**IN THE NAME OF THE QUEEN**

# judgment

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**THE HAGUE DISTRICT COURT**

Civil-Law Section

case number / cause-list number: 343983 / HA ZA 09-2540

**Judgment of 26 January 2011**

in the case of

1. the private limited liability company
**SANDOZ B.V.**,
having its registered office in Almere, the Netherlands,
2. the legal entity under foreign law
**HEXAL AG**,
having its registered office in Holzkirchen, Germany,
claimants,
attorney *mr*. P.J.M. von Schmidt auf Altenstadt, practising in The Hague, the Netherlands,

versus

the legal entity under foreign law
**GLAXO GROUP LIMITED**,
having its registered office in Greenford, Middlesex, United Kingdom,
defendant,
attorney *mr*. L.Ph.J. baron van Utenhove, practising in The Hague, the Netherlands.

Hereinafter the parties will be referred to as Sandoz and Glaxo; the individual claimants also as Sandoz BV and Hexal. The substance of this case was handled on behalf of Sandoz by *mr.* P. Burgers, *mr.* M.G.R. van Gardingen and *mr.* M.A.R. Vermunt, attorneys practising in Amsterdam, the Netherlands, with assistance from patent agents Dr. H.J.R. de Boer and *drs.* J. Mannaerts. The substance of this case was handled on behalf of Glaxo by *mr.* W.A. Hoyng and *mr.* B.J. van den Broek, attorneys practising in Amsterdam, the Netherlands, with assistance from patent agent Dr. J.H.J. den Hartog.

## 1. The proceedings

1.1 The course of the proceedings is evidenced by:
- the order given by the Preliminary Relief Judge of this District Court of 9 July 2009, granting leave to Sandoz to summon Glaxo under the accelerated regime in patent cases;
- the summons of 13 July 2009;

- the motion filing exhibits on the part of Sandoz of 29 July 2009 (Exhibits 1 through 24);
- the statement of defence, also motion filing exhibits of 14 October 2009 (Exhibits 1 through 40);
- the order given by the Preliminary Relief Judge of this District Court of 12 February 2010, removing this case from the accelerated regime in patent cases so that it could be continued in accordance with the national procedural regulations;
- the statement of reply of 24 March 2010 (Exhibits 25 through 38);
- the statement of rejoinder, also motion filing exhibits of 26 May 2010 (Exhibits 41 through 64);
- two motions filing exhibits on the part of Sandoz of 26 November 2010 (with Exhibits 39 through 44 and Exhibit 45, respectively) and a letter of 1 November 2010 from *mr.* Van Gardingen with a correction of Exhibit 41;
- the motion filing exhibits on the part of Glaxo of 26 November 2010 (Exhibits 65 through 67);
- an e-mail message of 22 November 2010 to the District Court indicating that the parties have reached agreement regarding the reciprocal claims for an order to pay the reasonable and proportionate costs of the proceedings of € 450,000;
- the oral arguments and the written arguments submitted on that occasion by the litigating attorneys.

1.2 Judgment was scheduled for today.

## 2. The facts

2.1 Glaxo holds European Patent 0 416 951, now expired (hereinafter also referred to as EP 951 or the patent), for: *medicaments comprising salmeterol and fluticason* (in the uncontested translation into Dutch: *geneesmiddelen die salmeterol en fluticason bevatten*). EP 951 was granted on 12 January 1994 based on an application of 7 September 1990, invoking the priority of GB 8920392 since 8 September 1989 and of GB 8923644 since 20 October 1989. EP 951 was valid in several countries, including the Netherlands. No opposition proceedings were instituted against the patent.

2.2 The claims of the patent - to the extent applicable in the Netherlands and elsewhere; other claims applied for Greece and Spain - read as follows in the original English text:

1. Compositions containing salmeterol and/or a physiologically acceptable salt thereof and fluticasone propionate for simultaneous administration by inhalation in the treatment of respiratory disorders.
2. Compositions as claimed in claim 1 wherein salmeterol is present as its 1-hydroxy-2-2naphthoate salt.
3. Compositions as claimed in claim 1 or claim 2 presented in the form of a metered dose inhaler or a metered dry powder composition.
4. Compositions as claimed in any of claims 1 to 3 in dosage unit form containing 25-100µg of salmeterol optionally in the form of a physiologically acceptable salt thereof and 25-500µg of fluticasone propionate per dosage unit.
5. The use of salmeterol and/or a physiologically acceptable salt thereof and fluticasone propionate in the manufacture of pharmaceutical compositions for simultaneous administration of salmeterol and fluticasone propionate by inhalation in the treatment of respiratory disorders.

6. The use of salmeterol and/or a physiologically acceptable salt thereof and fluticasone propionate according to claim 5 in the manufacture of pharmaceutical compositions for administration on a twice daily basis.

In the uncontested translation into Dutch these claims read as follows:

1. Preparaten die salmeterol en/of een fysiologisch aanvaardbaar zout daarvan en fluticasonpropionaat bevatten voor gelijktijdige toediening door inhalatie bij de behandeling van ademhalingsstoornissen.
2. Preparaten volgens conclusie 1 waarbij salmeterol aanwezig is als het 1-hydroxy-2-naftoaatzout daarvan.
3. Preparaten volgens conclusie 1 of conclusie 2, aangeboden in de vorm van een inhaleertoestel dat afgemeten doses afgeeft of een preparaat met een dosis droog poeder.
4. Preparaten volgens één der conclusies 1 - 3 in de vorm van een doseringseenheid die 25-100 µg salmeterol bevat, eventueel in de vorm van een fysiologisch aanvaardbaar zout daarvan, en 25-500 µg fluticasonpropionaat per doseringseenheid.
5. Gebruik van salmeterol en/of een fysiologisch aanvaardbaar zout daarvan en fluticasonpropionaat bij het vervaardigen van farmaceutische preparaten voor de gelijktijdige toediening van salmeterol en fluticasonpropionaat door inhalatie bij de behandeling van ademhalingsstoornissen.
6. Gebruik van salmeterol en/of een fysiologisch aanvaardbaar zout daarvan en fluticasonpropionaat volgens conclusie 5 bij het vervaardigen van farmaceutische preparaten voor twee maal daagse toediening.

The patent is not accompanied by figures. The description includes 11 examples.

