**BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS**

**BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE**

**CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS**

**Internal distribution code:**
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

# D E C I S I O N
## of 15 December 2004

**Case Number:** T 0885/02 - 3.3.1

**Application Number:** 99303151.7

**Publication Number:** 0970955

**IPC:** C07D 405/12

**Language of the proceedings:** EN

**Title of invention:**
Paroxetine methanesulfonate

**Patentee:**
SMITHKLINE BEECHAM PLC

**Opponent:**
Synthon B.V.

**Interveners:**
(1) CHIESI S.A.
(2) A.C.R.A.F.S.p.A.

**Headword:**
Paroxetine methanesulfonate/SMITHKLINE BEECHAM

**Relevant legal provisions:**
EPC Art. 23(3), 54(3)(4), 105, 114(2), 115(1), 123(2), 158(1)(2)

**Keyword:**
"Main request: novelty (no) - crystalline form claimed not distinguishable from the crystalline form disclosed in the prior art - enabling disclosure of the prior art (yes)"
"First and second auxiliary request: amendment - supported by the application as filed (no)"

**Decisions cited:**
G 0002/88, T 0396/89, T 0441/90, T 0793/93, T 1208/97

**Catchword:**
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0885/02 - 3.3.1

# D E C I S I O N
## of the Technical Board of Appeal 3.3.1
## of 15 December 2004

**Appellant:** (Opponent)
Synthon B.V.
Microweg 22
NL-6545 CM Nijmegen (NL)

**Representative:**
Duxbury, Stephen
Arnold & Siedsma
Sweelinckplein 1
NL-2517 GK Den Haag (NL)

**Intervener 1:**
CHIESI S.A.
11, avenue Dubonnet
F-92400 Courbevoie (FR)

**Representative:**
Kédinger, Jean-Paul
Cabinet Malemont
42, avenue du Président Wilson
F-75116 Paris (FR)

**Intervener 2:**
A.C.R.A.F.S.p.A.
Via Amelia 70
I-Rome (IT)

**Representative:**
Marchi, Massimo, Dr.
Marchi & Partners,
Via Pirelli, 19
I-20124 Milano (IT)

**Respondent:** SMITHKLINE BEECHAM PLC
(Proprietor of the patent) New Horizons Court
Brentford,
Middlesex TW8 9EP (GB)

**Representative:** -

**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 28 June 2002 rejecting the opposition filed against European patent No. 0970955 pursuant to Article 102(2) EPC.**

**Composition of the Board:**

**Chairman:** A. J. Nuss
**Members:** P. F. Ranguis
J. H. Van Moer

## Summary of Facts and Submissions

I. This appeal lies from the decision of the Opposition Division rejecting the opposition filed against the European patent No. 970 955 (European patent application No. 99 303 151.7) pursuant to Article 102(2) EPC.

II. The European patent was filed before the European Patent Office on 23 April 1999, claiming the priority of three British applications, i.e.

(a) GB 98 14 316 filed on 2 July 1998
(b) GB 98 21 732 filed on 6 October 1998
(c) GB 99 02 935 filed on 10 February 1999

III. The European patent comprised in the granted form nineteen claims. Independent Claim 1 read as follows:

"1. Paroxetine methane sulfonate in crystalline form having *inter alia* the following characteristic IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 ± 4 $cm^{-1}$.; and/or the following characteristic XRD peaks: 8.3, 10.5, 15.6, 16.3, 17.7, 18.2, 19.8, 20.4, 21.5, 22.0, 22.4, 23.8, 24.4, 25.0, 25.3, 25.8, 26.6, 30.0, 30.2, and 31.6 ± 0.2 degrees 2 theta."

IV. Notice of opposition had been filed by the Appellant (Opponent), requesting revocation of the patent in suit in its entirety on the ground of lack of novelty in view of document

(1) WO-A-98/56787

The following documents were cited by the parties before the Opposition Division in support of their submissions:

(2) Pharma Patent Bulletin, February 2000, vol. 3, No.1

(3) Overview of patents and patent applications for paroxetine methanesulfonate filed by SmithKlineBeecham

(4) X-Ray powder diffractogram of paroxetine methanesulfonate submitted by the Appellant

(5) List of peaks derived from document (4) submitted by the Appellant

(6) GB 98 14 316, first priority document of the patent in suit filed on 2 July 1998

(7) GB 98 21 732, second priority document of the patent in suit filed on 6 October 1998

(8) GB 99 02 935, third priority document of the patent in suit filed on 10 February 1999

(9) EP-B-0 970 955 (i.e. patent in suit)

