105. As a finale to this Background section, I have reviewed *some* of the large amount of the relevant published material before me which was available by about the 2003/04 era – without much reference to the expert evidence given upon it *at this juncture.* In fact, I believe that the material really speaks for itself. I have done this in order to try *directly* to enter the mentality of the skilled addressee whose thinking in resolving the issues in this case is as ever, supremely important.

106. I shall first record that both asthma and COPD are the subject of '**Guidelines'** and as one would expect, textbooks as well. These Guidelines, which are in fact bulky tomes, were much referred to at trial and were agreed to form part of the relevant common general knowledge. In the UK these were issued under the auspices of the British Thoracic Society (BTS) and in the US by the National Institutes of Health, the latter, I understand, being drawn up with the assistance of WHO.

[31] Combivent® prescribing information September 2001: [6A/11/. 5]

The Guidelines

107. The guidelines for asthma are known as **GINA** (2002**)** [7A/2] and those for COPD are known as **GOLD** (2001) [7A/3].The BTS itself also has its guidelines ('**BTS Guidelines'**) for both asthma (February 2003) [6C/19] and COPD (1997) [6C/20], respectively. The publication dates are so close to the conjoined priority dates in this case that I feel confident that they accurately reflect current thinking. The experts told me that these works were and still are highly regarded by clinicians, practitioners and others. I would mention that Boehringer's principal expert witness, Professor Peter Barnes FRS, was involved in the preparation of almost all of these publications.

108. So confident am I in the relevance of the contents of these publications to the issues which I have to decide, that I next propose briefly, with minimum comment and with an eye to what falls to be decided in this case, selectively to quote from them, starting with those devoted to asthma :

Asthma Guidelines

109. For the treatment of acute asthma in adults the 'BTS Guidelines' at 6.3.4 state under the heading 'Ipratropium bromide' that:

> Combining nebulised ipratropium bromide with nebulised β_2 agonist has been shown to produce significantly greater bronchodilation than a β_2 agonist alone, leading to faster recovery and shorter duration of admission…..

110. This is followed by the recommendation that:

> Nebulised ipratropium bromide (0.5mg 4-6 hourly) should be added to β_2 agonist treatment for patients with acute severe or life threatening asthma or those with a poor initial response to β_2 agonist therapy.

111. For children:

(a) over 2 years old, the BTS Guidelines at 6.8.5 makes the statement that:

> There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide used in addition to β_2 agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients…..
>
> If symptoms are refractory to initial β_2 agonist treatment, add ipratropium bromide……

(b) under 2 years old, the BTS Guidelines at 6.10.3 states that:

> The addition of ipratropium bromide to β_2 agonists for acute severe asthma may lead to some improvement in clinical symptoms and reduce the need for more intensive treatment…..
>
> Consider inhaled ipratropium bromide in combination with an inhaled β_2 agonist for more severe symptoms

112. The GINA Guidelines[32] (at p.112) also recognised the utility of the additive effect of nebulised ipratropium bromide and a β_2-agonist which, inter alia, significantly reduced the risk of hospital admission. At page 122 one reads the following:

> The greater efficacy of adding an inhaled long-acting β2-agonistto an inhaled glucocorticosteroid than increasing the dose of inhaled corticosteroids has led to the development of fixed combination inhalers….Controlled studies have shown that delivering glucocorticosteroids and long-acting β2-agonists together in a combination inhaler is as effective as giving each drug separately …Fixed combination inhalers are more convenient for patients, may increase compliance ensure that the long-acting β2- agonist is always accompanied by a glucocorticosteroid and are usually less expensive than giving the two drugs separately.

113. In the section on '*Reliever Medications'* that is, medications that are administered to bring rapid relief from symptoms, one finds in addition to the recommendation to use glucocorticosteroids and β_2-agonists (which are preferred), the recommendations to use anticholinergics (p126) and methylxanthines. As to the former the following is said:

[32] 7A/Tab 2/122-126

> The benefits of ipratropium bromide in the long term management of asthma have not been established although it is recognised as an alternative bronchodilator for patients who experience such adverse effects as tachycardia arrhythmia and tremor from rapid-acting β2-agonists.

114. In addition to their action as bronchodilators, β_2-agonists also have the potential to enhance airways flow by other mechanisms. See for example p.125:

> Mechanism of action- Rapid-acting inhaled β_2-agonists (sympathomimetics) are bronchodilators. Like other β_2-agonists, they relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability, and may modulate mediator release from mast cells.

COPD Guidelines

115. For the treatment of COPD in adults, the BTS COPD Guidelines summarise the pharmacological treatment of COPD at the Summary Table S2 (p.5) as follows:

> *Mild Disease*
> Bronchodilator Therapy: short acting β_2 agonist or inhaled anticholinergic as required ... depending on symptomatic response.
>
> *Moderate Disease*
> Bronchodilator Therapy: as for mild disease but regular therapy with either drug or a combination of the two may be needed. A corticosteroid trial should be considered in all patients.
>
> *Severe disease*
> Combination therapy with a regular β_2 agonist and anticholinergic; the addition of other agents (see below) should be considered.

116. The text of the BTS Guidelines give reasons for these recommendations, including convenience and patient compliance (p.14). For example, in discussing the

management of acute exacerbations of COPD, the Guidelines state that (p.21)

> "For moderate exacerbations a β agonist (salbutamol 2.5-5 mg or terbutaline 5-10 mg) or an anticholinergic drug (ipratropium bromide 0.25-0.5 mg) should be given. For severe exacerbations or if the response to either treatment alone is poor, then both may be administered".

117. The BTS Guidelines state at p.14:

> "*Anticholinergic drugs*
> Most clinical studies suggest that anti-cholinergic drugs such as ipratropium bromide are as efficacious as β_2 agonists in patients with COPD, and some studies suggest a greater and more prolonged bronchodilator response than β_2 agonists. The addition of ipratropium to a β_2 agonist may enhance exercise tolerance more than can be achieved by either drug alone"

> "*Which bronchodilator?*
> Beta agonists used "as required" can be tried in view of their more rapid relief of symptoms. If β agonists do not control symptoms adequately or if regular maintenance therapy is desired, an anticholinergic can be added or substituted. Combination bronchodilator therapy has the potential advantage of convenience and improved patient compliance. However, combinations of a β_2 agonist and an anticholinergic drug should be only be used if the single drugs have been tried and have failed to give adequate symptom relief. Combinations should only be continued if there is good subjective or objective evidence of benefit. Symptom severity and subjective benefit as reported by the patient are better guides to improvement in quality of life than are short term changes in spirometric values after bronchodilators."

118. The GOLD Guidelines state:

(a) At p.71 (Fig.5.3.4):

> Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

(b) At pp. 73-74

> *Combination therapy*. Combining drugs with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side

effects. A combination of a short-acting β_2-agonist and the anticholinergic drug ipratropium in stable COPD produces greater and more sustained improvements in FEV_1 than either drug alone and dose not produce evidence of tachyphylaxis over 90 days of treatment.

The combination of a β_2 agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function and health status. ….

(c) Under the heading '*Combination Therapy*', the GOLD Guidelines state as follows (at p.74):

"β_2 agonists and anticholinergics taken by inhalation are generally equipotent, with some studies suggesting that the latter are more likely to be effective in a given clinical setting (Evidence A). Consideration of costs and possible side effects will determine the choice of drug for monotherapy, but for patients with Stage I: Mild COPD or Stage II: Moderate COPD as-needed treatment with either is a reasonable first step. Failure of one of these bronchodilator classes to control symptoms should prompt a trial of the other class and if symptoms are still troublesome, regular treatment with a combination of drugs is appropriate"

.

(d) Under the sub-heading 'Airflow limitation and hyperinflation' the GOLD Guidelines has the diagram which I have reproduced below:

Figure 4-12. Causes of Airflow Limitation in COPD

Irreversible	• Fibrosis and narrowing of airways • Loss of elastic recoil due to alveolar destruction • Destruction of alveolar support that maintains patency of small airways
Reversible	• Accumulation of inflammatory cells, mucus, and plasma exudate in bronchi • Smooth muscle contraction in peripheral and central airways • Dynamic hyperinflation during exercise

Textbooks and articles

119. This is what Dr Costello, said about the use of textbooks[33]:

> "At the priority date of the Boehringer patent, physicians of ordinary skill in respiratory medicine would have access to and regularly used a number of general medical and specialist textbooks."

In relation to the extracts which follow, I have no doubt that like those quoted from The Guidelines, these also fairly epitomise current thinking in the treatment of respiratory disorders in the 2003/04 era.

120. Murray and Nadel's Textbook of Respiratory Medicine (USA, 2000 Edn), evidently a classic textbook in this area of medicine, [34] was referred to by both parties. The first extract is from Chapter 11 '*Airway Pharmacology'* [6B/16/12]

> " In asthmatic subjects, anticholinergic drugs are less effective than beta-agonists as bronchodilators and offer less efficient protection against various bronchial challenges, though their duration of action is longer….Nebulised anticholinergic drugs are effective in acute severe asthma, although they are less effective than $beta_2$- agonists in this situation. Nevertheless, in the acute and chronic treatment of asthma, anticholinergic drugs may have an additive effect with $beta_2$- agonists and should therefore be considered when control of asthma is not adequate with $beta_2$- agonists, particularly if there are problems with theophylline or if inhaled $beta_2$- agonists give troublesome tremor in elderly patients."
>
> "Fixed-combination inhalers of an anticholinergic and a $beta_2$ agonist are popular, particularly in patients with COPD. Several studies have demonstrated additive effects of these two drugs, providing an advantage over increased doses of $beta_2$-agonist in patients who have side effects".

In the same book, Chapter 38 'Chronic Bronchitis and Emphysema' is concerned with COPD. On page 36 in that chapter, under the sub-heading 'Symptomatic Therapy' one reads the following introductory sentence:

[33] Costello I, 6/2/§58
[34] "*It is probably the most widely used text book in respiratory medicine in the USA*", said Prof.Barnes $T3/445_{4-6}$

"Symptomatic relief is directed against the four reversible elements of airflow limitation: mucosal congestion and edema, increased secretions, bronchial smooth muscle contraction, and cellular infiltration and inflammation."

Fig 38.1 in that chapter (p. 4), illustrates, in the form of a non-proportional Venn diagram, the overlap between asthma and COPD.

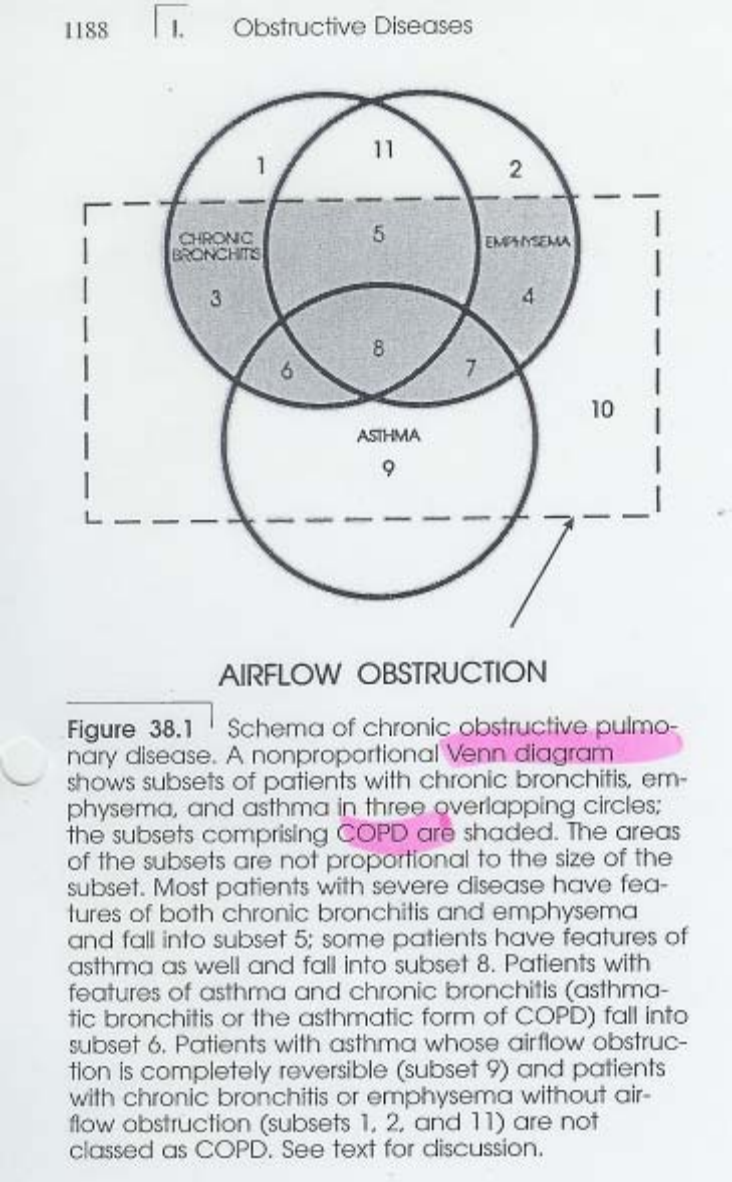


Figure 38.1 Schema of chronic obstructive pulmonary disease. A nonproportional Venn diagram shows subsets of patients with chronic bronchitis, emphysema, and asthma in three overlapping circles; the subsets comprising COPD are shaded. The areas of the subsets are not proportional to the size of the subset. Most patients with severe disease have features of both chronic bronchitis and emphysema and fall into subset 5; some patients have features of asthma as well and fall into subset 8. Patients with features of asthma and chronic bronchitis (asthmatic bronchitis or the asthmatic form of COPD) fall into subset 6. Patients with asthma whose airflow obstruction is completely reversible (subset 9) and patients with chronic bronchitis or emphysema without airflow obstruction (subsets 1, 2, and 11) are not classed as COPD. See text for discussion.