2.3 In the description of the patent, the invention is introduced as follows on p. 2, ll. 1-48:

> This invention relates to improvernents in the treatment of asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator drug in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients.
> Asthma is a condition characterised by variable, reversible obstruction of the airways which is caused by a complex inflammatory process within the lungs. In most cases, this process is initiated and maintained by the inhalation of antigens by sensitive atopic individuals (extrinsic asthma). However, in some patients it is caused by other mechanisms which at present are poorly understood but do not involve an allergic process (intrinsic asthma). The disease has therefore two components, spasm of the bronchial (or breathing) tubes and inflammation or swelling of the breathing tubes.
> Salbutamol, the first highly selective β2-adrenoceptor stimulant has been used successfully and effectively by inhalation for the immediate relief of spasm in asthma. However, when given by inhalation, salbutamol has usually a four to six hour duration of action, which is too short either to control nocturnal asthma or for convenient maintenance of the disease in some patients.
> It has been recognised that asthma may be treated by using both a bronchodilator for immediate relief and a prophylactic anti-inflammatory corticosteroid to treat the underlying inflammation. Such combination therapy directed at the two main underlying events in the lung (i.e. relief of spasm in the breathing tubes and treatment of inflammation in the breathing tubes) using a combination of salbutamol and beclomethasone dipropionate has previously been proposed (Ventide, Glaxo Group trade mark), but suffers a number of disadvantages in view of the above-mentioned short duration of action exhibited by salbutamol. Thus the need for a 4-hourly dosing regimen may discourage effective patient compliance and also renders the product less than satisfactory in the treatment of nocturnal asthma since the bronchodilator may not remain effective for the

> duration of the night, leading to impaired sleep for asthmatics troubled by nocturnal cough, breathlessness and wheeze.
> The present invention is based on the concept of a novel combination therapy which has markedly greater efficiency and duration of bronchodilator action than previously known combinations and which permits the establishment of a twice daily (bis in diem – b.i.d.) dosing regimen with consequent substantial benefits in, for example, the treatment of asthma, particularly nocturnal asthma.
> Thus we have found that if the β2-adrenoreceptor stimulant bronchodilator salmeterol and/or a physiologically acceptable salt thereof is combined with the anti-inflammatory corticosteroid fluticasone propionate in a form suitable for administration by inhalation, the resulting compositions may be administered on a b.i.d. basis to provide highly effective treatment and/or prophylactic therapy for asthmatics. In particular such administration has been shown to lead to significant improvement in daytime lung function, requirement for additional symptomatic bronchodilator and almost complete abolition of nocturnal asthma while giving rise to minimal systemic side effects.
> Salmeterol is one of a range of bronchodilators having extended duration of action which is described in GB-A-2140800, and is systematically named (...). Fluticasone propionate is one of a range of topical anti-inflammatory corticosteroids with minimal liability to undesired systemic side effects which is described in GB-A-2088877, and is systematically named (...). We have found these two compounds to be particularly compatible and complementary in their activity and thus highly effective in the treatment of asthma and other respiratory disorders. (emphasis added; District Court)

2.4. Glaxo holds the Supplementary Protection Certificate numbered 990012 (hereinafter also: the SPC or SPC 990012) that is based on the patent and was granted for:

> Salmeterol, if so desired in the form of a pharmaceutically acceptable salt, and Fluticasone Propionate, in particular Salmeterol Xinafoate and Fluticasone Propionate,

granted to Glaxo on 9 June 1999, valid from 7 September 2010 and expiring on 6 September 2013.

2.5. The individual substance salmeterol as β2-agonist, as well as fluticasone (di)propionate (hereinafter also referred to as: FP) as inhaled corticosteroid, were known on the priority date, as indicated in the description introduction of EP 951. Salmeterol was disclosed in GB 2 140 800 A. Page 1 of this application from 1984 states the following in lines 25-35:

> All β2-stimulants currently used in clinical practice suffer from the disadvantage that they have a relatively short duration of action when administered by inhalation. A β2-stimulant with a relatively long duration of action would therefore offer a significant advance in the treatment of bronchial asthma and related disorders.
> In a search for new β-stimulants with advantageous properties, we have now found a novel group of phenethanolamine derivates (including salmeterol; District Court), which differ structurally from the group of compounds described in (...: another patent application; District Court) and which in our tests have shown a potent selective stimulant action at β2-adrenoreceptors, and, in addition, have an advantageous profile of action. (emphasis added; District Court)

In the 1981 application GB 2 088 877 A, FP was disclosed on p. 1, ll. 34-36, in conjunction with ll. 43-44 (and in example 19 - not cited below):

> Especially preferred compounds according to the invention in view of their good topical anti-inflammatory activity and favourable ratio of topical anti-inflammatory activity to undesired systemic activity include:

(...)
(the chemical name for FP follows; District Court).

2.6. In a publication in SCRIP no. 1184 of 4 March 1987, which was two and a half years before the priority date, the following can be found regarding the on-going Glaxo research involving salmeterol and fluticasone:

> 14 OF 32
> **Salmeterol** and fluticasone
> The beta(2)-stimulant, **salmeterol**, and the anti-inflammatory steroid, fluticasone, are the resultant product candidates from research to improve salbutamol (Ventolin) and beclomethasone dipropionate (Beclovent/Becotide).
>
> 15 OF 32
> **Salmeterol**, a chemical analogue of salbutamol, is specifically designed for inhalation - its bronchodilating action in asthmatic patients at 50-200 mcg is at least as intense as that of salbutamol 200mcg with a duration of action about four times longer than salbutamol, according to Dr David Jack, research director (Glaxo Holdings), bronchodilation is maintained for at least 12 hours, he said.
> 16 OF 32
> The company believes that **salmeterol's** duration of action and selectivity makes it the ideal bronchodilator for maintenance treatment in chronic asthma "because for the first time maximal bronchodilation is achievable without side-effects throughout the day and night with simple twice daily dosage". Dr Jack stressed the control exercised by the drug on the diurnal variation in respiratory function in asthmatic patients, which causes acute attacks in early morning. He also pointed out that it did not alter heart rate.
> 17 OF 32
> The clinical trials comparing the effects of inhaled **salmeterol** and salbutamol will soon be extended to include comparison of **salmeterol** with oral theophylline. Glaxo expects to file for marketing approval of **salmeterol** in the last quarter of 1989.
> 18 OF 32
> Fluticasone dipropionate is substantially more active than beclomethasone dipropionate as a vasoconstrictor and anti-inflammatory agent on human skin but has no greater suppressive effect on the hypothalamic/pituitary/adrenal system, Dr Jack said. It may therefore, he added, have a more intense anti-inflammatory effect in the lungs at tolerated doses. Comparative studies with beclomethasone dipropionate are underway. Product license applications could be filed early in 1989. (emphasis added; District Court)

2.7. The more favourable effects of salmeterol on the one hand as compared to the salbutamol bronchodilator commonly used at the time, and of FP as compared to the corticosteroid anti-inflammatory agent beclomethasone dipropionate (often abbreviated as BDP) mostly used at the time, respectively, that follow from this SCRIP publication are also highlighted in scientific publications prior to the priority date.

2.8. For example, in Thorax 1988; 43: 674-678 Ullman/Svedmyr reported a comparative study of salbutamol and salmeterol in adult asthma patients[1] demonstrating the longer duration of action of salmeterol as compared to salbuterol:

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[1] Some of whom who took corticosteroids prior to participating in the study continued to do so during the study, and therefore during this study took corticosteroids in addition to the relevant bronchodilators, as follows from p. 675, right column, top section: "Patients taking inhaled corticosteroids continued this treatment at a constant dose, throughout the study."