(10) Declaration of I. R. Lynch dated 3 March 2000

(11) WO-A-00/01694 (international patent application from which EP-B-0 970 955 (9) is derived)

(12) US-A- 5 874 447 (US patent corresponding to document (1))

(13) Communication according to Rule 51(4) EPC from examining procedure concerning document (1) in the regional phase before EPO

(14) Infrared spectrum submitted by the Appellant

(15) to (18) Infrared spectra of paroxetine methanesulfonate obtained by J. H. Van der Maas submitted by the Appellant

(19) Table of infrared spectra (15) to (18)

(20) WO-A-96/24 595

(21) Declaration of J. H. Van der Maas dated 31 August 2000

(22) Declaration of T. H. A. Peters dated 3 July 2000

(23) Nl-B-1 012 271. Dutch counter-part of document (9)

(24) US-A- 4 007 196

(25) Declaration of E. de Rooij (Financial director of Synthon) dated 26 April 2000

(26) EP-B-0 223 403

(27) EP-A- 1 020 464 (divisional application of document (9))

(28) EP-A- 1 020 463 (divisional application of document (9))

(29) Decision of the District Court of The Hague dated 29 June 2001 on the infringement injunction

(30) Decision (in Dutch language) of the Court of Appeal of The Hague dated 17 January 2002 on the infringement injunction (English version submitted during appeal proceedings as document (52))

(31) Pharmaceutical Research, vol. 12, 1995, pages 945-954

(32) Statement of W. J. Genck dated 12 February 2002

(33) Declaration of M. T. Crimmins dated 17 January 2001

(34) Declaration of M. T. Crimmins dated 24 April 2002

(35) Statement of T. M. Niemczyk dated 27 March 2001

(36) Statement of J. Bernstein dated 27 March 2001

(37) Accounts of chemical research, Vol.28, No. 4, 1995, 193-200

(38) Angew. Chem. Int. Ed. 1999, 38, 3440-3461

(39) Infrared spectrum of Example 2 of the patent in suit provided by the Respondent with letter of 23 October 2001

(40) Exhibits from proceedings in the Netherlands relating to documents (14) to (18) submitted by the Respondent

(41) X-ray powder diffraction pattern simulation submitted by the Respondent

(42) Declaration of J. H. Van der Maas relating to the infrared spectra (15) and (16), (17), (18) dated 13 November 2000

(43) GB priority applications in the name of SmithKline Beecham in relation with salts of paroxetine.

V. The Opposition Division held that the Opponent had not provided factual evidence that the infrared spectrum (14) was the original spectrum of the compound of Example 1 of document (1). Neither was it proved that the X-Ray powder diffraction pattern (4) was obtained from a compound made according to Example 1 of document (1). Likewise it was not proved that the infrared spectrum (15) was obtained from a compound made according to Example 1 of document (1). In view of the documents (4), (14) and (15), the Opposition Division did not accept that the paroxetine methanesulfonate form disclosed in document (1) was the same as in the opposed patent.

As to the documents (33), (34) and (35), none of them could further clarify the discrepancies between the incomplete list of infrared spectra peaks disclosed in document (1) and the claimed subject-matter according to Claim 1.

VI. With the statement of grounds of appeal the Appellant submitted the following documents:

(44) Statement of J. H. Van der Maas with attached exhibits 1 to 24 dated 3 August 2001

(45) Witness statement of I. R. Lynch made before the Danish Court dated 22 August 2001

(46) Declaration of F. Benneker dated 12 June 2001

(47) US Pharmacopeia USP 24/NF19 of 1 January 2000

(48) Transcript of UK cross-examination

(49) Statement of E. Vlieg dated 12 April 2002

(50) Letter of R. Gelder dated 19 December 2001

(51) Experimental report of B. L. Feringa and R. Ebens dated 11 June 2001

(52) English translation of document (30)

(53) Time line of experiments carried out by F. Benneker.

VII. With a letter received on 28 March 2003, a third party filed observations pursuant to Article 115(1) EPC.

VIII. With the response received on 31 July 2003, the Respondent (Proprietor of the patent) submitted the following documents:

(54) Closing submissions of SmithKline Beecham plc before the UK High Court of Justice

(55) Judgment of the UK High Court of Justice dated 3 December 2002, revised and reissued 9 December 2002

(56) SmithKline Beecham's skeleton argument before the UK Court of Appeal

(57) Judgment of the UK Supreme Court of Judicature Court of Appeal dated 25 June 2003

(58) English translation of SmithKline Beecham's pleading notes before District Court of the Hague (Hearing of 22 November 2002)

(59) English translation of the Judgment of the District Court of the Hague dated 27 February 2003