121. "The Effective Management of COPD" by Wedzicha & Ind (London 2001) [6C/23/17] says this:

> Since β_2 agonists and anticholinergic agents produce bronchodilation by different mechanisms (acting on receptors distributed differently in the bronchial tree, Figure 5.1[35]) it is logical to combine inhaled therapy. Besides producing a greater bronchodilator effect than either agent alone, the rapid onset of action of a β_2 agonist with the greater duration of an anticholinergic agent is an additional rationale. Furthermore, given by a single combination inhaler, there are additional benefits of simplicity, reduced cost and potentially enhanced compliance. The European Respiratory Society (ERS), BTS and ATS guidelines also suggest a role for long-acting β_2 agonists in combination with anticholinergic drugs in stable disease.

122. Managing Chronic Obstructive Pulmonary Disease [CXX/4/40 [36]] says this:

> "Recommended use
>
> Regular treatment either as metered dose inhaler (MDI), dry powder inhaler (DPI) or nebulizer three or four times is recommended. Combination inhalers with an anti-cholinergic and a short-acting β_2-agonist (such as Combivent: ipratropium bromide and salbutamol) are very useful, giving a greater speed of onset of action and additive bronchodilator effects."

And again at p 62:

> Combination bronchodilator inhalers with an anticholinergic and a short-acting β_2-agonist, such as Combivent (ipratropium bromide and salbutamol) are a convenient way of giving bronchodilators and are preferred by patients.

123. "*Long-acting β_2-adrenoceptor agonists or tiotropium bromide for patients with COPD:Is combination therapy justified?"* (London, 2003) [37]: [CXX/10/270] has the following:

> "There is increasing evidence that long-acting agents such as the β2-adrenoceptor agonists salmeterol and formoterol and the new anticholinergic tiotropium bromide provide a better therapeutic option. In the treatment of COPD long-acting β2-agonists (LABAs) given twice daily cause the same degree of bronchodilation astiotropium given once daily. Combined use

[35] See §74 above.
[36] Chapter by Prof. Barnes FRS
[37] From *Current Opinion in Pharmacology* by Tennant co-authored by Prof Barnes.

of an inhaled LABA with tiotropium bromide should provide important therapeutic benefits, as these drugs have distinct and complementary pharmacological actions in the airways

124. Atlas of COPD CXX/1/136 (London, 2004) [38] says this:

> "Combining bronchodilators may improve efficacy for some patients, and this may cause less risk of side-effects than by increasing the dose of a single bronchodilator."

125. The Role of Anticholinergics in COPD & Chronic Asthma (London 1998)[39] [CXX/21/142] says this:

> "Importantly the combination of anticholinergics and beta$_2$-agonists gives more than enhanced efficacy as it has the benefit of no additional side effects. The use of combination therapy is therefore likely to result in improved compliance."

The '*Potential rationale for the use of anticholinergics and β2-agonists in COPD'* is then listed in Table 1 (p 142):

> (1) additive/synergistic; (2) Different sites of action (?) – proximal airways/distal airways; (3) Different mechanisms of action; (4) Onset of bronchodilatory effect; (5) Different side effect profiles; (6) Cost effective?; (7) improved compliance ?

126. *"COPD: Current therapeutic interventions and future approaches"* (2005)[40] [CXX/24/1087] says this**:**

> "Combination inhalers There is clear evidence for additive effects of short-acting anticholinergics with β_2-agonists, leading to the introduction of combination inhalers. There is emerging evidence that LABAs and tiotropium may also have additive effects, suggesting that a combination of LABAs and tiotropium or other long-acting anticholinergics may be useful. A once daily inhaler with a once daily β_2-agonist and anticholinergic would, therefore, be ideal."

The Combivent ® product literature

127. I have mentioned this Boehringer combination product several times. It is a combination of ipratropium bromide (an

[38] co-written by Prof Barnes.
[39] co-edited by Prof Barnes.
[40] *Eur Respir J*:25:1084-1106 by Prof Barnes & Stockley Though published in 2005, the paper was received on 7 December 2004.

anticholinergic) and salbutamol sulphate (a β_2-agonist) in the form of an inhaler presentation. Its recommended use is for the treatment of COPD and attention is drawn to the cardiovascular effects of the salbutamol component. I also again draw attention to the slogan with which the product is associated: 'THE POWER OF TWO' Combivent advertising [6A/4] and product literature [6A/11/3-4[41]] was exhibited to the Report of one of Almirall's experts Professor Page:

> Combivent Inhalation Aerosol:
>
> Mechanism of Action Combivent Inhalation Aerosol is expected to maximize the response to treatment in patients with chronic obstructive pulmonary disease (COPD) by reducing bronchospasm through two distinctly different mechanisms, anticholinergic (parasympatholytic) and sympathomimetic. Simultaneous administration of both an anticholinergic (ipratropium bromide) and a beta$_2$-sympathomimetic (albuterol sulfate) is designed to benefit the patient by producing a greater bronchodilator effect than when either drug is utilized alone at its recommended dosage."
>
> "From a pharmacokinetic perspective, the synergistic efficacy of Combivent Inhalation Aerosol is likely to be due to a local effect on the muscarinic and beta$_2$-adrenergic receptors in the lung."
>
> "Serial FEV_1 measurements (shown below as a percent change from test-day baseline) demonstrated that Combivent Inhalation Aerosol produced significantly greater improvement in pulmonary function than either ipratropium bromide or albuterol sulphate when given separately."

Summary to the Background section

128. In the latter part of this section, I have collected extracts, from a number of contemporary, documentary sources all dating from before and within the 2003/04 era, which were before the Court – assembled I would add, largely by Almirall. I have indicated that the three Guidelines were agreed to be part of the common general knowledge. Having regard to the wide availability of the product and experience of its clinical effect, I regard the Combivent product and its associated literature as also being part of the common general knowledge. Though the remainder of this documentary

[41] Boehringer, Revised 2001

material was not all agreed to be part of the common general knowledge, I nevertheless consider that it is either common general knowledge or is not controversial.

129. In some ways, this is an unusual case because the proper appreciation of the common general knowledge is, I think, the key to adjudicating a number of the issues which have to be resolved, particularly that of obviousness. In my view, this is a field wherein the Court may derive much assistance simply by reading the relevant contemporaneous technical literature - without the benefit of the expert's evidence. Once the clinical terminology has been assimilated, the task of deciding broadly what was common general knowledge is not difficult.

130. There has nevertheless been disagreement as to the extent of some of the common general knowledge and I shall in due course have to test certain of these Background findings in the light of the experts' evidence. For the time being however, what follows will epitomise my findings from the material so far presented:

(a) The physiological manifestations of asthma and COPD were well known. There were demonstrable cases of each, but there were also a significant number of patients whose condition manifested symptoms of both disorders – hybrid cases in fact. They were both treated in the same respiratory units.

(b) A number of single drugs were available to treat both disorders and a number of combined presentations were also available for the same purpose, particularly (but not exclusively) to alleviate symptoms in cases of overlap. Typically, delivery was by inhaler, including the delivery of combinations in a single inhaler. Oral treatments were also available.

(c) The classes of drugs available to treat asthma and COPD were (i) steroids (ii) β_2-agonists (iii) anticholinergics and (iv) methylxanthines, the first three being by far the most important.

(d) The ionic and stereoisomeric character of some of these drugs was known and taken into account.

(e) The modes of action of these drugs were well understood, as were their onsets and duration of action, dosage profiles - and their major (such as cardiac) side-effects.

(f) Though in most cases the initial choice of drug was driven by whether the patient was suffering from asthma or COPD, the clinician had some flexibility in the choice of remedy – including the use of the single or combination products then commercially available[42].

(g) Though at normal dosage levels, the first three categories of available drug seem to have been fairly well tolerated, side-effects appear to have been of concern (and were acted upon) among the elderly and those with some pre-existing or underlying cardiac malfunction, such as tachycardia.

(h) In the case of anticholinergics, which seem mostly to be ionic, I have noticed that the bromide salt is almost invariably used.

(g) In all cases, treatment was on an *ad hoc* basis and involved an empirical approach. 'One size' did not fit all patients.

III The Skilled Addressee

131. The Patent is deemed to be read and understood by the *skilled addressee.* The skilled addressee is a forensic construct who possesses the *common general knowledge* of the art. Though deemed to be uninventive, in this case, this notional person will nonetheless have to be a specialist. The concrete attributes of this important person in patent infringement cases have frequently been commented upon and I have no need to repeat them here. In the end, I do not believe that there was much between the parties as to who was to be regarded as being the appropriate skilled addressee in this case.

[42] Seretide, Symbicort, Combivent and Duovent – all ®.

132. The skilled addressee is obviously a specialist team[43]. The team will be basically composed of a clinical (here, a respiratory) pharmacologist and a respiratory clinician. These two core members may be considered to have access to the advice of a formulation specialist and a toxicologist, as required. They will also have access to and use

> (a) at least the three Guidelines to which I have referred, and
> (b) adequate laboratory facilities.

Unlike the expert witnesses who gave evidence, they will not however be at the top of their professions.

IV The witnesses

133. There were six witnesses in all, four experts and two witnesses of fact. Neither of the latter were cross-examined. Sr. Ramon Bosser of Almirall, gave evidence about the publication of Schelfhout II and M. Thierry Bouyssou of Boehringer supervised the conduct of Boehringer's experiments.

134. Three of the experts were outstanding figures in their fields in this country. They gave evidence clearly and with confidence. The fourth expert's evidence was not in my view, in the same category, as I shall explain. All the experts have at some time had connections with commercial pharmaceutical interests in this field, including with the litigants themselves. I have paid no attention to this.

For the claimant

Professor Clive Page

135. Professor Page is a pharmacologist having a PhD from London University (1984). He has considerable and long-standing research interests in respiratory diseases. He spent some time in the pharmaceutical industry (for example, with Sandoz AG of Basel) before becoming involved in university

[43] See the remarks of Pumfrey J in *Glaxo Group Ltd's Patent* [2004] RPC 843 @ 852-853. The subject matter was similar to that of the present case.

pursuits. He is currently Professor of Pharmacology at King's College, London University and director of the Sackler Institute of Pulmonary Pharmacology. He has a number of papers to his name (some of them jointly authored with Dr Costello -see below)) and has given evidence in other patent cases in various jurisdictions. Mr Thorley invited me to label him a poor witness who was incapable of answering the questions put to him either directly or succinctly. I disagree. I found Professor Page's evidence helpful.

Dr John Costello

136. Dr Costello is a consultant respiratory physician who has practiced for many years in the field of general and respiratory medicine. Starting his career in Dublin at the Mater Hospital, he has held a number of important and responsible posts in this country. He also has held academic positions and has published a number of papers. He has appeared as an expert witness in other patent cases. Of all the experts, I found Dr Costello's evidence to be the most clear and succinct. Mr Thorley raised no criticism of this witness.

For the defendant

Professor Peter Barnes, FRS.

137. Professor Barnes is Professor of Thoracic Medicine at the National Heart and Lung Institute. He is Head of Respiratory Medicine at Imperial College and is Honorary Consultant Physician at the Royal Brompton Hospital. His experience in the field of respiratory medicine, both as a pharmacologist and a physician, is I suspect, hardly rivalled in this country. He has authored and co-authored a very large number of technical materials and like others in this position, has found many of them returning via counsel to haunt him in this case. I have already referred to some of them in the Background section. His qualifications are numerous and, save that he is a Fellow of the Royal Society, I can refer to his evidence for details. He was an excellent witness.

138. Mr Waugh had a number of 'comments' on Professor Barnes' evidence which arose as a result of his cross-examination. In essence these related to disparities between

what he had stated in the numerous publications which he wrote (or to which he contributed) up to the 2003/04 era and what he had said in evidence. For example there was the question of whether cholinergic tone was the *main* or the *only* reversible feature of COPD. There was also the question as to why his contributions to the contemporaneous technical literature were redolent with references to combinations - which were not in his report. There was also the so-called 'sub-optimal dose' point. I have read his answers to these points and am not convinced that I need make any adverse comment upon the Professor's evidence as a result. The only outcome of the matter which I would record however is that I shall attach rather more importance to what was written than what was said in evidence.

Professor Johan Zaagsma

139. Professor Zaagsma is now retired (2005) but was Professor of Pharmacology and Therapeutics and head of the Department of Molecular Pharmacology at the University of Groningen in the Netherlands. He has lectured in pharmacology and therapeutics and has some 20 years experience in designing and commenting upon protocols and data obtained from animal models for the development of treatments for respiratory disease. He was ultimately responsible for Boehringer's experiments (though not for the initial work-ups) and for commenting upon Almirall's experiment in reply. Most of his cross-examination focussed on these aspects of the case.