**Discussion**

These data confirm that in asthmatic patients salmeterol is a potent long acting bronchodilator. All doses of salmeterol produced maximum bronchodilatation similar to that produced by 220 µg salbutamol. There were no significant differences in time of onset between the three doses of salmeterol and salbutamol. All three doses of salmeterol had a longer duration of action than salbutamol 200 µg and produced bronchodilatation throughout the 12 hour study period. There was a trend suggesting greater bronchodilatation by 200 µg salmeterol than by the 50 or 100 µg doses. (emphasis added; District Court)

2.9. Furthermore, FP and BDP were compared in two studies prior to the patent's priority date, in which FP proved more favourable:

Bauer et al., *The Effect of Inhaled Fluticasone Propionate (FP), a new Potent Corticosteroid*, European Respiratory Journal 1988 (Suppl. 2), p. 201S reports the following about FP:

FP is a new corticosteroid which has greater topical activity than beclomethasone dipropionate (BDP) and minimal systemic activity after oral dosing. We have performed a multicenter randomised, double-blind, parallel group study comparing BDP 750-1500 mcg with the same dose of FP in 97 patients with severe asthma who were symptomatic at entry into the study. (...) These data provide evidence that both inhaled FP and BDP are effective in the treatment of severe asthma but that FP is more potent when given in an equal dose. FP may therefore offer advantages over BDP in severe patients. (emphasis added; District Court).

Harding et al., *A Comparison of the Tolerance and Systemic Effects of Fluticasone Propionate (FP) and Beclomethasone Dipropionate (BDP) in Healthy Volunteers*, European Respiratory Journal 1988, p. 196S reports as follows:

FP is a novel topical active corticosteroid which is more potent than BDP and is under development for the treatment of asthma. Twenty-four male volunteers were randomly assigned to receive inhaled doses of either 0.75 mg FP or BDP twice daily over a 10-day period in a parallel group study. (...)

In conclusion, Fluticasone Propionate inhalations (1.5mg daily) by aerosol was better tolerated than Beclomethasone Dipropionate in healthy volunteers with respect to its effect on the hypothalmic-pituitary-adrenal axis over 10 days administration. (emphasis added; District Court)

2.10. A review article written by an authority in the field of asthma treatment around the priority date, Professor Barnes, titled *The Drug Therapy of Asthma: Directions for the 21st Century*, AAS 23: New anti-asthma drug 1988, pp. 293-313, includes the following excerpts:

**Summary**

There are several novel pharmacological approaches to asthma therapy which have resulted from a further understanding of airway smooth muscle function and inflammatory mechanisms involved in asthma. The most effective bronchodilators currently available are β2-adrenoceptor agonists and drugs with a prolonged duration of action after inhalation will be useful. (...) The most effective anti-inflammatory treatment is corticosteroids and efforts are being made to improve the topical potency of these drugs. (...)

**Bronchodilators**

Bronchodilators are presumed to act by reversing contraction of airway smooth muscle, although some may have additional effects on mucosal oedema. The biochemical basis of airway smooth muscle relaxation has been studied intensively, yet few new classes of bronchodilator have had any clinical impact. (...)

β-Adrenoceptor agonists

β-Adrenoceptor agonists remain the most widely used and effective bronchodilator in clinical practice (...) Many different β-adrenoceptor agonists are now available and of the commonly used drugs (salbutamol, terbutaline, fenoterol) there is little to choose between them. (...)
The most important advance will be the introduction of inhaled β2-adrenoceptor agonists with a long duration of action, and drugs such as formoterol and salmeterol are very promising in this respect, and would be predicted to be effective in preventing nocturnal asthma. It is difficult to imagine that any future drug could be more effective than a β2-adrenoceptor agonist as a bronchodilator.
(...)

**Corticosteroids and related drugs**

There is no doubt that corticosteroids are the most effective treatment currently available for the long term management of asthma. Steroids of high topical potency, such as budesonide and beclomethasone, are highly efficient when given by inhalation. Future developments will depend upon the development of inhaled steroids of even higher topical potency and which are metabolised locally, so that the local dose of steroids in the airways will be increased without the systemic effects which currently limit dose. This would seem to be the most important advance which can be made in asthma therapy at the present time. Since steroids suppress virtually every stage of the inflammatory response in asthmatic airways, they should probably be introduced much earlier in the management of asthma and β-adrenoceptor agonists, which have no effect on the inflammatory response, should be used for symptomatic control as required.

**Conclusions**

Many different therapeutic approaches to the treatment of asthma may be possible, yet there have been few new drugs. β2-Adrenoceptor agonists are by far the most effective bronchodilator drugs and lead to rapid symptomatic relief. It is difficult to imagine how these drugs could be improved, apart from a longer duration of action when given by inhalation, since they antagonise bronchoconstriction irrespective of cause, are virtually devoid of side-effects and over-dosage does not cause problems. Similarly, inhaled corticosteroids are extremely effective as chronic treatment in asthma and suppress the underlying inflammatory process. It follows that a combination of inhaled steroids and β-adrenoceptor agonists is required and combined inhalers would seem to be a sensible development, since they will improve the compliance of inhaled steroid (which is poor because of lack of immediate bronchodilator effect). (emphasis in text added; District Court)

2.11. By decision of 19 March 2004, the national British equivalent of the patent was nullified by Pumfrey J due to lack of inventive step. The Court of Appeal found Glaxo's appeal against that decision inadmissible by decision of Jacob LJ of 16 June 2004. The High Court of Ireland also nullified the validity of the patent for Ireland by decision of 26 June 2009. An appeal is pending against that decision. The same applies to the German part of the patent, which was found by the Bundespatentgericht to lack inventive step following a hearing on 23 February

2010. An appeal against that decision is currently pending before the Bundesgerichtshof. Proceedings regarding the patent are also ongoing in France, in which a judgment in first instance is expected in the course of 2011.

2.12. This District Court has rendered a decision on EP 951 in the past[2], but a substantive assessment of the patent's validity in the Netherlands was not performed at the time for procedural reasons.

## 3 The dispute

3.1 Asserting that the patent is invalid due to a lack of inventive step and insufficiency, and that as a result of this the SPC also lacks validity, Sandoz is seeking, in summary:
in the main action:
A) nullification of the Dutch part of EP 951 and
B) cancellation of the SPC,
C) with costs to be determined by the court pursuant to Article 1019h Dutch Code of Civil Procedure,
D) insofar as possible with immediate effect; and provisionally also:
E) in the event that the main action is delayed, an injunction for the duration of the main action against taking any legal action on the basis of the patent or the SPC against Sandoz or companies affiliated with Sandoz regarding reserved acts, such on pain of penalties,
F) also with costs to be determined by the court pursuant to Article 1019h Dutch Code of Civil Procedure, and
G) insofar as possible with immediate effect.