(60) English translation of SmithKline Beecham's statement of grounds of appeal before the Dutch Appeal Court dated 19 June 2003

(61) Statement of P. M. Inman dated 7 November 2002 together with exhibits PMI 1 to PMI 4, PMI 6 and PMI 7

(62) Statement of N. Ward dated 8 November 2002

(63) Expert report of T. M. Niemczyk dated 13 August 2002 together with exhibit TMN.2

(64) Expert report of T. M. Niemczyk dated 24 September 2002 together with exhibit TMN.4

(65) Expert report of J. Bernstein dated 19 August 2002

(66) Expert report of J. Bernstein dated 24 September 2002 together with exhibit JB.4

(67) Expert report of N. Ward dated 21 August 2002

(68) Expert report of N. Ward dated 25 September 2002 together with exhibits NW. 6, NW.7 and NW.9

(69) Witness statement of V. Jacewicz dated 19 August 2002 together with exhibits VJ.1 and VJ.2

(70) Witness statement of V. Jacewicz dated 20 September 2002 together with exhibits VJ.3 and VJ.4

(71) Declaration of E. Shapiro dated 31 July 2001 together with exhibit ES1

(72) Statement of L. R. Nassimbeni dated 1 August 2001

(73) Expert report of J. E. Baldwin dated 27 August 2002 together with exhibit JEB.4

(74) Expert report of J. E. Baldwin dated 23 September 2002

(75) Witness statement of R. M. Adlington dated 23 August 2002 together with exhibits RMA.2, RMA.4, RMA.5, RMA.6, RMA.8 and RMA.9

(76) Witness statement of R. M. Adlington dated 21 September 2002

(77) Witness statement of F. B. Benneker dated 23 August 2002

(78) Laboratory Notebooks pages of R. Ebens introduced into Danish Court Proceedings

(79) English translation of the transcript of the Court records for the Copenhagen City Court, 20 August through 24 August 2001.

IX. With a letter received on 21 October 2003, Intervener 1 (Chiesi S.A.) intervened into the appeal proceedings pursuant to Article 105 EPC. Against novelty or inventive step of the patent in suit the following documents were cited:

(109) Journal of Pharmaceutical Sciences, January 1997, Vol. 66. No. 1

(110) WO-A- 95 16448.

X. With a letter received on 13 January 2004, the same third party (cf. point VII above) submitted further observations.

XI. In response to the submissions of the Respondent, the Appellant submitted with a letter received on 2 February 2004 the following documents:

(80) Opinion of S. Thorley Q.C. dated 16 January 2004.

(81) Petition by Synthon B.V In the House of Lords on Appeal from Her Majesty's Court of Appeal (England)

(82) Judicial Office House of Lords. Decision on leave to appeal dated 21 January 2004

(83) Letter of S. Thorley Q.C. dated 29 January 2004

(84) Submissions of Synthon B.V before the Court of Appeal of the Hague, Session of 20 November 2003

(85) Declaration of B. L. Feringa dated 11 October 2001

(86) Declaration of E. W. Meijer dated 19 July 2001

(87) Expert report of J. H. Van der Maas dated 23 August 2002

(88) GB-A- 2 297 550

(89) Declaration of P. Janning dated 8 April 2003

(90) Letter of instructions of Synthon B.V to H. Waldmann dated 31 January 2003 (P. Janning is the associate of H. Waldmann)

(91) Declaration of R. Ebens dated 8 November 2001

(92) Declaration of E. W. Meijer dated 5 October 2001

(93) Vogel's, Textbook of Practical Organic Chemistry, fifth edition, pages 141-142, 1989

(94) Methoden der organischen Chemie, Band I/1, allgemeine Laboratoriumspraxis I, pages 355-359, 1958

(95) Laboratory Technique in Organic Chemistry, pages 104-105, 1960

(96) Declaration of G. van Koten dated November 8, 2001 in Dutch with English translation.

XII. With a communication dated 24 March 2004 accompanying the summons to oral proceedings scheduled on 14 and 15 December 2004, the Board informed the parties that novelty of the claimed subject-matter of the patent in suit would be discussed in view of the content of the disclosure of document (1).

XIII. With a letter received on 28 April 2004, the same third party (cf. point VII above) submitted further observations.

XIV. With a letter received on 13 May 2004, Intervener 2 (A.C.R.A.F.S.p.A.) intervened in the appeal proceedings pursuant to Article 105 EPC on the ground that the patent in suit lacked novelty and/or inventive step.