140. English is not Professor Zaagma's native language - though he spoke it rather well. In addition, he spoke softly, was a little hard of hearing and of a nervous disposition. He seemed not to have given expert evidence before. On occasion, I found his answers difficult to follow for these reasons and reference to the transcript did not much assist me.

141. I had however a more fundamental difficulty with his evidence and it was this: his inability to answer questions simply and without cocoons of qualification. He often persisted in providing surplus explanation to what appeared to

be straightforward questions[44]. I am sure that Professor Zaagsma was trying to be as accurate as possible so as to avoid being faulted, but he did make heavy weather of much of it. From time to time I felt that the cross-examination simply had to be moved on – and I said so. I record that this was the subject of specific comment by Mr Thorley in closing.

V Common General Knowledge topics: What the experts said.

142. Having introduced the experts, I now wish selectively to refer to some evidence given by them on the common general knowledge, the topic having been approached so far almost entirely in the absence of such evidence – for the reasons given. Most the documents to which I have referred were in fact put to them in cross-examination.

143. *Chirality*. Chirality has arisen at a number of points and I have already offered a brief explanation of it. But in the context of the physiological activity of enantiomers, something more needs to be said. As Professor Page's evidence on this was not only clear but was not the subject of cross-examination, I can perhaps do no better than quote from his first report [6/1/§§85-89]:

> 85 Although they have the same chemical formulae, enantiomers can have profoundly different effects in biological systems; one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of activity. It would be necessary to carry out further testing to better understand the pharmacological profiles of each enantiomer.
>
> 86 Generally, a biological activity associated with one enantiomer is not likely to be associated with the other enantiomer to the same extent. This can be understood by likening the interaction of an enantiomer with another molecule, such as a receptor, to fitting a hand into a glove. Just as a left-hand will not readily fit into a right-handed glove, the 'wrong' enantiomer will not readily bind with a receptor compatible with the other enantiomer.
>
> 87 Examples of unexpected effects of the supposedly 'inactive' enantiomer include thalidomide, where the R-enantiomer is an

[44] Mainly in relation to the experiments.

> effective anti-emetic whilst the S-enantiomer is teratogenic at the same doses; and penicillamine, where one enantiomer is an immunosuppressant used to treat rheumatoid arthritis and a metal chelator (used to treat heavy metal poisoning), whilst the other enantiomer is toxic as it inhibits the actions of pyridoxine (vitamin B6).
>
> 88 For β–agonists, the R form usually confers the desirable biological activity of bronchodilation and bronchoprotection whereas the S form is considered to be essentially inert as a bronchodilator at therapeutically relevant concentrations. However, I note, although I do not think it would have been a matter of common general knowledge, that S-isoprenaline and S-salbutamol have been shown to have an adverse effect on the airways.
>
> 89 By July 2003, a respiratory pharmacologist would have been likely to carry out tests on the enantiomers of a novel chiral compound to explore the extent to which each of the enantiomers had the desired biological activity and any adverse effects.

144. I accept this evidence. What is important (and follows from it) is that in '270 an 'unexpectedly beneficial therapeutic effect' is said to have been *observed* to be present in the racemate as well as in the enantiomers of formula 1, without distinction. To the skilled man, this is I think, a serious, technical statement.

145. *Bronchodilation and bronchoprotection*. These words are used in a possibly confusing way throughout this case. It is, I believe, important to distinguish between them in terms of the actions of drugs on the respiratory system. Again Professor Page provides a clear uncontroversial explanation [6/1/126]:

> The terms bronchoprotection (used in the Boehringer Notice) and bronchodilation (used in Boehringer's Statement of Case) are not interchangeable. Bronchoprotection refers to the ability of a compound to protect the airways from bronchial challenge, such as the introduction of a spasmogen; whereas bronchodilation refers to the ability of a compound to dilate the airways, regardless of whether they are abnormally constricted. A drug may have a bronchoprotective effect without acting as a bronchodilator.

146. *Combination Therapy*. I have also considered the experts' evidence on this , in particular the following passages:

Page I 6/1/53-56 and 90

Costello I 45,50-51 and 78-79

Barnes T3/483-485

147. This evidence amply confirms and re-enforces what the foregoing contemporary clinical literature teaches: that in the treatment of respiratory disorders, combination therapy was an integral part of the common general knowledge before 2003/04. The availability to a clinician of using a combination of steroid/β_2-agonist and/or an anticholinergic was there for use, if necessary.

148. *Approach to clinical practice in 2003*. In paragraphs 52-57 of his first report, Dr Costello gives evidence about how he would have approached treatment of asthma and COPD, mild and severe, at the time. I also accept this evidence. This confirms that the clinician's approach is flexible and pragmatic and that 'one size' does indeed not fit all. Unless there are *compelling* reasons for not doing so, in treating respiratory disease a clinician would routinely be prepared to combine drugs in a stepwise manner if he felt it would yield a therapeutically effective outcome. In his second Report, Dr Costello said this[45]:

> "…the practical approach of clinicians to the treatment of airflow obstruction is to provide a treatment regime to ameliorate as far as possible, all symptoms."

VI Construction of § [0008] of '270

149. The only significant point on construction in '270 related to the meaning of a phrase and a word in the key paragraph [0008] of the narrative. I say 'only' but as I have already indicated, it is in fact the most important passage in the entire patent. I shall now set this paragraph out again for

[45] 6/5/§16. See also §§14 and 17.

convenience, with added emphasis in the light of what follows:

> 'Surprisingly, an *unexpectedly beneficial therapeutic effect* can be *observed* in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if the anticholinergic of formula 1 is used with one or more betamimetics (2).'

150. There are of course a number of 'inflammatory and/or obstructive diseases of the respiratory tract' but there is no teaching that the combination of the substances proposed is only (or more) effective against any particular one of them. The experts agreed that the target disorders there identified would primarily be understood to be asthma and COPD – without distinction between them.

151. I would add that though one often sees the word used in patents, 'surprisingly' has no relevance to anything I have to consider. On the other hand, whether '*an unexpectedly beneficial therapeutic effect can be observed*' is at the very heart of the case and moreover, has been the cause of both parties' experiments.

152. '*Unexpectedly*' This presupposes that there was a norm at the time '270 was published: ie an 'expected' beneficial therapeutic effect resulting from the combination of the anticholinergics of formula 1 (or known anticholinergics in general) with known β_2-agonists in general. As the previous section has shown, the use of combinations of anticholinergics with β_2-agonists (and steroids) for the treatment of respiratory diseases was indeed part of the common general knowledge. It also shows that there were a number of 'beneficial' therapeutic effects which might have been expected by the skilled man from such combination therapy: thus 'double the effect of one agent on its own', 'some additive effect', 'the same benefit at lower doses of the components so as to avoid side effects', better patient compliance - to name but a few. Which benefit then is being referred to in '270?

153. '*Therapeutic*' But here is where the reader needs help and cannot find it. There are no relevant examples and there is no data in '270; in fact, there is *absolutely nothing* in the narrative to resolve the quandary. There is in truth no clue to

the nature of the benefit being spoken of. Yet this is obviously the mainspring (or the 'big point' as Mr Waugh called it) of this patent. It seems to me that without enlightenment, the reader must left with a puzzle. I felt this when first I read '270 and, so it seems, I am not the only one who felt this way; Dr Costello certainly did. In fact until recently, even Boehringer themselves were hard put to say what it meant. Not surprisingly, Mr Waugh uses the delphic quality of this key phrase to found a number of attacks on the patent. I shall therefore come back to it.

154. Before moving on however, I would add this: in the light of my analysis of the prior art, if (and it is an 'if') the 'expected' benefit bears the connotation of 'an addition to the efficacy of either agent on its own as a bronchodilator' (as for example, with Combivent), to the skilled reader, 'unexpected' must mean '*clearly* more than some doubling additive bronchodilator effect'. I would add that this *was* in fact the way Professor Barnes' understood it: 7/1/23 and see below.

155. '*Observed*' This is of course an ordinary English word but in a scientific context (such as in a patent), it carries in my view, the added implication of something (a figure or a phenomenon, for example) noted and recorded as a result of actual trial or experiment. We now know the genesis of '270. This statement is therefore false; in that sense, no one ever observed anything relevant.

An interlocutory episode

156. Mr Waugh also drew my attention to an interlocutory episode in this case which is both relevant to matters which I have to decide-and is frankly, prejudicial to Boehringer. He says that Boehringer has itself maintained a 'fluctuating and uncertain' position with regard to the meaning of the phrase '*an unexpectedly beneficial therapeutic effect'* even five years after it was written. How then, he asked, can the skilled reader possibly be expected to make anything of it? The episode involved both Mr Thorley and the parties' solicitors, Bristows for Almirall and Powell Gilbert LLP for Boehringer.

157. On 16 November 2007, a case management conference took place before Kitchin J at which (*inter alia*) the question now

under consideration was raised by Almirall: what does this phrase mean? Boehringer indicated (Trans. p32) that the surprising effect was (or at least included) *a reduction in cardiac side effects*.

> MR. JUSTICE KITCHIN: Have you come out with it? Have you said what your surprising beneficial therapeutic effect is?
> MR. THORLEY: Yes. The surprising beneficial therapeutic effect is the cardiac side effect. It is exactly the same.
> MR. JUSTICE KITCHIN: So that is the beneficial therapeutic effect?
> MR. THORLEY: As I understand it.
> MR. JUSTICE KITCHIN: It does not have an enhanced activity but it has less harmful side effects?
> MR. THORLEY: My Lord, that aspect we are still taking instructions on.

158. Mr. Thorley continued as follows (Trans. p33):

> What I am not able to do today is to give chapter and verse as to precisely how wide our case on beneficial therapeutic effect is. I know it goes to cardiac side effects, because that is what I have already discussed with my clients. I have not discussed matters wider than that.

159. In the light of these exchanges, Boehringer was ordered to provide a Statement of Case **[**2/19**]** as to both what the skilled person would understand the effect to be and what the effect is. This was served on 20 December 2007. The unamended pleading referred to reduced side effects and also improved efficacy but, so Almirall considered, was cast in such nebulous terms as to provide no useful information **[**2/8**]**:

> *"The skilled person would understand the unexpectedly beneficial therapeutic effect referred to in paragraph 8 of the patent in suit to be, and the unexpectedly beneficial therapeutic effect of the pharmaceutical compositions claimed in the patent in suit is, an unexpectedly beneficial therapeutic effect in the treatment of inflammatory and/or obstructive diseases of the respiratory tract, which <u>may be</u> manifested by improved efficacy (<u>such as</u> improved bronchodilation) <u>and/or</u> reduced side effects (<u>such as</u> reduced cardiac side effects)."* (emphasis added)

It is I believe, significant that the "improved bronchodilation" was <u>not</u> said to have a "greater than additive effect".

160. Almirall's concern about the continuing lack of particularity of Boehringer's Statement of Case was raised by letter of 14

March 2008. But, so they felt, no satisfactory response was forthcoming **[**ISC/2/83**]**.

161. Following service of Boehringer's Notice of Experiments on Friday 13 May 2008, enquiry was made by letter of 16 May 2008 as to whether Boehringer could confirm that it was their case that the addressee would understand that the 'unexpectedly beneficial therapeutic effect' referred to improved bronchodilation *and no other effect* [ISC/3/117]. Powell Gilbert's response the same day was that the Statement of Case was

> "perfectly clear, citing both improved bronchodilation and reduced side effects as beneficial therapeutic effects." [ISC/3/125].

162. However, during his cross-examination ($4/582_{23\text{-}25}$), Professor Barnes FRS said that he had earlier told Powell Gilbert (in March 2008 in fact) that paragraph [0008] was:

> (i) not simply referring to improved bronchodilation but <u>greater than additive</u> bronchodilation" and
>
> (ii) was <u>not</u> referring to reduced side effects.

163. Bristows regarded this state of affairs as unsatisfactory and in May sought clarification of Boehringer's Statement of Case[46]. By 13 June 2008 Powell Gilbert were no longer prepared further to discuss the matter in correspondence **[**ISC/4/168**]**.

164. Under threat of an application to the court, Powell Gilbert's letter of 8 September 2008 nonetheless provided some degree of clarification, namely, that Boehringer's case was [2/12/1]:

> "i. Improved efficacy: The Defendant will rely upon improved bronchodilation;
> ii. Reduced side effects: The Defendant will rely upon reduced cardiac side effects;
> iii. The Defendant will rely upon both (i) and (ii) alone and in combination; and

[46] See letters of 23 May 2008 **[**ISC/3/135**]**, 6 June 2008 **[**ISC/ 4/153**]** and 12 June 2008 **[**ISC/4/164].

> iv. For the purposes of these proceedings only, the Defendant will not rely upon any other therapeutic benefit."

Therefore, as well as still including as a therapeutic benefit, reduced cardiac side effects, the improved bronchodilation was not said to be a "greater than additive effect". Furthermore Boehringer still maintained the reference to reduced side-effects, apparently in direct contradiction to the view of Prof Barnes, expressed some six months previously.