3.2 Glaxo presented a defence.

3.3 Insofar as relevant, the parties' arguments will be discussed in more detail below in the assessment.

## 4 The assessment

*Inventive step*

4.1 Like its foreign counterparts that have adjudicated on the validity of the patent or its national equivalent, the District Court finds the patent null and void, if only on account of its lack of inventive step. It finds as follows in this regard.

*Problem-solution approach*

4.2 Most suitable as the closest prior art is the review article by Barnes of 1988, because most of the structural features from the patent claims can be found in it and its solution/problem is also the most similar to that of the patent. This will be discussed in more detail below.

[2]The Hague District Court, 26 November 2008, *Glaxo/Cipla*, IEPT20082611.

4.3 Sandoz takes, *inter alia*,[3]Barnes as the closest prior art in its invalidity analysis. At the hearing Glaxo indicated that, in itself, it has no serious objections to taking Barnes as the closest prior art. In the understanding of this District Court, Glaxo nevertheless advocates a different approach to assessing the patent's inventive step. That approach is not based on taking a single statement as the closest prior art, but rather on a consideration of the entire prior art, including what Glaxo refers to as positive and negative pointers; see, in this respect, below in 4.32 et seq. It was unclear, incidentally, in which phase of the problem-solution approach (hereinafter also referred to as PSA) that approach should be followed and how that should be done according to Glaxo; in the District Court's opinion, no unambiguous answer was given to questions regarding this during oral arguments. The District Court is of the opinion that Sandoz correctly argued that, in essence, Glaxo intends to assert that Sandoz must prove the obviousness of each individual document from the prior art.

4.4 The District Court does not agree with Glaxo's different approach. It aligns with the established case law in the Netherlands that - as is common practice at the EPO - as a rule (and there are very few exceptions to the rule) the PSA is applied in assessments of inventive step in cases such as this one. The District Court sees no cause for exception in this case, which is well-suited to the structured approach of the PSA.[4] Glaxo also failed to clarify why this case might not be suitable for assessment on the basis of the PSA. Therefore, in this case as well, a single statement will apply as the closest prior art. Any other prior art is addressed in assessing the inventive step firstly to the extent that it can be considered to be part of the common general knowledge and secondly to indicate the progress line of the categories of asthma medicines that are the subject of the patent, and therefore as background prior art.

4.5 It very much remains to be seen whether the various approaches used in Europe in determining the inventive step would still lead to different outcomes. To the extent that the method of assessment advocated by Glaxo conforms, in essence, to the more *traditional*, English-tinged state-of-the-art approach from the *Pozzoli/Windsurfing*[5] case law, the District Court finds the following. English patent case law repeatedly indicates that, although a strict PSA as established in the TBA's case law is usually not applied, the "English" inventive step assessment does not differ in essence and should not lead to different outcomes.[6]Incidentally, surpris-

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[3]Sandoz also argued that Ventide, a combination of salbutamol as brochodilator and BDP as topical corticosteroid anti-inflammatory agent, can be considered the closest prior art, too. In oral arguments, Sandoz indicated that in terms of feature similarity, Barnes is closer than Ventide (written arguments by *mr.* Burgers and *mr.* Van Gardingen, no. 28).

[4]It is held *ex officio* that exceptions such as those recently identified by Jacob LJ in *Fluvastatin* [2010] EWCA Civ 82 at 35-37 where the PSA fails in his opinion, such as for "problem" inventions and the "5 1/4 inch plate paradox", do not exist in this case, while the reformulation of the objective technical problem is minimal in this case, as explained below.

[5] Jacob LJ reformulated the English test for inventive step from *Windsurfing* as follows in *Pozzoli* [2007] EWCA Civ 588 at 23: (I) (a) Identify the notional "person skilled in the art"
(1)(b) Identify the relevant common general knowledge of that person
(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it
(3) Identify what, if any, differences exist between the manner cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed.

[6]In the case regarding the parallel English patent, in his refusal to admit appeal Jacob LJ also indicated the following under 4: *I can detect no real difference in approach between the EPO and the UK on obviousness - in the end it all (as it must) comes back to the statutory question*.

ingly enough, Jacob LJ recently *did* explicitly apply the PSA in the *Fluvastatin* case referred to above.

4.6 As already known, the PSA comprises the following three-part structured approach, in which the average person skilled in the art - in this case a team consisting of a formulation expert and a physician specialising in treating asthma and respiratory disorders, where relevant supplemented by an organic chemist and a pharmacologist - serves as the reference person using his common general knowledge:

a) identification of the closest prior art;
b) formulation of the objective technical problem; and
c) assessing whether the claimed invention would be obvious to the average person skilled in the art from the premise of the relevant closest prior art (cf. Guidelines, C-IV, 11.5, April 2010 version).

4.7 Applied as the closest prior art is the statement showing the combination of features that provides the most suitable point of departure, known as the "most promising springboard", towards an obvious development to the invention being claimed. This selection must involve a technical area or objective that is the same as or closely related to that of the claimed invention. Inherent to the PSA is the fact that this closest prior art is determined using the knowledge of the invention. Whether the springboard from the prior art was successful is irrelevant when applying the PSA, as correctly argued by Sandoz; the issue is the distance to the invention. The contents of the closest prior art are considered by the average person skilled in the art in their entirety - meaning the entire technical content - and in context. From the Summary of the last edition of *Case Law*[7]:

> ... when investigating inventive step, it should be borne in mind that the technical disclosure in a prior art document should be considered in its entirety, as it would be done by a person skilled in the art and that it is not justified arbitrarily to isolate parts of such document from their context in order to derive from them technical information which would be distinct from the integral teaching of the document (...). According to **T 95/90, different parts of text in a document** can be combined if there is nothing to stop the skilled person from doing so.

4.8 Given this closest prior art, the technical problem to be solved is then objectively formulated - and, if necessary, reformulated in comparison to the relevant formulation in the patent itself - under consideration of the elected closest prior art and the structural or functional differences this renders as compared to the features from the claims, thereby considering the technical effect ensuing from those differences; non-technical aspects are not taken into consideration when assessing the inventive step. As formulated in the Guidelines loc cit.:

> In the context of the problem-and-solution approach, the technical problem means the aim and task of modifying or adapting the closest prior art to provide the technical effects that the invention provides over the closest prior art.

This need not involve a technical improvement; an alternative can be sufficient. Lastly, the objectively formulated problem may contain no pointers to the solution in the patent, lest the test

[7] Case law of the Boards of Appeal of the European Patent Office, 6th edition 2010, LD.8.3, *Technical disclosures in a prior art document*, p. 199.

fail through hindsight. The District Court agrees with Sandoz' substantiated[8] assertion that the formulation of the objective technical problem may not be so general that clear pointers in the closest prior art are circumvented, as the test of inventive step would then be insufficiently selective.