XV. In a further letter received on 1 October 2004, the Respondent submitted as first auxiliary request a set of two claims and as second auxiliary request a single claim. Both auxiliary requests had the same Claim 1 which read:

"1. Paroxetine methanesulfonate in crystalline form having the following characteristic IR peaks: 1603,

1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 $cm^{-1}$.; and the following characteristic XRD peaks: 8.3, 10.5, 15.6, 16.3, 17.7, 18.2, 19.8, 20.4, 21.5, 22.0, 22.4, 23.8, 24.4, 25.0, 25.3, 25.8, 26.6, 30.0, 30.2, and 31.6 degrees 2 theta."

Several documents were also submitted:

(97) Declaration of T. H. A. Peters dated 18 October 2000

(98) Statement of T. M. Niemczyk dated 2 November 2001

(99) Affidavit of N. Ward dated 26 January 2003

(100) Correspondence between Patentee and Appellant relating to Christmann's experiments

(101) Laboratory notebook of P. Janning from 3 February to 4 April 2003

(102) Transcription of the Laboratory notebook of P. Janning

(103) Pull-out table of P. Janning's repeat of "Experimental" section of document (1)

(104) Pull out table of Christmann's repeat of "Experimental" section of document (1)

(105) Affidavit of G. P. Stahly dated 26 January 2004

(106) Extracts of the deposition of J. E. Baldwin before the Board of Patent Appeals and Interferences of the USPTO dated 30 October 2003

(107) Declaration of V. Jacewicz dated 1 August 2001 together with exhibits VJ.1 and VJ.2

(108) Declaration of V. Jacewicz dated 16 November 2001.

XVI. With a letter received on 10 November 2004, the Intervener 1 submitted without comment document

(111) Expert report of B. Legendre dated 5 July 2004

XVII. With a letter received on 11 November 2004, the intervener 2 submitted a further argumentation supported by documents

(112) National Journal of Pharmaceutical, 42 (1988), 135 to 143

(113) US-A- 5 276 042.

XVIII. With a letter received on 13 November 2004, the Appellant submitted the following documents:

(114) Expert opinion of J. F. Cierco dated 30 December 2003 together with an English translation

(115) Statement of R. M. Adlington dated 12 November 2004 together with Annexes 1 and 2

(116) Letter of M. Christmann dated 12 November 2004

(117) Laboratory Technique in Organic Chemistry, pages 104 to 106, 1960

(118) Practical Organic Chemistry, pages 129-130, not dated

(119) Experimental Organic Chemistry, pages 127 to 132, 1989

(120) Declaration of E. W. Meijer dated 12 November 2004

(121) Decision of the Board of Appeals and Interferences of the United States Patent Office dated 16 September 2003

(122) Decision of the Board of Appeals and Interferences of the United States Patent Office dated 25 May 2004

(123) Polymorphisms in Molecular Crystals by J. Bernstein, 2002.

XIX. With a letter received on 3 December 2004, the Respondent requested that the documents (111) to (123) be disregarded as late filed.

XX. Oral proceedings took place on 14 and 15 December 2004.

XXI. The arguments of the Appellant submitted in the course of the written proceedings and during the oral proceedings may be summarized as follows:

The Appellant argued that a comparison of limited numbers of IR peaks in both document (1) and Claim 1 did not justify any conclusion as to the existence of polymorphism. A skilled person would never have drawn any conclusions from a comparison of such two IR peaks lists but would have compared full spectra instead. Furthermore, none of the lists contained any indication of the peak intensity. The limited number of IR peaks did not form a sufficient basis for any relevant conclusion. There was no evidence whatsoever that the Appellant had ever made any other crystal form of paroxetine methanesulfonate than that claimed in the patent in suit.

Document (32) showed that after thousands of experiments to induce the formation of different crystal structures of paroxetine methanesulfonate the same crystal structure was obtained which proved that paroxetine methanesulfonate only existed in one crystalline form which automatically meant that the paroxetine methanesulfonate disclosed in document (1) was novelty destroying for the patent in suit.

Furthermore, this conclusion was also clear from the fact that the general and specific processes disclosed in either did not include any specific conditions intended to obtain any specific crystal form of paroxetine methanesulfonate such as prescribing the use of a specific solvent for (re)crystallisation (cf. paragraphs [0011]-[0039] of the patent in suit).

In spite of this opposition and numerous court proceedings having been conducted for a number of years on this issue, the Respondent had not produced a thread

of evidence for the existence of another form of crystalline paroxetine methanesulfonate. The Respondent had only referred to solvates of paroxetine methanesulfonate which however were not relevant as they were not and could not be polymorphs because solvates as compared to the anhydrates did not fulfill the basic requirement for polymorphs, i.e. to have the *same chemical composition*.