165. Prof Barnes' evidence was served on 3 October 2008. Paras 78 and 79 of his First Report stated that **[**7/1/ 23**]**:

> "78 …..Consequently, I believe that the skilled person would undoubtedly consider that the beneficial therapeutic effect in the treatment of obstructive and/or inflammatory diseases referred to in paragraph [0008] of the Patent would relate to bronchodilation. This was my first response when I was asked by Powell Gilbert what I thought paragraph [0008] would have meant to the skilled person in 2003.
>
> 79 The skilled person would be aware that therapeutic combinations previously used in this field had been useful but had never been shown to achieve anything more than an additive (and, in many cases, less than additive) effect. Consequently, the skilled person would consider that the unexpected part of the beneficial therapeutic effect referred to in paragraph [0008] was that administration of the anticholinergic and beta-agonist combination disclosed in the Patent resulted in a *more than additive bronchodilator effect.* (emphasis added)

166. The "more than additive" bronchodilator effect set out in Prof Barnes' first report seems to have eluded Boehringer over the preceding 5 years and the absence of any reference to this proposition in Boehringer's Statement of Case is I think, striking. Likewise the absence of any reference to reduced side effects in the Professor's evidence is notable given what Powell Gilbert had been saying in correspondence.

167. By letter of 24 October 2008, Powell Gilbert enclosed what it called *"our client's amended Statement of Case"* with no further explanation or intimation that it would apply to amend **[**ISC/7/309**]**. By that 'amended' Statement of Case, Boehringer at last sought to raise the "*more than additive*" bronchodilation benefit and delete any reference to cardiac effects. An explanation for this late amendment to

Boehringer's Statement of Case was sought by letter of 28 October 2008 **[**ISC/7/318-319**]**. The explanation provided was as follows [ISC/7/321**]**:

> "In the course of discussions with our client's experts following receipt of your client's evidence in chief and in the preparation of our client's evidence in reply, it became apparent that the possible benefit of a reduction in cardiac side effects does not exist and/or has not been proved by the data set out in your client's patent. Accordingly, in order to narrow the issues for trial, we have been instructed by our client to serve the Amended Statement of Case."

Thus, no attempt was made to explain Boehringer's reliance, for the first time, of the alleged "*more than additive*" effect - alone.

168. The events which I have described in the paragraphs preceding, in my judgment do not reflect well on *any* aspect of Boehringer's case. It also has implications for all the validity aspects of this action.

The experts' views on § [0008]

169. In so far as it may be of assistance in resolving how the addressee would have reacted on reading this phrase, I have noted the following from the expert evidence of Professors Barnes and Page and Dr Costello[47]. In fact, there was no consensus among the experts as to how this phrase might be understood at the time.

170. I have already recorded that, in relation to this phrase, *Prof Barnes* thought in terms of 'more than additive bronchodilation' – and nothing else. That is of course a perfectly reasonable reading of the phrase. He was cross-examined on this and remained unmoved in his opinion[48]. Nonetheless he fairly acknowledged that others might hold a

[47] *Professor Zaagsma* took up Professor Barnes' point of view without comment and through Boehringer's experiment (see below) tried to prove that his interpretation was indeed correct. He even suggested that it would have been '*very easy'* for the addressee to observe a 'more than additive effect' by carrying out experiments of the type described in Boehringer's Notice of Experiments: 7/5/15

[48] T4/572-587

different view and think in terms of say, reduced side-effects[49]:

18 Q. Would you have thought that the way that it was put prior to
19 amendment, the case on this unexpectedly beneficial
20 therapeutic effect, is an interpretation that a skilled reader
21 could have interpreted the patent as?
22 A. Do you mean ----
23 Q. The way that it was expressed between December 2007, the bits
24 that were deleted .
25 A. Yes, I think that some people might have interpreted this as
2 that there could be reduced side-effects. It is not my
3 interpretation, as I described to you.
4 Q. That is fair enough, if others might differ.

And later at 586:

4 MR. WAUGH: When you said "others", a moment ago, professor, when
5 you say "others", we are not talking about the man on the
6 Clapham omnibus but other respiratory specialists. Correct?
7 A. Yes.

171. *Prof Page* at first said that there was insufficient information for the addressee to be sure of *what* the therapeutic benefit was. On cross-examination[50], he felt that if he *had* to take a position on the matter, for him the unexpected effect was more likely to have to do with the inflammatory aspect of respiratory disease, since a combinative effect on bronchodilation was to be 'expected'. Again in my view, a reasonable response. This extract from Prof Page's cross-examination show his way of thinking[51]:

21 Q. Having read that, can we go back to paragraph 8 where we are
22 talking about unexpectedly beneficial therapeutic effect.
23 What therapeutic effect do you think the skilled addressee
24 would expect from the use of the combination? I am talking
25 here of a combination of compound 1 with either salmeterol or
2 formoterol. What therapeutic effect do you think the
3 skilled addressee would expect from use of this combination in
4 the treatment of respiratory disease?
5 A. Well, if it was unexpected, I wouldn't have considered it to
6 be anything to do with bronchodilation because that was
7 a known beneficial effect of both classes of drug in the
8 combination. To be unexpected in the way I read this, and

[49] T4/583-584 and 586.

[50] T2/219-229
[51] 2/224-225

9 particularly with the emphasis being put on inflammatory
10 and/or obstructive diseases, my immediate reaction was that
11 maybe this particular combination of an anticholinergic with
12 a beta-agonist may have some truly unexpected effect on the
13 inflammatory response, which I think would have been
14 unexpected.

172. Finally, *Dr Costello* also at first said that it was not clear what the 'unexpected effect'was[52]. In cross-examination, he tended to discount 'better bronchodilation' and in answer to a question from the Court, said this [T3/414]:

> A Well, just to go back to what I said a moment ago,a therapeutic effect can be either in terms of its mode of action -- it can have unexpected actions -- or some unexpected outcome in terms of the patient's symptoms. Either way, the way this is phrased would say to me that there is something quite unusual in this combination that is going to give you a beneficial effect, either in terms of mode of action or in terms of the patient's symptoms by putting these two drugs together.
>
> Q. Now, finally, having read this patent, what is it?
>
> A It is ----
>
> Q. Reading the patent, you have told us that what the expectation is. Now, do we find it in the patent?
>
> A. Well, I have to say my answer to that is I don't. No.

Paragraph of [008]: Conclusion

173. I have reviewed the material set out in Part VI of this judgment for help in trying to reach a view as to how § [0008] would have been understood by the skilled reader at the date of the publication of '270. In my judgment, the addressee would simply be left guessing. This is of course an unsatisfactory conclusion but since the public has a right to know what technical contribution has been made by the patent, this is no place for indulgence. Speculative statements, guesses and unsupported predictions are not good enough. In

[52] Witness statement 6/2/81-89.

my judgment, this finding has a decisive resonance in the resolution of this entire case.

VII Speculative patents and ex post facto *justification.*

174. This topic also relates to the difficulties with para [0008]. Mr Waugh drew my attention to authority on sufficiency of disclosure in relation to 'speculative' or unsupported patents and the effect of after-acquired knowledge aimed at perfecting what would otherwise be a deficiency: see EPC, Art 83. This particularly applies to the relevance (if any) of the experiment which Boehringer chose to perform in this action so as to try to justify the statement in § [0008]

175. The upshot of such authority is this: sufficient justification for the solution to a technical problem must be found in the patent *as filed*. Experiments performed thereafter cannot be relied on at law to make good an initial deficiency of disclosure. It is not even enough that the teaching of the patent is such that it is 'at least plausible' that what was proposed was capable of solving the problem it purports to solve. That said Mr Waugh, is applicable to this case. I agree.

176. The authorities relied on came from both domestic and EPO sources. From the EPO, Mr Waugh relied on *Salk* [T609/02] and *Johns Hopkins* [T1329/04]. Both were cases in the pharmaceutical field in which an element of speculation arose as to whether the claimed substances (a steroid hormone and a polypeptide, respectively) possessed the claimed therapeutic activity.

177. In *Johns Hopkins*, §12 the Board said:

> "The definition of an invention as being a contribution to the art i.e. as solving a technical problem and not merely putting forward one, requires that it is at least plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve."

178. The EPO's approach to after-acquired knowledge is consistent with that taken in the United Kingdom. See for example the statement of Jacob J. (as he then was) in *Richardson-Vicks' Patent* [1995] RPC 568 at 581:

"Whether or not there was synergy demonstrated by experiments conducted after the date of the patent cannot help show obviousness or non-obviousness. Nor can the amended claim be better if only the components of the amended claim (as opposed to the unamended claim) can be shown to demonstrate synergy. The patent does not draw any such distinction and it would be quite wrong for later-acquired knowledge to be used to justify the amended claim

179. In *Glaxo Group Ltd's Patents* (*supra*) Pumfrey J. made the following observations:

Synergy

113. It is sometimes thought that a patent may be saved from a finding of obviousness if a combination otherwise obvious has some unexpected advantage, and, in particular, an advantage caused by an unpredictable cooperation between the elements of the combination. I do not consider that such an approach is in general justified. There is a limited class of cases in which the patentee has identified an advantageous feature possessed by some members only of a class otherwise old or obvious, has described the advantageous effect in his specification and has limited his claim to the members of the class possessing this advantageous feature. Such a claim may be justified on the basis of what is called selection. Unexpected bonus effects not described in the specification cannot form the basis for a valid claim of this kind. I think that the matter is described with complete correctness by Jacob J in *Richardson-Vicks' Patent* [1995] RPC 568 at 581:

[*citing the passage referred to above*]

114. If a synergistic effect is to be relied on, it must be possessed by everything covered by the claim, and it must be described in the specification. No effect is described in the present specification that is not the natural prediction from the properties of the two components of the combination. …

180. In his later decision in *Ranbaxy UK Ltd v Warner-Lambert* [2006] FSR 14 Pumfrey J. noted at para 72.

"[I]n this jurisdiction after-discovered advantages are highly unlikely to be capable of supporting inventiveness, for the reasons given by Jacob J. in *Richardson-Vicks Inc's Patent*"

181. The same approach was adopted and applied by Kitchin J. in *Generics (UK) Ltd v. Lundbeck A/S* [2007] RPC 32. See in particular the following at §§ 232 and 235:

"Likewise, I do not believe it permissible to take into account surprising technical benefits which are not described or foreshadowed in the specification."

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

182. Kitchin J. also stated the following in *Eli Lilly v. Human Genome Sciences* [2008] EWHC 1903 (Pat) at §274:

"The further obviousness case, that the invention provides no technical contribution, is to be determined by considering whether the invention lies in making the products of the claim or rather whether, as in the Johns Hopkins case, it must lie in a disclosure that the DNA products of claim 1 code for useful proteins and, if so, whether the specification does no more than speculate as to what those uses might be. Any deficiency cannot be remedied by evidence coming into existence after the application"

VIII The parties' experiments.

183. Two sets of experiments were conducted, both being performed on beagles which had been anaesthetised and then subjected to laboratory testing[53]. The first experiments were conducted by Boehringer, the second were experiments in reply, using substantially the same beagle model[54]. The burden of proof lies of course on the party proposing the experiment. In the case of Boehringer's experiment, not surprisingly in view of the previous section, I was looking for *clear* proof of an alleged super-additive effect.

184. I must state at the outset, that in my view (even if they were relevant), these experiments proved to be of little more assistance to the Court than the experts' evidence alone. Yet the controversy over their detail (for example, the nature of

[53] The results (together with correspondence relevant thereto) are conveniently collected in Bundle 5.
[54] Boehringer did not agree that these were even substantially the same.I think this criticism is unjustified

the protocols, the need for antecedent dosage studies, the propriety of using beagles as models for human response, the effects of solvent, etc) took more time at trial than any other topic. Indeed, the case seemed to me to be in danger of slipping into a sub-debate about the methodology of clinical testing in general.

185. The principal witnesses on this topic were Professors Zaagsma and Page. In what follows, I am not proposing to go into and try to resolve all this detail to any great extent since it is my view that all the experiments were largely a waste of time. In case I am held to be wrong about this, I shall nevertheless make a number of observations on the experiments and briefly state my conclusions.

Boehringer's experiments [5/A]

186. Boehringer's experiments sought to compare the *bronchoprotective* effects of three compositions with a view to showing that the bronchoprotective effect of the combination of the racemate and formoterol was greater than the calculated sum of the bronchoprotective effects of each of them when administered separately: the so called "*Greater Than Additive Effect".* The three compositions were:

> (1) formoterol
> (2) a racemic mixture of the Almirall Compound ("the Racemate"), and
> (3) a combination of formoterol and the Racemate ("the Combination").

187. The experiments were conducted by means of four studies on six beagles. On each occasion the animals were treated with the vehicle alone or one of the test substances. There was a 'washout' period of two weeks between each study. For each study, the animals were anaesthetised and connected to a device called a pneumotachograph which measured two parameters (differential pressure and respiratory flow) from which airways resistance may be calculated.

188. Each animal was dosed with the test substance by inhalation (time point '0') and was then challenged with injections of acetylcholine (ACh) at specific time points over the following

180 minutes. At each time point, airways resistance was measured immediately before and immediately after the acetylcholine injection. The difference between the two values was characterised as "Resistance" and was used to calculate percentage bronchoprotection **[**5/4/3-6**]**. Baseline airways resistance is taken to be 100% bronchoconstriction.

Preliminary points

189. Almirall take two preliminary points which were I consider, entirely justified. Both count against being able to draw any reliable conclusion from the Boehringer experiments.