4.9 The last step of the PSA is particularly relevant in view of Glaxo's position in this case and pertains to the could-would test, on which the Guidelines state the following in C-IV 11.5.3:

> **11.5.3 Could-would approach**
>
> In the third stage the question to be answered is whether there is any teaching in the prior art as a whole that **would** (not simply could, but would) have prompted the skilled person, faced with the objective technical problem, to modify or adapt the closest prior art while taking account of that teaching, thereby arriving at something falling within the terms of the claims, and thus achieving what the invention achieves (...).
>
> In other words, the point is not whether the skilled person could have arrived at the invention by adapting or modifying the closest prior art, but whether he **would have done** so because the prior art incited him to do so in the hope of solving the objective technical problem or in expectation of some improvement or advantage (see T 2/83, OJ 6/1984, 265). Even an implicit prompting or implicitly recognisable incentive is sufficient to show that the skilled person would have combined the elements from the prior art (see T 257/98, T 35/04, not published in OJ). This must have been the case for the skilled person before the filing or priority date valid for the claim under examination.

The importance of the could-would distinction and of avoiding an assessment affected by hindsight is endorsed in Dutch case law (cf. HR 15 February 2008 (*Rockwool/Isover*), finding 3.4.4 at the instigation of A-G Langemeijer, under 2.24 and 2.28 of his opinion, LJN: BB5066):

> The section rightly assumes that the question of the degree of inventive step may not be answered by looking for previous disclosures to which the patented method can be traced using hindsight, with knowledge of this method, but that it is important in this assessment whether the average person skilled in the art would have recognised the problem solved by the patented method and would have examined the publications referred to by the Court to find a solution and would (not could) also have deduced this method as the obvious solution from the then prior art, using common general knowledge in the art.
> (...) To the extent that this section is arguing that, in the assessment of the inventive step, the Court must always include a finding indicating that it is aware of the danger of assessing the inventive step under the influence of hindsight, it is not supported by the law.
> Contrary to what this section assumes, the Court of Appeal did not search on the basis of its knowledge of the patented method for earlier disclosures to which that method can be traced, but rather investigated it and explained in detail in findings 8 and 11 on the basis of what documents (...) the average person skilled in the art, using his common general knowledge, would have arrived at the method of claim 1 of Rockwool's patent.

[8] Idem p. 171: The problem can be no more general than the disclosure of the prior art allows. Otherwise, a problem could be formulated as to circumvent indications in a prior art document towards the claimed solution.

*Barnes as the closest prior art*

4.10 Barnes is a review article of asthma treatments by an authority in the field, acknowledged as such by the parties, from 1988, which is the year preceding the priority date. It follows from that review article that the treatment of asthma essentially consists of two components: bronchodilatation to remedy the bronchial spasms and anti-inflammation to combat the underlying bronchial inflammation.

4.11 The person skilled in the art learns from Barnes - which describes the same objective, effective asthma treatment, as the patent - firstly that β2-agonists are the most effective bronchodilators: "most widely used and effective in clinical practice". Pointing in the direction in which advancement can be made in this, Barnes names new agonists that have a longer duration of action than that most commonly used at the time, salbuterol: "most important advance will be introduction of agonists with long duration" ; the substance salmeterol, which is related to salbuterol, is said in so many words, together with formoterol, to be "very promising in this respect". Barnes also discusses the other bronchodilators in the field. He indicates the state of affairs in 1988 with regard to each of these, whether they are clinically effective and specific, under development or not, whether they have side effects; in short, the entire spectrum. However, Barnes expresses a clear preference for β2-agonists in his article.

4.12 For the anti-inflammatory component in asthma treatment the person skilled in the art finds in Barnes a strong preference for topical inhaled corticosteroids: "no doubt that corticosteroids are the most effective". Barnes names beclomethasone and budesonide here as "steroids (...) of high topical potency" that are "highly efficient". Developments directed at that aspect of the treatment of asthma are sketched by Barnes in the area of research into more potent topically active corticosteroids, while minimising their undesired systemic effects: "future developments will depend upon the development of inhaled steroids of even higher topical potency (...) so that the local dose of steroids in the airways will be increased without systemic effects which currently limit dose". The rest of the field of asthma anti-inflammatory agents in 1988 was also identified by Barnes, as were the various bronchodilators. Moreover, Barnes' conclusion teaches that an effective asthma treatment exists - or needs to exist: "is required" - comprising administration of both a β2-agonist and a corticosteroid: "it follows that a combination of inhaled steroids and β-adrenoceptor agonists is required", and finally that a combination in a single inhaler is expected: "and combined inhalers would seem to be a sensible development".

4.13 Thus Barnes taught the person skilled in the art in 1988 the following technical features for asthma treatment:

1) an inhaled β2-agonist such as salmeterol as a bronchodilator, which works better/longer than salbuterol, the bronchodilator most commonly used at the time;
2) combined with an inhaled corticosteroid with high topical potency for the anti-inflammatory treatment component, such as beclomethasone or budesonide, in which respect even more effective corticosteroids of this category can be sought;
3) in which respect combining these two necessary treatment components in a single inhaler would be an obvious development.

*Differences between Barnes and EP 951*

4.14 As compared to the technical features from claims 1, 5 and 6 of the patent, Barnes actually only lacks FP as an alternative for the topical inhaled corticosteroids beclomethasone and budesonide.

4.15 Barnes points the person skilled in the art directly to the more effective substance salmeterol for the bronchodilating component, and considers a combination inhaler with such a β2-agonist with a topical corticosteroid an obvious future development. Barnes also gives the person skilled in the art a direct pointer to search for a more potent topical inhaled corticosteroid with minimal systemic effects for the anti-inflammation treatment component. After all, the corticosteroids used at the time were "dose limiting" due to that systemic activity, according to Barnes.

*Objective technical problem*

4.16 As a result, the objective technical problem is finding a combination therapy suggested by Barnes in the form of a combination inhaler with a longer-working β2-agonist - for example salmeterol, as suggested by Barnes, in combination with a topical inhaled corticosteroid component that works better - meaning with a better topical potency than beclomethasone or budesonide and minimal undesired systemic activity.