The NMR data of Table 1 clearly showed that the paroxetine methanesulfonate referred to in document (1) was not a solvate (no peaks relating to the solvent). The same conclusions could be drawn from the DSC curve.

By comparing the preparation methods in document (1) and in the patent in suit and especially those in "Experimental" section and "Example 1" in document (1) and those in paragraphs [0009] up to and including [0032] and in a large number of Examples in the patent in suit, especially in Examples 13 and 15 in which ethanol and ethyl acetate were used as solvents, the skilled reader would have found that these methods overlapped and he would have found that there was no reason to assume that these methods would have led to a different result. Polymorphs required very specific preparation methods.

The use of a particular solvent such as ethyl acetate did not have any effect on the resulting crystalline form.

The arguments of the third party regarding the solubilities of paroxetine methanesulfonate, paroxetine acetate and paroxetine maleate in document (1) and the

patent in suit were irrelevant. The conditions were not identical in both documents.

Regarding the implicit disclosure issue, the decisions T 793/93, T 396/89 and T 441/90 were not relevant as relating to different situations where the final products were not disclosed.

Furthermore, documents (33), (34), (51), (73) to (75), and (89) showed that reworking of the "Experimental" section in document (1) had always resulted in crystalline paroxetine methanesulfonate. Clear evidence that the experiments were carried out in an unseeded laboratory was that the crystallisation in seeded environment occurred more or less in a matter of minutes.

Regarding the declarations (73) to (75), the failure due to water presence showed simply that the experiments were not carried out in conformity with the instructions in document (1) to evaporate to dryness. It was true that Experiment A disclosed in document (102) did not lead to a crystal yet. However, crystallization being controlled by the statistical law of Boltzmann, that process required, therefore, sometimes more and sometimes less time.

Document (32) confirmed that whatever conditions were applied one would always obtain the same crystalline form of paroxetine methanesulfonate.

Documents (69) to (72) could not be taken into account in view of the declarations set out in documents (92)

and (96) and (34) showing that too much solvent or impurities were left in the oil.

The third party did not give any details on how its experiments were performed. The third party observations lacked factual basis and did not provide any evidence of the existence of more than one form of crystalline paroxetine methanesulfonate.

The subject-matter of Claim 1 of the first and second auxiliary requests extended beyond the content of the application as originally filed and violated the provisions of Article 123(2) EPC.

XXII. The arguments of the Respondent submitted in the course of the written proceedings and during the oral proceedings may be summarized as follows:

The case essentially concerned the issue of novelty and determining what was made available to the public in the disclosure of document (1), when understood by the skilled person. The claimed subject-matter was neither explicitly, nor implicitly disclosed by document (1).

The IR peak listing in Table I of document (1) could not be reconciled with the IR data referred in Claim 1 of the patent in suit. In his declaration Van der Maas expressed his reluctance to compare peak lists at all (cf. document (87), paragraph 41). There was, therefore, no explicit disclosure of the claimed subject-matter. Furthermore, the XRD data relied upon by the Appellant was not part of the disclosure of document (1) and therefore no valid comparison could be made.

The processes disclosed in the patent in suit were not identical to the process of document (1). The examples of the patent in suit disclosed technical information to obtain the claimed crystal which was not the case of document (1).

Nor was the claimed subject-matter implicitly disclosed in the sense that in carrying out the teaching of document (1), the skilled person would inevitably arrive at a result falling within the terms of Claim 1.

Documents (32) to (34) did not follow the instructions disclosed in the "Experimental" section of document (1). Neither did the experiments of R. Ebens disclosed in document (78). Those results would have been, in addition, the consequence of seeding.

The evidence provided by documents (71) and (72) showed that a reworking of the "Experimental" section could not yield a crystal of paroxetine methanesulfonate even when going beyond the explicit disclosure of document (1).

This was confirmed by the experiments of J. E. Baldwin and R. M. Adlington (cf. documents (73) to (76)) which were intended to be repeats of the "Experimental" section of the document (1), i.e. experiments numbered "RMA.06" and "RMA.07", repeated under observations of the Respondent under the numbers "RMA.08" and "RMA.09". It became eventually apparent that a very large number and a variety of steps had been taken in response to the simple information in the "Experimental" section to leave to stand at room temperature for one month. It was manifest that the efforts to induce crystallisation

went well beyond what could have been expected from the skilled person.

Furthermore, if as alleged by J. E. Baldwin, the difficulty of crystallisation was due to water, that realisation, after having devised the theory that methanesulfonic acid induced the condensation of two moles of ethanol to produce ether and water, went well beyond what could have been expected from a person skilled in the art.