190. First, it emerged in Professor Zaagsma's cross-examination that Boehringer had conducted two kinds of hitherto undisclosed antecedent or workup experiments. The first experiments used *two* dose levels of β_2-agonist, a low and a high level. The high level dose did not it seems, show any 'super-additive effect' and so, in the experiment, only the low dose experiment was retained. The 'super-additive effects'

> "were hardly if not as I remember, visible at a 3μg dose and that implies that the phenomenon of potentiation of the bronchoprotection of formoterol by the anticholinergic is clearly seen with a lower dose."[55].

191. In addition, some work had, it seems, been carried out by Boehringer on baseline levels of the airways smooth muscle tone of the beagles in connection with the preparation of the Notice of Experiments. This also had not been disclosed[56].

192. Bristows had asked Powell Gilbert for workup data but were told (16 May 2008) that there was not any: ISC/3/126.

193. The second preliminary point taken by Mr Waugh was that Boehringer did not adopt the experimental approach it had taken in its 'tiotropium' combination patent US № 6,455,524 ('Bozung' of 2002)[57]. This patent was for a combination of an anticholinergic with a β-mimetic for the treatment of respiratory illness. Col 1 lines 40-45 reads as follows:

---

[55] See Prof. Zaagsma's cross-examination at T4/672
[56] See Prof. Zaagsma's cross-examination at T5/784-786
[57] CXX-27. It is dated 9 May 2000.

> ‘ ..it was also very surprisingly discovered that the bronchospasmolytic effects of the anticholinergic which has a long lasting effect and the β-mimetic which has a long-lasting effect, increase in a superadditive manner’

194. For the purposes of that patent, Boehringer had tested low doses (3 μg) and high doses (10 μg) of tiotropium and formoterol alone and had shown that a low dose combination of the two compounds (3 μg + 3 μg) exceeded the sum of the individual effects at that dose and each of the 10 μg doses. This is just the sort of approach which Professor Page said was necessary in order to show a genuine super-additive effect. Professor Zaagsma said of Professor Page that *“in a way he is right and in a way he is wrong”* (5/714$_{15}$), although his reason or reasons for the qualification are, I find, unclear (see 5/714$_{16}$-720$_{18}$). In any event, Professor Zaagsma clearly endorsed the approach taken by Boehringer on Bozung: **(**5/705$_{19}$- 708$_{25}$**)**.

Conclusion

195. In the light of these criticisms and of my view that the experiments were unnecessary anyway since the S-enantiomer was substantially inactive, I am not proposing to overburden this judgment with lengthy discussion of the critical views of the experts on the technical side of these experiments and whether they do demonstrate any super-additive effect.

196. I have nevertheless re-examined this evidence and do not find that Boehringer have clearly discharged the burden of proving the existence of any ‘super additive effect’ resulting from the combinations claimed.

Almirall’s experiments in reply [5/C]

197. The origin of the Almirall experiment in reply lies I think in the basis of the dose of racemate used in Boehringer’s experiment. In response to a request for further information on this, Powell Gilbert told Bristows that[58] :

[58] Letter 20/6/08 in 5/6/1

> 'Publicly available information indicates that LAS 34273[59]…has been tested in COPD patients at clinical inhaled doses of 100-300µg resulting in a mean numerical dose of 200µg.It is assumed that this dose would need to be doubled if the racemate…is used i.e. 400µg.'

198. As a result, Almirall guessed that Boehringer were implicitly admitting that the S-enantiomer was inactive[60]. As a result of a consent order, Boehringer replied as follows:

> 'The doubling of the dosage recognises that the R-enantiomer is likely to be more active than S-enantiomer, but in no way suggests that the S-enantiomer is inactive. The doubling of the dose simply provides a 'ballpark' dosage for the racemate.'

199. In the light of this reply, Almirall decided that it had nevertheless to prove by experiment that 'the S-enantiomer [chemical name set out] is substantially devoid of bronchoprotective activity' [5/C/16/2] and performed an experiment to show it.

200. 'Devoid of bronchoprotective activity' does not, I consider, mean that a substance shows no relevant activity whatsoever; the assessment of any therapeutic activity falls to be made on an informed, practical basis, a relative quality being under scrutiny.

201. In Professor Zaagsma's oral evidence it became apparent that both he and Boehringer were well aware, and had been aware for a number of years, that the R-enantiomer was the active enantiomer and that the S-enantiomer was therefore the 'inactive' enantiomer. Although he *knew* that the R-enantiomer was the active enantiomer, he did not question why the experiments were to be undertaken with the racemate ($4/655_{13}$-657_{10}). He said:

> Q But you had seen that Boehringer had done the experiment on the active enantiomer, the R-enantiomer, yes? Did you ask them why they were deciding to do this experiment on the racemate?
>
> A. No, I didn't comment on that. The suggestion was made to use the racemate and that was fine for me, because in the

[59] The Almirall code name for the aclidinium mentioned in the two Schelfhout posters. This was (as we now know) the R-enantiomer, though this fact is not mentioned in information given in the posters.
[60] Prof Page could think of no other reason for doing so:[6/1/129].

anticholinergic field racemates and enantiomers can have a difference in potency.

202. Moreover, Boehringer's experiment was, as I have said, predicated upon the assumption that the S-enantiomer was substantially inactive. Under cross-examination, Professor Zaagsma accepted this to be correct: ($5/773_{25}$-774_{19}):

> Q. Volume 5, tab 16. The third point to be proved by this experiment was that in this model -- you see paragraph 3 -- the S-enantiomer is substantially devoid of the bronchoprotective activity?
> THE JUDGE: Substantially.
> MR. WAUGH: Substantially devoid of bronchoprotective activity. You don't disagree with that, as I understand it.
> A. You observe it.
> Q. I am correct, yes?
> A. You described it yourself a moment ago.
> Q. I think the answer is yes then.
> THE JUDGE: So you agree that the result of the experiment ----
> A. That in this model the S-enantiomer is substantially devoid of bronchoprotective activity, that of course means in the concentration present in the racemate. What was not tested was in putative.

203. I consider therefore that Mr Waugh was right in submitting that the antecedent admission sought by Almirall could and should have been provided by Boehringer so as to avoid the need for Almirall to conduct any reply experiments.

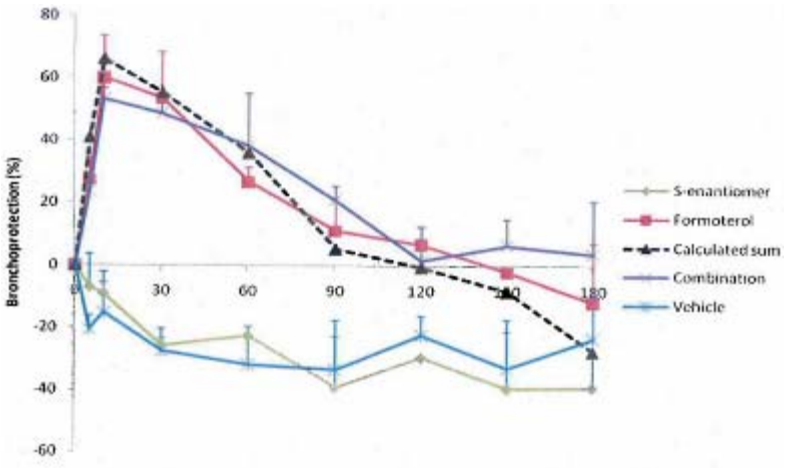
204. Notwithstanding this, Boehringer's case was that though the S-enantiomer may be substantially inactive *at the dose used in the Boehringer and Almirall experiments*, it is likely to display activity at higher doses (Zaagsma I 7/2/44-45). If it is contended that the S-enantiomer is nevertheless active at some <u>other</u> dose, the evidential burden of proving the same remains firmly with Boehringer – and one would have thought that it would be in Boehringer's interest to prove it. But in spite of having all the relevant information in their possession, they did not do so.

The Almirall results

205. The Almirall experiment involved measuring the bronchoprotective effect of test compounds in beagles using substantially the same model as Boehringer. Animals were dosed with the test substance by inhalation and challenged

with acetylcholine at specific time points. Airways resistance was measured on each occasion.

206. Almirall conducted two experiments. The first involved testing the same compounds as Boehringer i.e. the Racemate alone, formoterol alone and then the combination. The results are set out in graphical form at Page I [6/1/142**]**. The data for the second experiment using the S-enantiomer provide the following graphical result (Page I **[**6/1/143**]**):



207. Within the margins of error, the curve for the S-enantiomer (green line in the original) tracks the vehicle (blue line in the original). The bronchoprotective effect of the Combination follows the profile of formoterol alone (see Zaagsma 5/772$_{9-19}$). The S-enantiomer is plainly devoid of bronchoprotective activity.

208. Importantly given the criticisms of the experiment, the data in Figure 3 (racemate plus formoterol) **[**5/16/9] serve as a positive control for the experiment with the S-enantiomer **[**5/16/10].

209. For these reasons, I consider that Almirall have shown by experiment – for what it was worth - that the S-enantiomer is 'substantially devoid' of therapeutic activity in the treatment of respiratory disease and thus that the alleged 'super- additive effect' of '270 cannot be supported across claim 1.

IX Validity of '270.

Lack of Novelty: The law: PA '77 s 2(1)

210. There was no difference between the parties as to the law to be applied to this issue. For the record however I should state my general approach. A claim will be anticipated if the prior art is enabling, that is, if it gives the skilled reader clear and unambiguous directions to do something which, if done after the priority date, would infringe: see per Sachs LJ in *General Tire v Firestone Tyre* [1975] RPC 457 at 485, endorsed by the House of Lords in *Synthon v SmithKline Beecham* [2006] RPC 10 at paragraphs 21-25.

211. Both parties also invited me to consider authority on novelty as it applies to disclosures of a generic chemical class as discussed by Floyd J. in *Dr Reddy's Laboratories v Eli Lilly* [2008] EWHC 2345. The learned judge reviewed EPO case law in respect of anticipation by general disclosures[61]: [79]-[90]. For a prior art document to deprive a compound of novelty, that compound has to be disclosed in the prior art, he said, in an "*individualised form*" [91]. Accordingly, a general formula with multiple substituents chosen from lists of some length will not normally take away the novelty of a subsequent claim to an individual compound [78].

212. It is sometimes said that if the prior art discloses a number of alternative options there is no clear and unambiguous disclosure. This is wrong: see per Pumfrey J in *Ranbaxy v Warner-Lambert* [2006] FSR 14 at paragraph 52 (and in the Court of Appeal). In that case, the claim was for the hemi-calcium salt of one of 4 potential isomers (the R*R* isomer). The prior art disclosed all four isomers (R*S*), (S*R*), (R*R*) and (S*S*), one of which, the R*R* was said to be preferred. In addition the prior art said (see para 48 of the judgment)

> 'In the ring-opened dihydroxy acid form, compounds of the present invention react to form salts with pharmaceutically acceptable metal and amine cations formed from organic and inorganic bases. The term "pharmaceutically acceptable metal salt" contemplates salts formed

[61] See for example T12/81 *Bayer Diastereomers*

with the sodium, potassium, calcium, magnesium, aluminium, iron and zinc ions.'

213. Accordingly Pumfrey J held that:

> 49. It follows that the material claimed in claim 1 is an expressly specified salt (calcium) of the preferred isomer of one of the three materials explicitly specified. If one is in any doubt, it is easy to compare the final structural formula on page 12 of '281 against formula XII on page 40 of '598. They are identical, save that in '281 the calcium salt, and in '598 the acid, are shown. In fact, the synthetic route described in '598 actually produces a racemate. But this time, the precise enantiomer (4R,6R) is specified. This notation means the same thing as the [R-(R*,R*]… used in respect of the acid in claim 1 of '281. The evidence (which I have already discussed) was that resolution to obtain the enantiomers was common general knowledge. It is no answer to an allegation of anticipation that the specification gives clear and unmistakable directions to use the common general knowledge to produce a specific material.
>
> 50. I conclude that this is a clear case of anticipation of claim 1 of '281. '598 gives specific directions to make the three preferred enantiomers, one of which falls within the claim.

214. This approach was endorsed by the Court of Appeal: [2007] RPC 4 , at paras 36 – 40

> 40 To my mind this, in context, clearly teaches by way of explicit disclosure that one of the things you can make is the single enantiomer of the acid and it is that acid which can be used to make the calcium salt. In truth that way of carrying out the teaching of the earlier patent would necessarily infringe the later claim. So that claim is invalid as lacking novelty. I reject Mr Thorley's submission that one is here straying into the impermissible territory of obviousness. Alighting on atorvastatin calcium is merely picking one of the class of compounds disclosed by '598. If the claim were valid it would cover one of the alternatives *explicitly taught* by the citation. This is not a case of any adaptation of the prior art. [Emphasis added]

Application № WO 01/04118 (‘Forner’)

215. This early Almirall application is the only citation under this head of objection. Forner is directed to ‘therapeutically useful’ quinuclidine derivatives, methods for their preparation and pharmaceutical compositions containing them.

> 'The novel structures according to the invention are antimuscarinic agents with a potent and long-lasting effect. In particular these compounds show high affinity for muscarinic M3 receptors (Hm3)'.

In other words, they are anticholinergics, later described as M3 antagonists (see also p1 line 26).