*Barnes and SCRIP 1148*

4.17 Because Barnes himself already urges, as explained, a search for a better-working alternative for BDP - on the market in the form of Ventide - or budesonide, and given Barnes' conclusion that an adequate asthma treatment consists of bronchodilatation, preferably by means of a β2-agonist (while suggesting salmeterol, which works longer than salbuterol) and anti-inflammation by means of a topical corticosteroid (observing a development towards more potent substances from this category with a minimal undesired systemic activity), where the person skilled in the art also reads that Barnes believes that a combination inhaler would be a sensible development, when confronted with said objective technical problem he would search for such a better-working alternative for beclomethasone/budesonide taking Barnes as a starting point. Glaxo's argument that the person skilled in the art would not do so because Barnes indicates that beclomethasone and budesonide are "highly effective" is rejected. Barnes unmistakably urges the person skilled in the art to search for a better alternative because the substances used at the time of the priority date are said to be "dose limiting". Incidentally, Sandoz' assertion that the person skilled in the art is deemed to always be searching for improvements is correct.[9]

4.18 A literature study into salmeterol, named in Barnes, will lead the average person skilled in the art to SCRIP 1148. There the person skilled in the art will also find, in addition to salmeterol as bronchodilator, that he can test the topical anti-inflammatory agent FP for the other treatment component, as a promising development in a better direction, albeit with regard to these two components not as a combination inhaler in this SCRIP publication. All of the elements named in SCRIP 1148 indicating that FP is a better alternative for BDP/budesonide are

[9] Case Law. op. cit.. p, 205 with reference to T 15/81, T 195/84.

confirmed for the person skilled in the art in peer-reviewed literature from before the priority date (cf. Bauer and Harding, referred to above in 2.9).

4.19 That Barnes leads away from FP as it were, because Barnes urges the person skilled in the art to search for "inhaled steroids of even higher potency and which are metabolised locally", while FP is not a "locally metabolised steroid", as argued by Glaxo, is unconvincing. Sandoz correctly points out that this argument disregards the syntax and context within which Barnes discusses local metabolism: local metabolism as referred to here by Barnes (p. 303 ll. 7-8) has the objective of reduced systemic side effects, and that is exactly what is clearly highlighted in SCRIP 1148 and Harding. 303).

4.20. The argument that it would not be obvious to use salmeterol in a combination inhaler due to a slower onset of action than, for example, salbutamol, is also disregarded. Glaxo considers salmeterol highly unsuitable for a combination inhaler on the priority date because the only known advantage of a combination inhaler at the time, named by Barnes - improved compliance in the administration of corticosteroids - is negated by that slower onset. It is not in dispute that a slower onset makes salmeterol unsuitable for use in what is known as a rescue inhaler for acute attacks, in which this speed of onset is of primary importance. Because of its slow onset salmeterol is only suitable for regular, preventive use. That nevertheless does not mean that salmeterol is unsuitable for use in a combination inhaler or that the person skilled in the art starting from Barnes would not arrive at the use of salmeterol in a combination inhaler. The benefit of a combination inhaler named by Barnes also occurs with regular use of a bronchodilator. The compliance advantage means that each time a bronchodilator is administered to alleviate acute or other spasms, corticosteroids are also administered to combat the inflammation. Use of a combination inhaler therefore provides a guarantee that the treatment does not stop with combating symptoms but will also combat the inflammation. That benefit occurs irrespective of whether the administration is intended for acute relief of symptoms or is regular and preventive, and irrespective of the onset of the bronchodilator.

4.21. That the person skilled in the art could just as well have used another long-working β2-agonist, as argued by Glaxo, is not an argument that works particularly in favour of the inventive step considering the clear pointer in Barnes towards salmeterol. But even if that were the case, that fact in itself does not make the choice for salmeterol inventive, in light of the pointer towards salmeterol in Barnes and the combination to be made with SCRIP 1148, as correctly argued by Sandoz.

4.22. The District Court also rejects Glaxo's argument that Barnes points away from regular use of β2-agonists due to the excerpt cited above on p. 303 (cf. 2.10 above): "β2-adrenoreceptor agonists (...) should be used for symptomatic control as required". Glaxo's assertion that this can be interpreted to point away from regular administration of β2-agonists is incorrect. This excerpt does not point to a rescue inhaler, but rather to combating bronchoconstriction when it occurs. An integral reading of Barnes, after all, ends in the suggestion of a combination inhaler with salmeterol and a corticosteroid with improved topical activity. With this reasoning Glaxo does exactly what the excerpt from the latest edition of Case Law cited above (cf. 4.7 above) warns against, as Sandoz again rightly argues: "it is not justified arbitrarily to isolate parts of such document from their context in order to derive from them technical information which would be distinct from the integral teaching of the document".

*Could-would test*

4.23. In the District Court's opinion, the combination of Barnes - SCRIP 1148 is a combination the average person skilled in the art would reasonably make. It is directly the same field, improved asthma treatment, in which one of the improvement components suggested by Barnes, salmeterol, is already used, together with the other treatment component FP - which is necessary according to Barnes - as a better working alternative for BDP/budesonide. There is no *ex post facto* analysis to be avoided, as argued in vain by Glaxo. In fact, the average person skilled in the art thus follows exactly the path that Barnes has mapped out for him. He is looking for a) a combination inhaler as suggested by Barnes, with b) the better-working salmeterol already named by Barnes, and c) starts looking for a topical corticosteroid that works better than beclomethasone/budesonide as indicated by Barnes. That alternative is presented to him in SCRIP 1148. Glaxo's suggestion that the person skilled in the art would not be able to see the wood for the trees cannot be understood and is rejected. In the District Court's opinion, it is the most obvious path when "departing" from Barnes. And the literature described for the separate components salmeterol and FP also provided the person skilled in the art with a legitimate expectation of success. In other words, this can't-see-the-wood-for-the-trees problem is overcome by the could-would test, as formulated by A-G Langemeijer in his opinion of the aforementioned *Rockwool/Isover* judgment under 2.24 and 2.28. It is true that the average person skilled in the art does not have a route description to the solution on the reference date. When looking for a solution to a technical problem, he will have to find his way in all the publications available, which have not been selected and sometimes point in a different direction. Precisely because Barnes has already "filtered out" so much in his review article, this unequivocally pushes the person skilled in the art in the indicated direction, which he *would* follow in the District Court's opinion (following up on the corresponding opinions of the English, German and Irish courts).

*Bonus effect*

4.24. One of Glaxo's key arguments in favour of the patent's inventive step is that the patented invention contains a synergistic and therefore surprising effect due to the mutual interaction between the two components salmeterol and FP. This surprising effect resulted in a pioneering innovation in asthma treatment according to Glaxo, which it is now referring to as the "golden standard" and which was to result in a resounding commercial success for Seretide, the combined application of the patent as placed on the market by Glaxo, currently Glaxo's best-selling medicine with sales amounting to billions of euros.

4.25. The District Court agrees with Sandoz that this is deemed a "bonus effect" under patent law that must be disregarded when assessing the inventive step, because it simply arises as soon as the average person skilled in the art follows Barnes' clear path and combines the teaching from the review article with SCRIP 1148. In the wording of, once again, the Guidelines, loc. cit. section *11.10.2 Unexpected technical effect; bonus effect*:

> An unexpected technical effect may be regarded as an indication of inventive step. However, if, having regard to the state of the art, it would already have been obvious for a skilled person to arrive at something falling within the terms of a claim, for example due to a lack of alternatives thereby creating a "one-way street" situation, the unexpected effect is merely a bonus effect which does not confer inventiveness on the claimed subject-matter (see T 231/97, not published in OJ and T 192/82, OJ 9/1984, 415).