The experiments conducted by J. E. Baldwin demonstrated that following the "Experimental" section in document (1) did not inevitably lead to a crystalline product. Because the seeding crystal was required for use in the subsequent experiment, namely Example 1, this inability to produce those seeding crystals meant that the paroxetine methanesulfonate of Example No. 1 could not be prepared.

Regarding the experiments of P. Janning in (89) and (102), they were not conducted using exactly the conditions as described in the "Experimental" section. They went beyond what a skilled person would have done during a routine attempt to make crystalline paroxetine methanesulfonate.

Regarding M. Christmann's experiments (104), these experiments were interrupted after six weeks without crystallisation.

The third party observations confirmed the non inevitability of the result of "Experimental" section and Example 1.

Even if the skilled person were to turn to the generality of document (1), there was also no inevitability that:

(1) the skilled person would even make paroxetine methanesulfonate having regard to the wide generic disclosure of the compounds of the invention,

(2) the material would be crystalline since oils and non-crystalline forms are also embraced or that even if it was crystalline, then:

(3) the material would be in the same crystal form as that claimed in the patent in suit.

As regards this last aspect, solvates were specifically described in document (1), which were different crystal forms to the form as claimed.

In summary, crystalline paroxetine methanesulfonate was by no means the inevitable result of following document (1). Even if a crystalline product was obtained, it certainly was not inevitably the particular crystal form claimed in the patent in suit.

It was not disputed that paroxetine methanesulfonate could exist in different crystalline forms such as solvates, hydrates and polymorphs. Therefore, the issue could not be to decide whether the teaching of the document (1) enabled the production of crystalline paroxetine methanesulfonate.

The observations of the third party regarding the solubility of the various salts of paroxetine methanesulfonate in both the document (1) and the patent in suit were incorrect. There were considerable differences in the experimental conditions used in each pair of experiments (cf. point XXV below).

The subject-matter of Claim 1 of the first and second auxiliary requests found support in Example 1 of the application as originally filed and did not violate the provisions of Article 123(2) EPC.

XXIII. The arguments of the Intervener 1 submitted in the course of the written proceedings and during the oral proceedings may be summarized as follows:

Document (1) disclosed crystalline paroxetine methanesulfonate as set out in "Experimental" section and Example 1.

Claim 2 of the patent defined a process for preparing paroxetine methanesulfonate forming the subject-matter of Claim 1 and the features necessary to solve this problem which according to the wording of Claim 2 required "to crystallize or re-crystallize the compound from a solution of paroxetine methanesulfonate in a solvent". That meant that the nature of the solvent and the means and conditions of crystallisation were of no importance for obtaining the paroxetine methanesulfonate of Claim 1.

The process disclosed in document (1) was clearly the process of Claim 2 of the patent in suit, so that this

known process inevitably led to the paroxetine methanesulfonate of Claim 1.

XXIV. The arguments of the Intervener 2 submitted in the course of the written proceedings and during the oral proceedings may be summarized as follows:

In the granted Claim 1, the listed infrared and XRD peaks were irrelevant for distinguishing the crystalline paroxetine methanesulfonate claimed from that disclosed in document (1). In the examining proceedings, the patentee had acknowledged that paroxetine methanesulfonate could be advantageously formulated in view of its high solubility, low hygroscopicity and good stability in referring to Synthon application. No reference to infrared or XRD data was put forward. Since those features were to be disregarded as non distinguishing features, Claim 1 did not satisfy the novelty requirement pursuant to Article 54 EPC.

After six years nobody had proved that several forms of crystals for paroxetine methanesulfonate existed.

XXV. The arguments of the third party submitted in the course of the written proceedings may be summarized as follows:

In terms of solubilities, the paroxetine methanesulfonate of document (1) was more soluble than the paroxetine acetate and paroxetine maleate. The paroxetine methanesulfonate of the patent in suit was less soluble than the paroxetine acetate and paroxetine maleate. Whilst the experimental conditions in both

documents were not exactly identical, there was a clear difference of behaviour. The two crystalline forms of paroxetine methanesulfonates were not identical.

An attempt to prepare a sample of paroxetine methanesulfonate according to document (1) was unsuccessful yielding neither paroxetine methanesulfonate or any crystalline product.

XXVI. The Appellant requested that the decision under appeal be set aside and the patent be revoked.

The Respondent submitted the following requests:

Request 1: That the submissions by the Appellant by fax dated 13 November 2004, and the documents filed therewith, the submissions by the intervener 1 by fax dated 10 November 2004 and the document filed therewith and the submissions filed by the intervener 2 by fax dated 11 November 2004 and the documents filed therewith, be not admitted in these proceedings and/or disregarded.