216. The reader is told that these compounds have three clinical (or therapeutic) applications: First, for treating respiratory diseases (such as COPD and asthma), secondly for urological disorders and thirdly for gastrointestinal disorders. The narrative continues (p1, line19):

> 'The compounds claimed are also useful for the treatment of the respiratory diseases detailed above in association with β2-agonists, steroids, antiallergic drugs and PDE IV inhibitors.'

However, that appears to be the only teaching in Forner of making a combination with a β_2-agonist.

217. The general formula ('formula 1') of the new compounds is set out on page 3 of Forner. The application runs to some 81 pages of A4 paper and contains 159 preparative examples of chemical compounds; these are all examples of 'individualised' compounds and by this means the patentability of any of these compounds is prevented. Aclidinium is one such compound: see p 8, lines 13- 14 (where it is named) and also example 44 (which describes its preparation)[62]. It is also the subject of claim 20. Under the '*Pharmacological Action'* section of Forner, aclidinium is also one of five compounds tested which has a favourable IC50 value of less than 5nM[63]. The skilled reader would obviously recognise aclidinium as an example of the invention of Forner which shows real promise as an M3 receptor antagonist, having properties similar to the reference compound, ipratropium.

218. There are the usual long lists of substituents to formula 1, isomers, salts, tests, possible presentations and so forth and like many patents in the pharmaceutical field, Forner is well-nigh unreadable as a narrative piece of English.

[62] Example 85 is the S-enantiomer of formula 1 of the '270 patent.
[63] Page 24 line 26-page26 line 25

219. The specific combination of formula 1 and β-agonists claimed in the '270 Patent is not clearly and unambiguously disclosed in Forner. To arrive at something falling within the claims, the skilled team must make a cascading set of choices from amongst the lists of compounds in Forner in order to arrive at the invention in the claims.

220. Neither examples 44 or 85 are clear and unambiguous disclosures of the combination with the betamimetics (2) required by the claims of '270. First, the skilled man has to make a number of initial choices. He must decide what disease he is going to treat. There are quite a few. Secondly he must decide which antimuscarinic agent or agents to use to treat this disease. Forner gives no particular directions in this regard. Thirdly he must decide to use the selected compounds in combination rather than on their own – the latter also being a variant.

221. If he gets this far and chooses to go down the route of combination, there is no direct teaching to use any particular compound in combination with any β-agonist. Forner teaches a list of 4 classes of compounds which could be used (β_2-agonists, steroids, antiallergic drugs or phosphodiesterase IV inhibitors) together with any of the compounds of the wide class taught. The choice of which to use will depend on the treatment under consideration – and, as I have shown, on the patient. This will depend on the disease he wishes to treat. Depending on the disease on which one is focussed, different choices will be made (see Page $T2/246_{4\text{-}11}$).

222. In my judgment, claim 1 of '270 is not anticipated. The addressee of Forner is left with a bewildering list of choices. These are not concrete 'options' within the meaning of the *Ranbaxy* case. Forner does not amount to clear and unmistakeable directions to make the combination of claim 1 of the 270 Patent. No 'individualised combination' within the claims of '270 has been disclosed.

223. *Claim 6.* In respect of the choice of β-agonists, the choice in claim 1 of '270 is a fairly comprehensive list but claim 6 claims a more restricted list of β_2-agonists. There is no teaching in Forner to select this list of particular compounds

from the general teaching to use β_2-agonists generally. Claim 6 is therefore also not anticipated.

224. Selection. In the event that I came to a contrary conclusion on novelty in the light of Forner, I was addressed by the parties on the question of whether Boehringer's '270 nonetheless represented a valid selection from the prior art. Though it is therefore not necessary for me to make findings on the issue, I shall do so in case the matter goes further. For this purpose, I was of course directed to the classic judgment of Maugham J in *I.G. Farbenindustrie AG's* Patents (1930) 47 RPC 289. In that case, the patentee asserted that the claimed azo dyestuffs had specific advantages over the much broader class of compounds disclosed in the prior art. Maugham J. identified three general conditions which had to be satisfied in order to support a valid selection patent (see pages 322-323):

(1) The patent must be based on some substantial advantage (or avoidance of a disadvantage) to be secured by the use of the selected members.

(2) The whole of the selected members must possess the advantage in question.

(3) The selection must be in respect of a quality which can fairly be said to be peculiar to the selected group.

225. In the light of my findings thus far, I am of the view that none of these conditions is satisfied by '270.

Obviousness

Obviousness: The Law [PA '77, s.3]

226. There was no issue between the parties as to the applicable law. The correct structured approach to obviousness is that set out in *Windsurfing v Tabur Marine* as 'arranged' by Jacob LJ in *Pozzoli v BDMO [2007] EWCA Civ 588 at [23]*, namely:

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

(b) Identify the relevant common general knowledge of that person
(c) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
(d) 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;
(e) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?"

227. I have already addressed enquiries (a)-(d) in various parts of this judgment.

228. In addition, the parties drew my attention to a more recent authority on obviousness. In *H. Lundbeck A/S v Generics (UK) Limited* [2008] EWCA Civ 311; [2008] RPC 19 at [24] Lord Hoffmann (sitting as a member of the Court of Appeal) approved without qualification a statement of principle by Floyd J in *Dr Reddy* (supra) which reads as follows:

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

229. Almirall also drew attention to what has sometimes been called 'the golden bonus' in the obviousness enquiry. This is illustrated by the following statement of principle in the case of *Hoechst/Enantiomers T296/87* where the Technical Board of Appeal stated at § 8.4.1

> "… Under established Board case law, an enhanced effect cannot be adduced as evidence of inventive step if it emerges from obvious tests. Since, in the present case, tests with the enantiomers were obvious in view of the task at hand, discovery of the claimed effect of the D-enantiomers compared with corresponding racemates does not involve an inventive step.

….

> 8.4.4 The conclusion reached above is not affected even by the circumstance that the D-enantiomers in question exhibit not merely double but approximately four times the effectiveness of the relevant racemates - a fact adduced by the appellants and accepted by the Board. After all, if tests with enantiomers suggested themselves to a skilled person as an obvious way of arriving at a solution offering increased activity, the extent of that increase could not as a rule be taken as an indication that the tests - obvious as they were - involved

This approach is entirely consistent with the original 'golden bonus' case in this jurisdiction, *Hallen v Brabantia* [1991] RPC 195. If it is obvious to make a combination for one reason (in that case the combination of the Teflon coating on a corkscrew) it does not cease to be obvious if it is found that there is a surprising advantage in doing so (page 216, lines 11-25).

230. Before considering the pleaded prior art under this head of objection there are a few preliminary matters (and some evidence of Professor Barnes) which may usefully be re-stated in mind in the light of my earlier findings.

> (a) No '*unexpectedly beneficial therapeutic effect'* has been identified in '270 and none has been proved by experiment. The expert's views on the meaning of the phrase, though all plausible, are not consistent. The skilled reader is thus left with a problem.
>
> (b) By the 2003/04 era, the classic trinity of drugs for treating respiratory disorders were anticholinergics, β-agonists and steroids,
>
> (c) The use of combinations of β-agonists with the other drugs for the treatment of respiratory disorders was *very well known* by the priority date.
>
> (d) There were a number of reasons for combining such drugs ('additive effect', the same effect but at lower proportionate dosages, avoiding side effects, better patient compliance etc). These reasons were also well known at the time

(e) ‘270 does not differentiate between asthma and COPD treatments – which is not surprising. There is in practice a degree of overlap in the presentation of symptoms by patients and in their treatment.

(f) The skilled reader ‘team’ includes a respiratory pharmacologist.

231. The evidence of Professor Barnes to which I referred is I consider, of general importance under the obviousness enquiry. This evidence was given in connection with the statement in §[0008] of ‘270 but in my view, has broad application to the validity of both ‘270 and ‘819. In his evidence in chief, Professor Barnes said this[64]:

> 79. The skilled person would be aware that therapeutic combinations previously used in this field had been useful but had never been shown to achieve anything more than an additive (and, in many cases, less than additive) effect. Consequently, the skilled person would consider that the unexpected part of the beneficial therapeutic effect referred to in paragraph [0008] was that administration of the anticholinergic and beta-agonist combination disclosed in the Patent resulted in a more than additive bronchodilator effect.

232. In other words the skilled person would *know* that at least an additive effect is *to be expected* from the combination. This was put in XX at $4/577_{22} – 578_{20.}$

> 22 MR. WAUGH: What was not your first reaction, professor, if you
> 23 look at paragraph 79, this reads on to say: "The skilled
> 24 person would be aware that the therapeutic combinations
> 25 previously used had been useful but had never been shown to
> 2 achieve anything more than an additive (and, in many cases,
> 3 less than additive) effect."
> 4 Just pausing there a moment, you are saying it would
> 5 have come as no surprise to the skilled reader that these
> 6 combinations would provide an additive effect in the sense
> 7 that two together gives more than either alone.
> 8 A. Yes, and by the example of Combivent that we have already
> 9 discussed.
> 10 Q. So that would be entirely predictable.
> 11 A. Yes.
> 12 Q. And on the basis of even though you have no data on this
> 13 particular drug, that is predicated on the basis that because
> 14 it is a long-acting cholinergic and because you are putting it
> 15 together with a beta-agonist, it is entirely predictable, to

[64] 7/1/79

16 be expected indeed, that you would get some degree of additive
17 effect.
18 A. You may expect some additive effect, allowing for how much
19 room for improvement there was, as we have repeatedly
20 discussed.

233. And later at $583_{2\text{-}17}$

2 Q. Subsequent to March, subsequent to that meeting, professor,
3 did you discuss with them the extent to which reduced cardiac
4 side-effects might be embraced within the term "the unexpected
5 beneficial therapeutic effect"?
6 A. I think it was subsequently discussed at some point, yes, but
7 my view of that paragraph 8 was that this was unlikely to be
8 an unexpected benefit because it might be something you would
9 expect because we already have the examples of reduced
10 side-effects in Combivent, because I was trying to make an
11 interpretation based on the fact that it was a benefit and
12 something that was unexpected.
13 Q. So, again, I take it from your last answer that the skilled
14 reader as of 2003 would have expected reduced side-effects to
15 be something that you get with a combination.
16 A. Well, I would have thought so, based on the precedent of
17 Combivent.

234. There can therefore be no doubt that to the skilled addressee, use of the claimed combination is at least likely to yield *an additional bronchodilator effect with perhaps, reduced side effects*. These were to be expected. It is not an answer to say 'but a more than additive effect is in fact found', even it were true and could be shown by experiments carried out 5 years after the event. It is also worth keeping in mind the answer given by Prof Barnes in the light of his paper in Lancet at C-XX tab 11 - see $4/551_{2\text{-}15}$

2 Q. If you go to page tab 11 please, "Prospects for new drugs".
3 Perhaps go to 986, "New bronchodilators". This is a seminar
4 in thelancet.com, "Prospects for new drugs". I don't think
5 the Lancet requires -- this is a sort of online Lancet, is it,
6 professor?
7 A. No, this was a published paper in the Lancet.
8 Q. And if you look at "New bronchodilators" on page 986 ----
9 THE JUDGE: Now, this is 2004.
10 MR. WAUGH: This is 2004. So we have gone from 2001, 2003 and now
11 we are into 2004. "New bronchodilators", last sentence,
12 "Tiotropium is likely to have additive effects when combined
13 with long-acting B2-agonists, and once-daily combination
14 bronchodilator inhalers are a likely development".
15 A. Yes, a likely development.
16 Q. Professor, assume another well tolerated long-acting
17 anticholinergic comes along which is said to allow for once
18 daily dosing, it is said to have a favourable safety profile,
19 because it is an anticholinergic it has a different mechanism
20 of action, then certainly the additive effects that you talk

21 of with tiotropium would provide a logical rationale for
22 combining that new anticholinergic with the long-acting
23 beta-agonist.
24 A. Well, it would be something to look into.

WO 01/04118 ('Forner')

235. I have extracted what I believe to be the relevant passages of Forner in the Lack of Novelty section. It must be borne in mind of course that the obviousness enquiry is not the same as that undertaken when lack of novelty is in issue.

236. The following salient features of Forner would in my view at once strike the skilled reader who had an interest in new treatments for respiratory disease:

> (i) the compounds are potent and long lasting antimuscarinic agents with high affinity to M_3 receptors (page 1, lines 4-10);
>
> (ii) the compounds are suitable for treating a variety of respiratory and non-respiratory diseases including COPD, chronic bronchitis, bronchial hyper-reactivity, asthma and rhinitis (see page 1 lines 11-18);
>
> (iii) the compounds are useful for the treatment of these diseases in association with β_2 agonists (see page 1 lines 19-21);
>
> (iv) examples are provided which demonstrate the excellent pharmacological activities of the compounds described (see page 24, from line 17);
>
> (v) data are provided from an M_3 receptor binding assay which uses atropine and ipratropium as reference compounds. A handful of compounds show comparable activity, including compound 44. Example 44 is aclidinium.
>
> (vi) Although three clinical applications are proposed in general terms, the thrust of the specification is plainly directed to the first viz. the treatment of respiratory disorders[65]

237. The opinion of Professor Page[66] and Dr Costello[67] is that the claimed combination is clearly obvious for the reasons

[65] For example, three of the five pharmaceutical composition examples are for inhalants.
[66] Page I [6/1/160–162]

they give. Furthermore, Prof Page in his second report responded to the evidence of Prof Zaagsma thus:

> 40. ….A handful of these compounds, including the R-enantiomer, have an IC50 value of less than 5nM. The respiratory pharmacologist would naturally be most interested in these compounds, since their binding data compare most favourably with that for the known and widely used anticholinergic ipratropium bromide.
>
> 41. I do not agree with the suggestion in paragraph 51 of Professor Zaagsma's report that a further step would be required after the respiratory pharmacologist takes either Example 44 or 85 and follows the direction on page 1, lines 19 to 21 to use either compound for the treatment of respiratory disease in association with β2-agonists. It was absolutely routine to use a combination of an anticholinergic and a β2-agonist in the treatment of asthma or COPD and, in any case, Forner expressly suggests this at page 1, lines 19 to 21, referring to the respiratory diseases listed on page 1, lines 11 to 14.