4.26. In addition, despite Glaxo's assertions in this respect, the patent specification does not disclose anything substantively relevant about this synergistic effect. It simply does not describe this effect. Glaxo wants to base this on the notions from the description on p. 2 of EP 951 that are too vague in the District Court's opinion, to be discussed below, and invokes the taxol judgment of this District Court (LJN: BB2074) in substantiation of its argument.

4.27. This invocation is not successful. A striking difference is that in that case an expected favourable effect (of taxol to prevent restenosis) was justified on the basis of everything *disclosed in the patent specification* about the *in vitro* CAM assay. There is no such basis in the present description. Glaxo is stretching the doctrine from the taxol case law much too far and outside of context by hypothesising that the excerpt *particularly compatible and complementary in their activity and thus highly effective in the treatment of asthma and other respiratory disorders* can serve as a parallel of said CAM assay basis in order to say now that the synergistic effects "follow naturally" from this due to the combined application of salmeterol and FP. In the District Court's opinion, the aforementioned notions, which were not further elaborated or substantiated by means of examples, are nothing more than platitudes. Glaxo's reasoning would open the door wide for "patents arising from wishful thinking", for which the applicant of a patent could confine himself to advancing unsubstantiated characterisations such as *highly effective, significant improvement* and *particularly compatible and complementary in their activity and thus highly effective* in order to be able to link a surprising effect to them to be discovered at a later stage. By basing the synergistic effects that were not found until long after the priority and granting dates (in 2003) on these vague excerpts, Glaxo avails itself of a line of reasoning that takes the colour it wishes only with the hindsight knowledge of proven synergy of the invention's combination - hindsight reasoning in the District Court's opinion, which cannot be accepted. This also does not correspond to the TBA precedents with regard to taking into account a further substantiation of effects *already described*, as rightly argued by Sandoz. If Glaxo had disclosed these surprising effects that were apparently not "discovered" until later by describing them in the description and/or the examples so that they could be reproduced, Glaxo could be right with its claims from a patent-law perspective. In the District Court's opinion, however, that is not the case here. In other words, the sufficiently substantiated and described effects of the combination - remedy salbuterol's short duration of action - do not sufficiently relate to the effects discovered later in order for them to "follow naturally" from the effects found earlier, as correctly formulated by Sandoz in its oral arguments.

4.28. Incidentally, this reproducible explanation of the benefits in a patent or patent application is entirely different from the English pre-*Angiotech* inventive step test, which was stopped by Lord Hoffmann in the House of Lords' decision in that case, in which the old test *seemed* to result in a refusal to take a new product's surprising, favourable characteristics into account in the assessment of inventive step if those characteristics were not fully included in the application and were not supported by proof based on tests. Phrased differently: merely applying the obvious-to-try test without considering whether there was "a reasonable expectation of success", as pithily worded by Glaxo in its oral arguments. Glaxo's assertion that there was no reasonable expectation of success is not appreciated by the District Court in light of Barnes in combination with SCRIP 1148 and is therefore dismissed, as indicated above.

4.29. Sandoz rightly commented in respect of these assertions that Glaxo had not submitted anything about these synergistic benefits in the English proceedings at the time. If this is the quintessence of the invention, as it currently would have us believe, it would have been logical

that the necessary attention had been paid to this in the relevant - extremely thorough - fact-finding instance before the High Court ("trial").

4.30. Glaxo's assertion that - as the District Court understands its argument - the surprising effects do not need to be described at all because they are inherent in the claimed combination, which simply has those effects, is also disregarded. Sandoz rightly argues that this does not make sense in this case from a patent-law perspective, because effects that are not discovered and not described, but that do in fact exist (as it turns out later), do not contribute to the prior art on the priority date.

*Preliminary conclusion: not inventive based on Barnes and SCRIP 1148*

4.31. In principle, Barnes in combination with SCRIP 1148 thus deprives the patent of inventive step. This could only be different if there was a *prejudice* against the use of such a combination preparation (and a treatment with a combination inhaler). In the District Court's opinion, this is not the case, because of the following.

*No prejudice*

4.32. Firstly, Glaxo does not explicitly put forward the defence that such a prejudice exists, as rightly indicated by Sandoz. And that is actually already the end of the matter.

4.33. Everything it does put forward in its argument in this respect ("concerns" or "negative pointers" the person skilled in the art allegedly has) also cannot objectively qualify as a prejudice[10] that would prevent the average person skilled in the art from making the combination suggested by Barnes. The District Court dismisses Glaxo's argument that the alleged "negative pointers" to a combination inhaler with a β2-agonist and a topical corticosteroid in general, and salmeterol and FP in particular, would still not make it obvious to follow the clear instructions in Barnes. Sandoz rightly asserts that accepting this approach of inventive step would render the strict requirements for assuming a technical prejudice illusory; in this light, this results in a negative extended scope of application.

4.34. In the District Court's opinion, Sandoz correctly characterises this line of reasoning by Glaxo as follows: if, in addition to "positive pointers" (use of a combination inhaler, regular use of both β2-agonists and corticosteroids), there are also publications that point in a different direction (disadvantages of combination inhalers and of regular use of the two aforementioned components), the person skilled in the art would, on balance, not receive a "general pointer" or "general indication pointing in the right direction", so that following "positive pointers" despite these negative pointers would be inventive. The assessment of inventive step is not a sum of positive and negative indications. This is only relevant for the issue of inventive step if these negative pointers put forward by Glaxo can qualify as technical prejudices, and that is not the case. That would be different if the teaching is evidently technically defective, but this has not been sufficiently substantiated by Glaxo in light of Sandoz' substantiated objections.[11]Conse-

[10] Case Law, op. cit., pp. 214-216: strict requirements apply in this respect: it must pertain to an "opinion or preconceived idea widely held or universally held by experts in that field", "their unanimous experience and notions".
[11] Case Law, op. cit. p. 167, referring to T 211/01: a document which is so obviously defective as to be readily recognized as such by those skilled in the art when trying to reproduce its disclosure cannot be taken as the most promising and appropriate starting point for the assessment of inventive step.

quently, in Sandoz' wording in its oral arguments, there is nothing inventive in following a "positive" pointer, even if the prior art contains objections or concerns in this respect or pointers pointing in another direction, at least as long as there is no prejudice.

4.35. This is no different if different pointers to different solutions to a problem can be found in the prior art, so that the person skilled in the art can and must choose. Choosing one of the alternatives does not constitute inventive step, unless a prejudice is overcome. Glaxo bases its assertion to the contrary on the Court of Appeal's decision in the Sahajanand/Angiotech case (LJN: BI9993), but the District Court holds that this cannot be deduced from the decision. A striking difference in that case is that the prior art did not give an explicit pointer to taxol in the event of restenosis. In view of Barnes, that equivalency definitely falls short here. Apart from that, Sandoz rightly noted that the Court of Appeal had not formulated the rule in this matter that a negative pointer can be deducted from a "clear indication pointing in the right direction" in order to see whether a "general pointer" remains, as argued by Glaxo.