Request 2: As request 1, save that the statements of Mr Adlington and Mr Christmann (responsive to material in the case) be admitted.

The Respondent further requested that the appeal be dismissed or, in the alternative, that the patent be maintained on the basis of the first or second auxiliary request filed with letter of 1 October 2004.

The interveners 1 and 2 requested that the decision under appeal be set aside and the patent be revoked.

XXVII. At the end of the oral proceedings the decision of the board was announced.

## Reasons for the Decision

1. The appeal is admissible.

2. *Article 105 EPC - Admissibility of the interventions*

Both intervening parties intervened in the proceedings pursuant to Article 105 EPC within three months of the date on which the infringement proceedings were instituted. Both notices of intervention were filed in a written reasoned statement and the required fees were paid in due time (opposition and appeal fees). Therefore, both interventions are admissible. This finding was neither contested by the Appellant nor by the Respondent.

3. *Article 54(3)(4) EPC - Novelty*

3.1 Document (1) corresponds to the international patent application WO-A-98/56787 filed on 10 June 1997, namely before the three priority applications of the contested European patent, i.e. documents (6), (7) and (8), and published on 17 December 1998. It is not contested that this document is state of the art according to Article 54(3)(4) EPC and Article 158(1),(2) EPC for all the designated States of the European patent except for CY.

3.2 In the present case, assessing novelty of the subject-matter of the patent in suit requires to determine the content of the disclosure of document (1) and to compare it with the claimed subject-matter. However, subject-matter described in a document can only be regarded as having been made available to the public, and therefore as comprised in the state of the art pursuant to Art. 54(1) EPC, if the information given therein to the skilled person is sufficient to enable him, at the relevant date of the document, to practise the technical teaching which is the subject of the document, taking into account also the general knowledge at that time in the field concerned.

3.3 In that context, what the inventors of document (1) or the patent in suit may or may not have done in the privacy of their laboratories is of no relevance whatsoever to what is disclosed by document (1) or the patent in suit. Under the EPC, assessing novelty according to Article 54 EPC is not tantamount to any first to invent issue. Therefore, the documents relating to the various information drawn from the notebooks of F. Bennecker, the infrared spectra from which the infrared peaks of the examples of the patent in suit and document (1) are said to be derived, the comparison between those spectra and the comments about them are disregarded, i.e. documents ((4), (5), (14), (15), (16), (17), (18), (19), (22), (39), (40), (41), (44), (46), (49), (50), (53), (77), (97) and (98).

Since it is well established jurisprudence under the EPC that novelty must be assessed in view of **one** prior art disclosure, the documents of the prior art which are not part of the common general knowledge must be

also disregarded, i.e. documents ((2), (3), (20), (23), (24), (26), (31), (37), (38), (43), (88), (109) and (110).

Documents (11), (12), (13), (25), (27), (28), (47), (76), (85), (86) and (106) are neither prior art nor experts' statements relevant to the novelty issue and are also disregarded.

Moreover, documents (29), (30), (52), (55), (57) and (59) relate to decisions of some national Courts. However, in proceedings before the instances of the EPO questions of patentability are to be decided solely in accordance with the EPC and the Board is not bound by any of these decisions (Article 23(3) EPC). If a party wants to take up arguments or facts from those decisions, it may of course do so. However, this must be made in an independent manner separated from the decisions themselves. For those reasons, the Board did not consider the above cited documents.

Documents (80), (81), (82) and (83) relating to the petition for leave to appeal to the House of Lords raise legal issues not relevant for deciding the present case and, therefore, are also disregarded.

Documents (54), (56), (58), (60) and (84) relate to submissions of the Respondent and the Appellant in the proceedings which led to the above cited national decisions. The Board could at best consider those submissions as arguments. However, it is constant jurisprudence of the Boards of Appeal that the arguments set forth by the appealing party in the statement of grounds of appeal must be clearly and

concisely presented to enable the Board and the other party or parties to the appeal proceedings to understand immediately why the appealing party regards the contested decision as incorrect (Case Law of the Boards of Appeal of the European Patent Office 4th edition 2001, VII. D. 7.5). The Board does not see any reasons not to apply this principle also to the other parties to the appeal proceedings thus also to the Respondent in the present case. The need to select in those submissions relating specifically to some national proceedings the arguments which might apply to one of the issues of the present appeal proceedings does not comply with the above principle. Either the arguments are the same as those used in the line of appeal argumentation and they are mere repetitions of no real use, or they are different and in that case, the parties failed to present them properly in the line of appeal argumentation. Under these circumstances, it is not a matter for the Board to sift through each of these documents and speculate about the possible relevance of parts thereof for one of the issues to be decided by the Board. The above cited documents are, therefore, also disregarded.