238. In his cross-examination, Professor Zaagsma accepted that he had no reason to doubt the statement in Forner that the compounds claimed are also useful for the treatment of the respiratory diseases detailed above in association with β_2-agonists. At $5/827_{20} – 828_8$ he gave the following answer:

> Q. You certainly have got no reason to doubt the statement here, that the compounds claimed are also useful for the treatment of the respiratory diseases detailed above in association with B2-agonists. You have no reason to dispute the plausibility of that statement.
> A. No, I have no reason to dispute it.
> Q. And you would not in 2003. Please assume all my questions are asked as of 2003.
> A. At 2003 Combivent and Duovent and (unclear), etc. were known combinations effective in particular in the more severe diseased state. So it is logical to have an idea of the combination of aclidinium plus a B2-agonist.

239. After it had been put to the Professor that the most preferred compounds would be the best place to start, the following exchange occurred.

> MR. WAUGH: Assume that selection has been made, professor, you have got information in this document that enables you to both make those compounds and to test whether you have made the right compound from the data in example 44, would it not be the best place to start, professor, with that handful of compounds, on the basis of the data that the patent gives you?
> It may not be a single place, but that handful of compounds would be a group of compounds well worth making in the expectation that it will have the properties that this document tells you.

[67] Costello I [6/2/98/99]

> A. You could take these compounds to start with, and as soon as you see a negative result about bioavailability, for instance, common in that selection, you could have to take another selection, etc.
> Q. I accept that, what may prove to be toxic in 10 years time, but in terms of a place to start, that would be the best place to start, would it not?
> A. Correct. It is a selection of assuming that these 155 compounds have been prepared. You have to trust, that is my point, that this table reflects the most potent compounds within the package of 100, etc.
> THE JUDGE: Let's assume it does.
> MR. WAUGH: On that basis, professor, that would be a place to start in practical terms?
> A. It would, yes.

240. Forner is a document which makes it clear that the claimed anticholinergic compounds are suitable for use alone or in association with β-agonists for treating 'respiratory diseases'. As a matter of common general knowledge, the skilled person would have known about combining anticholinergics and β-agonists, both from the literature and from products actually on the market. It would indeed have been therefore logical to follow the express teaching of Forner and try using the new compounds in combination in the *strong* expectation of getting one or more of the benefits known to come from doing so[68]. The skilled reader would read that a handful of compounds are proposed which are most preferred for having a beneficial respiratory activity and would be likely first to focus on those compounds. There is in my view no invention in taking forward any of Forner's most promising anticholinergic candidates (eg that of Example 44) and working with it in combination, as was generally known.

241. The claims of '270 in my view, are obvious in the light of Forner.

Schelfhout I and II

242. I have already recounted the circumstances of the separate publication of these two 'posters' on two successive days at a Thoracic Conference in Seattle. An initial question arises as to whether it is legitimate for present purposes to combine (or more emotively, to 'mosaic') them. Dr Ramon Bosser of Almirall recalled that Schelfhout II generated considerable interest at the conference. The main difference between the

[68] Cf. *Conor Meisystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49 at [42]

two posters is that Schelfhout II provides bronchodilatory and bronchoprotective double blind data from 16 male COPD patients whereas Schelfhout I presents the data on healthy males. In both cases the compound called LAS 34273 was used, the full chemical name of this substance being set out in Schelfhout I only: '*LAS 34273 is a new selective M_3 antimuscarinic drug from Almirall SA'* –and the chemical name is set out as its bromide salt. It was agreed that this would alert the skilled reader to the fact that the compound was chiral but neither of the posters reveals what enantiomer Schelfhout *et al*. were working on[69].

243. In my view, for present purposes it is legitimate to combine the reading of the two posters – though in the end, I doubt whether it makes a great deal of difference. One can hardly suppose that a mass exodus of attendees would take place after day one, only to be replaced on day two by entirely fresh faces. Moreover, there is a reference in Schelfhout I to the study in COPD patients and a reference in Schelfhout II to the study in healthy volunteers. The posters were obviously complementary and intended to be read together.

244. The purpose of Schelfhout I is to present the results of a small clinical study of the bronchodilatory and broncho protective effects of 'a new long acting anticholinergic antagonist' LAS 34273 inhaled by healthy volunteers. No other 'concomitant medications' were allowed[70]. The two graphs show that LAS 34273 was a good bronchodilator (top graph) and a good bronchoprotector (bottom graph). In addition, it is well tolerated. This is restated in the 'Conclusions':

> 'LAS 34273 has long-acting anticholinergic activity at doses from 300 mcg'.

245. However, Schelfhout I and II contain no direction to combine the new long-acting anticholinergics with anything else.

246. Almirall's argument is predictable. When notice of a new long-acting anticholinergic like LAS 34273 is given together

[69] We now know it to have been the R-enantiomer of formula 1 in '270, in fact.
[70] Unlike Schelfhout II where no *changes* to concomitant medications were allowed.,

with impressive clinical performance data to go with it, albeit in relation only to healthy people and COPD volunteers, the skilled addressee at once takes interest. Here, he would say, is a potentially a new treatment for *any* respiratory disease – whether asthma or COPD. He would think in terms both of its use alone (as described for COPD) or use in combination with the well-known steroids or β-agonists with which he has long been familiar – the combination being expected to engender some well known spin-off benefits. The use of such combinations is therefore obvious. That was the gist of the evidence of Professor Page[71] and Dr Costello[72].

247. In the light of my findings as to the common general knowledge, I would expect cogent evidence from Boehringer to cast doubt on (or displace) the stance taken by Almirall, namely that this new anticholinergic (*un*like the known ones) was for some reason *un*suitable for use even to try in combination. Boehringer via Professor Barnes, proposed three main answers to show why the addressee would not think (let alone go) further than the strict teaching of Schelfhout, that is to use the LAS 34273 on its own and moreover *in the treatment of COPD only*. Note the latter qualification since none of this evidence was said to be applicable to the treatment of asthma patients[73]. In the light of the fact that claim 1 of '270 is not limited to any particular form or forms of respiratory disease, I therefore found this evidence of be of marginal significance.

248. First, it was said that since cholinergic tone was the *only* reversible component in COPD patients (whereby airflow could be increased), there would be no point in combining the Almirall Compound with anything else; no further benefit was to be expected. This was the Professor's view when he wrote his report but on being shown in cross-examination a number of articles written (or co-written) by him at or before the priority date, he readily agreed that at that time he believed that it was a *major but not the only* reversible component in COPD: see T3/494- 496.

[71] 6/1/169-170
[72] 6/2/100
[73] T3/475

249. The second argument, the so-called 'optimal dose' argument, follows from the first. Because the dose in Schelfhout appeared to be maximal, there would be no additional benefit to using the LAS 34273 in combination – given that there was no other bronchodilatory mechanism at work. First, I have found no evidence which might cause the skilled addressee to think that LAS 34273 in this respect was in any material way acting in a different way (or was otherwise materially different to) other anticholinergics in use at the time. Some of these found their way into combination with β-agonists even though the doses in commercially available presentations were in some cases maximal e.g. ipratropium[74]. Professor Barnes was also cross-examined on papers which showed the benefit of combining ipratropium with a β-agonist at doses which were maximal: T4/636.

250. Professor Barnes himself recommended using anticholinergic bronchodilators "*first, once at maximum dose then add β-agonist bronchodilators."* [75] And as Mr Waugh showed during cross-examination, in none of Professor Barnes' papers dating from around this time was there any suggestion that just because an anticholinergic was being used at maximum dose, that fact at once disqualified it from being considered for use in combination. There was extensive cross-examination of the experts on this point which, I felt, got bogged down in inconclusive detail. There was even sometimes disagreement over what was an optimal dose.

251. What emerges from this is not very clear. But I have seen nothing in either the evidence or still less, the contemporaneous papers to which I have referred to suggest that in the treatment of respiratory disease, the use of maximal dosing of either component alone acts a brake or disincentive to any further investigation of the potential benefit of a combination –or that combinations only arise in practice where the dosing is sub-optimal. Again, it is the clinician's pragmatic and flexible approach to treatment which matters: see §147 I think Professor Barnes put the matter succinctly in a passage of re-examination[76], thus:

[74] T3/428-429
[75] Barnes et al., Atlas (2004) CXX/1/210 fn1
[76] On a paper referred to as 'The Combivent Study' (1994): 6A/12/8

> "An alternative hypothesis is that a larger dose of either ipratropium or albuterol could have produced a similar increase in airflow and volumes; however, this hypothesis has not been tested."
>
> Would you tell my Lord whether you think it would have been useful to have tested that hypothesis?
>
> A. Well, I agree that that would be an important thing to look at. I think it goes back to an earlier discussion where I said that a clinician would have a choice to increase a drug when the patient had not improved, optimally or to add another drug; so there is a choice. I think that this statement is saying that that needs to be tested.

252. Finally, it is said that the 300mcg dose of LAS 34273 achieves maximal reversal of cholinergic tone and since the drug is well tolerated, there is therefore no incentive to reduce the dose. The riposte from Almirall's experts was this –and it seems to be true: so too are ipratropium and tiotropium well tolerated and yet there were regularly 'cut' with β-agonists at the priority date to achieve added benefit. See the cross-examination of Professor Barnes: T4/605-606.

253. In the circumstances, on this issue, I have generally given more weight to the contemporaneous documentary evidence which has been reviewed in the Background section above. My conclusion on it is that '270 is also obvious in the light of Schelfhout I and II whether taken alone or (as I think they should be) together.

Insufficiency PA '77, s 72(1)(c)

254. This ground of objection was pleaded thus [2/3/2]:

> In so far as the defendant contends that the claimed invention is novel and not obvious on the grounds that the combination of one or more salts of 'formula 1'….. with one or more betamimetics gives rise to an unexpectedly beneficial therapeutic effect, the patent does not disclose such an invention clearly and completely still less does it do so across the full width of the claims. The specification does not teach and the skilled person would not know the nature of such beneficial therapeutic effect nor how to ascertain whether any claimed combination had the effect in question.

255. This attack is appears to be made both on the basis of 'classic' insufficiency (where the directions in the patent are inadequate and do not enable the addressee to perform the invention without undue effort) and also on the basis of '*Biogen* insufficiency', so-called after the House of Lords case of *Biogen Inc v Medeva plc* [1997] RPC 1 at 53. The latter type of insufficiency arises when the patent describes an invention but its claims are of broader scope than its description. Nevertheless, in either case, the overriding purpose behind the section (and also of PA '77, s. 14(3) and (5)) is to ensure that the patentee provides an '*enabling disclosure'*. The patentee is not permitted protection wider than his contribution to the art. I once ventured to put the requirement in rather more colloquial terms by saying that a patent is invalid if it fails 'to deliver the goods'[77].

256. Having thus introduced the objection I can dispose of it as briefly. My views on the relevant parts of §[0008] have been recorded on a number of occasions. I have held that there are a number of plausible readings of this key paragraph. I have also found that Boehringer's experiments do not prove what they set out to do and that Almirall's experiments show that the S-enantiomer (which of course falls within claim 1) is substantially devoid of *any* relevant therapeutic benefit. I have also rejected the riposte of Boehringer made through Professor Zaagsma, that at some higher dosage (unspecified), the S-enantiomer *might well* become a more promising therapeutic agent in the treatment of respiratory disease. In the context of insufficiency, I would observe that the latter is surely a grave-digging exercise on the part of Boehringer.

257. There is thus uncertainty as to the meaning of the key passage of the key passage of '270 and in addition, a claim therein which (whatever be the meaning of the key passage) cannot be supported across its breadth. I therefore find that '270 is additionally invalid on the ground of insufficiency.

X Amendment of '270

258. In the light of my conclusions as to the validity of '270, I have no need to consider this aspect of the case. But again, as

[77] *Wesley Jensen v Coopervision* [2003] RPC 20

the matter may however go further, I shall therefore state my conclusions on amendment briefly.

259. Boehringer have unconditionally applied to amend '270 in the manner shown at [1/2]. The amendment file is [3] and their Reasons are at [3/2]. The reason for amendment is to limit the scope of the claims.

260. The amendment restricts the monopoly by limiting the β-agonists to four only, two of which were well known at the time, being formoterol and salmeterol. The other two are identified by their long chemical names. All four are long-acting and are disclosed in '270 as being particularly preferred (page 3 lines 52-54). This was also in the application as filed (p4 lines 22-25). The Comptroller has raised no objection to the proposal to amend and, so says Mr Thorley, that should be the end of the matter. Amendment should be allowed.