*Aversion to combination inhalers?*

4.36. The aversion allegedly consists of not being able to vary the dosage due to the fixed combination of the two active ingredients. Sandoz convincingly indicated that a multitude of other publications from the prior art precisely point out the benefits of a combination inhaler, particularly that the masking effect produced by bronchodilators, resulting in undertreatment because patient compliance with regard to taking corticosteroids combating the underlying inflammation is reduced. Glaxo's assertion in the rejoinder that there was no disposition, let alone a preference, for such a combination on the priority date, is thus factually untenable. There was no general aversion, let alone a prejudice.

*Is regular use of corticosteroids a sensitive issue?*

4.37. Glaxo asserted that the regular use of corticosteroids was "controversial" on the priority date and not preferred by everyone at the time. Although the fact that the pharmaceutical precept advises against regular use is a reason for concern, the problem at issue here - that no regulation is possible for regular use - is not solved in the patent, either. It may be true that there were concerns about side effects of these medicines, but Barnes, for example, shows that the application of topical corticosteroids was clearly preferred in the field for treating the underlying inflammation of the bronchial tubes. Other publications dating from before the priority date also demonstrate this. Again, Glaxo failed to convincingly substantiate that there was general aversion, let alone a prejudice.

*Does regular use of β2-agonists cause problems?*

4.38. Glaxo put forward that the obviousness of the salmeterol component relating to that use of β-agonists for non-symptomatic but regular use is controversial, which Sandoz disputed. According to Sandoz, there was at most some concern about the high dosages in the event of monotherapy with β-agonists. Said use is allegedly controversial because it only fights symptoms (tightness of the chest due to bronchial spasms) and not the underlying cause (inflammation of the bronchial tubes), but in the combination therapy with corticosteroids, which also combats the underlying inflammation, this is precisely not the case, so that this argument is not deemed valid by the District Court. In addition, it was adequately argued and substantiated on Sandoz' behalf that Ventolin of Glaxo itself (with salbuterol as the only active ingredient) was

also explicitly prescribed for prophylactic, so regular use in 1988/1989. This is not only evidenced by the Ventolin data sheet submitted, but also, for example, by the *Rote Liste* ("Dauertherapie"). Glaxo's Ventide, as already stated a combination of salbuterol and BDP, was also prescribed for regular use on the priority date. The concerns raised by the party experts on Glaxo's behalf in relation to the masking effect of the regular use of the agonists referred to here (masking of symptoms, due to which the underlying inflammation is not treated), of tachyphylaxis (decreased responsiveness to these agonists in long-term use) and bronchial hyperactivity (a symptom of deteriorated asthma) may have been legitimate on the priority date, but they are not decisive when answering the question of inventive step, because it has been convincingly demonstrated that there was definitely no general concern, let alone prejudice, against the regular use of β2-agonists for bronchodilatation - quite the contrary.

*Is chemical incompatibility to be expected?*

4.39. According to Glaxo, the person skilled in the art was also prevented from applying the claimed combination on account of the chemical instability to be expected. This instability entails that FP's thioester group could react with the nucleophilic amino group of salmeterol, so that the average person skilled in the art would not expect this combination to have a sufficiently long stability for medicines such as the present ones.

4.40. This stability problem is not referred to in the description of the patent. This is the first indication that it did not play an important role on the priority date. It also was not an issue in the English trial phase with debates between experts that lasted for days.

4.41. In the field of medicine formulation, this District Court assumed earlier that theoretical reflections about possible stability or formulation problems will not frequently be decisive for the person skilled in the art. Should this person expect stability problems in the present case, the team would examine them by means of standard tests.[12] Should these problems then occur, the team would first try to solve them using standard formulation methods, such as a "stress test", in which artificial circumstances are created (e.g. increasing the temperature and humidity) to show in an accelerated process what happens to the combination in the event of long-term storage. The average person skilled in the art is expected to perform such routine tests and the results of those tests do not lead to inventive step (Case Law, op. cit., p. 178, "try and see"). It has been established that a stress test would not produce incompatibility.

4.42. The Court dismisses the argument that also combinations that pass a stress test could give rise to such concerns that testing the combination would nonetheless be abandoned, as argued by Glaxo.

*Preliminary conclusion about concerns: can be left unresolved*

4.43. Because none of the "concerns" raised by Glaxo lead to the opinion that a technical prejudice had to be overcome in a patent-law sense, these concerns or objections cannot lead to a different opinion on the inventive step. Al these "objections" were rejected by the Bundespatentgericht on similar grounds.

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[12]Undisputed is Sandoz' assertion that the professional discussion between the party experts about this subject is based on the assumption that FP and salmeterol are formulated in an acid or base solution, because only then can nucleophilic substitution take place, while this is a situation that virtually never occurs, as the combination of FP and salmeterol is not formulated in solution but in dry state.

*Conclusion*

4.44. The patent will be held invalid in its entirety due to lack of inventive step. Everything stated that is not part of claims 1, 5 and 6 does not constitute inventive subject matter in the form of dosage forms and ditto regimes.

4.45. As the patent has already been held invalid due to lack of inventive step, the District Court need not assess the non-enablement asserted.

4.46. Since a final judgment will be rendered in the main action, it is not necessary to rule on Sandoz' provisional claims, which were instituted under the condition that the main action would be delayed.

4.47. As the party ruled against, Glaxo will be ordered to pay the costs of the proceedings, estimated at € 450,000 in accordance with the agreement made between the parties in this respect, which order will be immediately enforceable.

4.48. The District Court sees no reason to allow Glaxo to produce the evidence offered. The opinion about the patent's inventive step that is implicit in the findings is of a legal nature and, in essence, does not subscribe to the alternative approach suggested on Glaxo's behalf for the assessment of inventive step, which is incorrect in the District Court's opinion. The (extensive) offers of proof boil down to the wish to hear the party experts presented on its behalf as witnesses. It is unclear how this could lead to a different assessment of the relevant facts in the present matter. The offers of proof will be rejected as irrelevant.

**5. The decision**

The District Court:

5.1. revokes the Dutch part of EP 0 416 951;

5.2. declares null and void the Supplementary Protection Certificate with number 990012;

5.3. orders Glaxo to pay the costs of these proceedings, estimated until this decision at € 450,000 on the part of Sandoz;

5.4. declares that this judgment is immediately enforceable until here;

5.5. dismisses any additional or different claims.

This judgment was rendered by *mr*. G.R.B. van Peursem, *mr.* E.F. Brinkman and *mr.* P.H. Blok, and pronounced in public on 26 January 2011.

[signed] [signed]

[stamp: The Hague District Court] [Issued as a true copy

26 January 2011
The Court Clerk]

[signed]