261. The proposal to amend is opposed by Almirall on the ground that it adds matter: see EPC, Art 123(2). Mr Thorley (rightly I think) recognised a squeeze in this move. If Boehringer now wish to improve their position to say that the benefit of the notorious §[0008] of '270 is confined to the use of those four β-agonists only, matter would be added. I agree that that would indeed amount to objectionable added matter; the selection is nowhere suggested to have some special advantage. Alternatively, if it is not so, the selection is arbitrary and the claims are still obvious. Either way, amendment should not be allowed, said Mr Waugh.

262. But the first part of the squeeze is not Boehringer's case. Mr Thorley did not contend for such a construction; Boehringer simply desired to limit the scope of the claims in this way, he said. The 'unexpectedly beneficial therapeutic effect' evidently applied with all the β-agonists and not just to these four.

263. The debate on the amendment proposal developed into a full sub-argument. Counsel referred me to *inter alia* decision G1/93 *Advanced Semiconductor Products* of the Enlarged Board of Appeal of the EPO. They also referred to *European Central Bank v Document Security Systems* [2008] EWCA Civ 192.

264. I accept what Mr Thorley has said on Boehringer's behalf. If this application to amend were to be considered in isolation, the amendments might I think, be allowable. However, seeing that '270 is in my judgment invalid, there is no point in pursuing this issue further.

XI Validity of '819 [1/3]

265. This patent claims the R-enantiomer of the substance whose structural formula is shown as formula 1 of '270 (that is, aclidinium) in combination with a long-acting β_2-agonist. Page 2, lines 16-21 of '819 identifies the specific combination of a long-acting β_2-agonist together with aclidinium (in the form of a pharmaceutically acceptable salt). The preceding paragraph identifies the therapeutic benefits of this combination as follows[78]:

> "Surprisingly, it has now been found that a combination of certain specific antagonists of M3 muscarinic receptors (further on referred to as the M3 antagonists of the invention) with long acting β2-adrenergic agonists (further on referred to as long-acting β2-agonists) *produce* significantly less heart side-effects, such as tachycardia, than the combinations proposed in the art, yet retaining a robust activity in the respiratory tract." [Emphasis added]

266. The 'Background of the Invention' section of '819 points out that when it came to treating patients who suffer from *underlying* (i.e. pre-existing) heart disease with anticholinergic/β_2-agonist combinations, the risk could be so great that there was in fact a limit to the utility of such combinations (p2, lines 2-6).

267. Pages 2-20 exemplify suitable long-acting β_2-agonists, suitable salts of aclidinium, different dosage forms and various means of administration. The specification then goes on to describe animal experiments comparing the cardiac side-effect profile of aclidinium bromide with that of tiotropium bromide. The compounds are used at therapeutically equivalent doses (page 21 lines 10-11) in combination with a long acting β_2-agonist (formoterol or salmeterol).

[78] See also p21 lines 8-11.

268. In all three experiments with beagles, the combination of anticholinergic plus β_2-agonist produces a rapid increase in heart rate. The key difference between aclidinium and tiotropium is not so much in the magnitude of the peak effect but the speed at which it declines. The time taken for the heart rate to fall to 50% of the maximum value (referred to as t_{50}) is much shorter for the aclidinium combination than for the tiotropium combination. The difference in t_{50} is said to be statistically significant (see page 24 lines 5-26). That is why the combination is a step forward in the treatment of patients with an underlying cardiac history, particularly, those with tachycardia.

269. As already noted, I gained the impression from Counsel that for present purposes I really need only consider claim 20 of '819[79]. Two principal issues arise on the validity of '819: first, lack of novelty and/or obviousness in the light of the same citations as were made against '270 and secondly, Boehringer's more recent 'method of therapy' objection (PA '77, s 4A(1)(a)). In relation to the first allegation, the objection need only I think, be considered under the obviousness objection (see above under Lack of Novelty in the section on the validity of '270).

270. Though the disclosures of '270 and '819 are different, Boehringer adduced no evidence in chief specifically directed to '819. On the other hand, Almirall did put forward some evidence in this regard.

271. Claims 10 and 20 read as follows:

> 10 Use of (a) a long-acting β2-agonistas defined in any one of claims 1and 3-6 and (b) an antagonist of M3 muscarinic receptors as defined in claims 1 or 2, for the preparation of a medicament for simultaneous, concurrent separate or sequential use in the treatment of a respiratory disease which is asthma, acute or chronic bronchitis, emphysema, [COPD] bronchial hyperreactivity or rhinitis in a patient.

[79] Though in view of ongoing examination of the European equivalent of '819 at the EPO involving similar claims, Mr Thorley invited me to give a full, reasoned judgment in relation to claims 1-19 if I was against him on '270. I do not think that is necessary. I shall assume that if '270 is invalid, so too are claims 1-19 of '819.

> 20 Use according to any one of claims 10, 18 and 19 wherein the patient is suffering from a pre-existing heart condition or condition that would be aggravated by tachycardia

272. The claim thus covers (a) patients with *any* pre-existing heart condition[80] or (b) patients with any (other) condition which is aggravated by tachycardia (increased heart rate) caused by the use of the combination. This is discussed in '819 at page 1, line 29 - page 2 line 6 and again at page 21, lines 8-11. Dr Costello considered 'pre-existing heart condition' to be a 'fairly general term'[81].

Validity of claim 20

273. At the priority date of the '819 patent, the existence of side-effects arising from use of the combinations of anticholinergics and β-agonists used to treat respiratory disease was of course, well-known and when it came to patients with heart problems, the β-agonists seem to have given cause for particular concern. However, by then, combination therapy (with its benefits of lower dosage etc) had also become important.

274. Turning to patients being treated with combination therapy who also had *underlying* heart problems, such risk was obviously even greater. Extra care had therefore to be taken with patients on combinations who had concomitant cardiac problems. All this was known and was part of the common general knowledge.

Evidence on claim 20

275. Turning next to the evidence on claim 20, I regard that of Dr Costello as being particularly important having regard to his qualifications. In his first report, he set out his understanding of claim 20. He said this [82]:

> Claim 20 is aimed at specifying the use in a patient who suffers from episodes of pathological tachycardia or in whom tachycardia of any kind may compromise the output of their heart, which delivers blood to the vital organs. For example, in an elderly patient with poor heart

[80] This would of course include tachycardia.
[81] T3/372.
[82] Report I 6/2/§107

muscle function a sustained tachycardia might compromise cardiac output and therefore the delivery of blood to vital organs.

276. And later, addressing obviousness, he added (§ 111):

> As I have indicated above, claim 20 of the Almirall Patent specifies a particular patient group. Presented with such a patient before May 2004, I would have used an anticholinergic and/or an inhaled corticosteroid. I would not have used a β-agonist either alone or in combination with another drug, unless the relief of airflow obstruction was an absolute clinical necessity, i.e. the need to open the airways outweighed the risk associated with cardiac side-effects.

277. This rather puzzled Prof Barnes who said that some 30% of COPD patients have heart disease of one sort or another and that it was the 'normal' practice to treat patients with COPD with β-agonists: T4/641. Mr Thorley took the issue up with Dr Costello and it turned out that Dr Costello had been talking *only* about a limited class of patients viz those with underlying tachycardia: T3/368-372.There are it seems, few patients of the kind Dr Costello had in mind. Prof Barnes stated that (T4/523):

> A. Yes, I accept that tremor is quite a common side effect of beta-agonists in COPD patients who are elderly, but I think tachycardia is very uncommon and has never, in my experience, been a reason to discontinue the normally recommended doses of beta-agonists in these patients.

Claim 20: Obviousness and Schelfhout I and II

278. The skilled team on reading Schelfhout I and/or II would have assumed that the new compound LAS 34273 would have substantially the same side-effect profile as tiotropium. When it came to treating patients with heart problems, if used in combination with a β-agonist, the expectation was that the combination would have behaved in the much the same way as such known combinations. But, so the Almirall patent says, aclidinium was different. The 'cardiac-sparing' properties of aclidinium (as Mr Waugh called them) as shown in the experiments reported in '819, are unexpected and clinically useful (but, I note, no more than that), in the context of

treating patients with pre-existing heart condition; see Page I [6/1/194-195] and Costello I **[**6/2/111-113**]**[83].

> 112. The data in the Almirall Patent suggest that the combination of aclidinium and a long-acting β_2-agonist would be more appropriate in such patients than a corresponding combination using tiotropium. This is useful information in the context of treating such patients.
>
> 113. In my view, a skilled Respiratory Physician would not have expected a combination of the anticholinergic reported in Schelfhout 1 and 2 with a long-acting β_2-agonist to have a significant advantage over known combinations of anticholinergics and β-agonists in the treatment of patients with cardiac problems.

279. Furthermore, neither the R-enantiomer itself nor the 'cardiac-sparing' properties of aclidinium are revealed by either of Schelfhout's posters or by Forner. Thus, Almirall say that it would not be obvious to treat a patient with a pre-existing heart condition (or a condition aggravated by tachycardia) with the claimed combination.

280. Boehringer's first response was to attack (via Professor Zaagsma) the validity of the experiments reported in '819. I have mentioned this before and am not convinced that this evidence would entitle me to disregard these experiments as being without value, let alone as being in some way, 'cooked'.

281. Where I find difficulty with Almirall's argument however is that useful though the 'cardiac improvement' may be to a clinician, on Dr Costello's evidence alone, it would be obvious to try the claimed combination on patients suffering from *any* pre-existing heart condition. This is part of his 'step by step' approach to treatment. That is covered by claim 20 and adds nothing inventive over claims 1-19.The claim is not after all, for the new combination.

282. In my view claim 20 is obvious in the light of the cited prior art. Claim 20 of'819 is therefore invalid.

Method of Therapy objection

283. By its recent amendment, Boehringer has raised the allegation that claim 20 contravenes section 4A(1)(a) Patents

[83] Since that was written, the Grounds of Invalidity have been amended to bring in Forner. But I do not think this affects the substance of Dr Costello's evidence.

Act 1977 as being to a method of treating the human body by therapy. Section 4A(1)(a) states that:

> A patent shall not be granted for the invention of:
> (a) a method of treatment of the human or animal body by surgery or therapy,"…

284. Claim 20 is dependent on claims 10, 18 and 19, each of which are to the uses of a long acting β_2-agonist and M3 muscarinic receptor *for the preparation of a medicament for use* in the treatment of the respiratory disorders listed. Hence under claim 20 the manufacture of the medicament is for use in the treatment of the respiratory disorders listed *wherein the patient is suffering from a pre-existing heart condition or condition that would be aggravated by tachycardia.*

285. In recent years there have been a number of reported cases, both domestic and from the EPO, wherein the dexterity and drafting skills of patent attorneys have been tested to the limit in order to avoid the prohibition of both this section and EPC, Art 52(4). The latter ends with these words:

> 'This provision shall not apply to products, in particular substances or compositions for use in any of these methods.'

286. Claim 10 may be unobjectionable on this basis but claim 20 was certainly intended to go further.

287. The case law follows the decision of the Enlarged Board of Appeal in *Eisai* (OJ EPO 1985,64), to which my attention was drawn. My attention was also drawn to a number of other cases in this field but I do not believe that a review of the interesting (and in my view not always consistent) case law is called for. An authority which I do however consider to be germane to the structure of the present claim is that of the Court of Appeal in *Bristol-Myers Squibb v Baker Norton* [2001] RPC 1.

288. In *Bristol Myers Squibb*, claim 1 concerned taxol. Taxol was known to interfere with cell division and the idea behind its use (by infusion) was to stop cancer calls replicating. Claim 1in issue, stripped of its trimmings was for :

The use of taxol [and other medications] for manufacturing a medicamntation (sic) for…the administration of [an amount] of taxol for about 3 hours…as a means for treating cancer ..

The invention was in essence, that by changing the infusion time from 24 hours to 3 hours, a similar effect was obtained to that previously achieved but with less neutropenia. My attention was particularly drawn to the judgment of Aldous LJ at pages 20 -21and that of Buxton LJ at 28. Aldous LJ said this :

> " The section has the limited purpose of ensuring that the actual use by practitioners, of methods of medical treatment when treating patients should not be subject to restraint or restriction by patent monopolies."

Buxton LJ put it thus:

> "It is in reality not a self-standing operation but subordinate and incidental to the doctor's treatment of the patient. True it is that in treating the patient, the doctor will or at least may administer the drugs according to the guidance contained in the patent. But that merely underlines what the patent teaches is not how to manufacture a drug for use in the treatment of the patient which would be in form at least a Swiss-type claim, but how to treat the patient, which is the teaching that the Swiss-type claim is designed to avoid."

289. The addition to claim 10 (which is I think, in itself unobjectionable) is a treatment that the clinician carries out on certain kinds of patients. It is part of his treatment. The inventiveness (if any) in claim 20 lies solely in the identification by the clinician that his patient suffers from a pre-existing heart problem (or any other condition which would be aggravated by tachycardia) and that for that reason he should use the particular combination of claim 10 in the treatment of quite another illness viz respiratory disease.

290. In my judgment, this claim falls on the wrong side of section 4A(1)(a). Claim 20 is therefore invalid for this reason too.

XII Conclusion

291. Boehringer's patent '270 is invalid and will be revoked. Almirall's patent '819 is also invalid and will be revoked. I

shall hear Counsel in due course on the form of order to be made and on the question of costs.