3.4 As pointed out above, the first step in assessing novelty in the present case requires to compare the content of the disclosure of document (1) with the claimed subject-matter.

3.4.1 The subject-matter of Claim 1 is related to a paroxetine methanesulfonate in crystalline form having *inter alia* the IR peaks and/or XRD peaks as defined in Claim 1 (cf. point III above).

3.4.2 Document (1) discloses in the section "Experimental" the preparation of a seeding crystal of paroxetine methanesulfonate. This seeding crystal was subsequently used in Examples 1 and 2 (cf. page 9, line 32 to page 10, line 18).

Example 1 describes the preparation of paroxetine methanesulfonate in the presence of the seeding crystal obtained according to the "Experimental" section (cf. page 10, line 24 to page 11, line 3). The obtained white solid was characterized, in particular, by the following list of infrared peaks (KBr, in $cm^{-1}$): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900 and 3023. (cf. Table I, page 14).

3.4.3 The first question to be answered is whether Example 1 of document (1) discloses unambiguously for a skilled reader paroxetine methanesulfonate in crystal form.

Since Example 1 describes the preparation of paroxetine methanesulfonate in the presence of a seeding crystal, it is unambiguously derivable from this disclosure that the white solid form obtained is in crystalline form. This was not contested by the Respondent. The Board observes that this is also reflected by the narrow melting point range of 142°-144°C of the paroxetine methanesulfonate obtained according to Example 1 (cf. page 14, Table I). A narrow melting range is indeed typical of relatively pure crystalline material as also pointed out by N. Ward in its declaration (cf. document (99), paragraph 66).

3.4.4 Given that paroxetine methanesulfonate in crystalline form is disclosed in document (1), the sole remaining question to be answered is whether the crystalline paroxetine methanesulfonate disclosed in document (1) anticipates the claimed subject-matter according to Claim 1 of the patent in suit.

The Respondent argued that paroxetine methanesulfonate could exist under several crystalline forms. In the patent in suit, besides the claimed crystalline form, a solvate of paroxetine methanesulfonate with acetonitrile in crystalline form was disclosed as comparative Example 26. The Respondent also submitted that solvates of paroxetine methanesulfonate with N-methyl pyrollidone and dimethyl formamide could exist (cf. document (66), Exhibit JB.4, document (68), NW. 9, document (70), Exhibits VJ.3 and VJ. 4 and document (108), point 9).

3.4.5 It is uncontested that crystal forms include solvates, including hydrates, and non-solvated forms, including anhydrates. Solvates or hydrates occur when solvent or water is incorporated into the crystalline structure of the compound.

However, the NMR peak list disclosed in Table 1 of document (1) does not reveal any peak(s) corresponding to any solvent, including water. Likewise, the DSC curve only reveals one peak, whereas, should a solvent have been present, a peak for the solvent would have come up. Furthermore, the Respondent did not submit any piece of evidence showing that a solvate of paroxetine methanesulfonate with ethylacetate, which is the solvent in which the reaction according to Example 1 of

document (1) is performed (cf. page 10, lines 30 to 36), could exist. There is no evidence pointing to a solvated crystalline form.

For the above reasons, the paroxetine methanesulfonate obtained according to the Example 1 is disclosed neither as a solvated, nor a hydrated crystalline form. No difference can be found in that respect with the claimed subject-matter.

3.4.6 The Respondent disputed however that the crystalline form of paroxetine methanesulfonate disclosed in document (1) anticipated the claimed subject-matter, whereas the Appellant and both interveners asserted the contrary. The parties have submitted several experts' declarations in that respect.

At this stage, as a preliminary remark, the Board observes that the content of the disclosure of a prior art is to be understood in the way it would be understood by a skilled reader, i.e. a notional "person skilled in the art" who is a person of ordinary skill aware of what is common general knowledge in the art at the relevant date.

The opinion of an expert does not necessarily reflect the view of the skilled reader for various reasons. The declarations are necessarily made after the filing date of the patent. Those experts who are in the present case eminent scientists have their own experience which is not necessarily common general knowledge. Furthermore, apart from a few exceptions, those declarations are not supported by references to textbooks so that the Board is not in a position to

easily distinguish between what is common general knowledge in the context of a particular declaration and what is not.

Those observations do not mean that those declarations are to be disregarded but rather that common general knowledge can be inferred from the contentions of the experts when they can be cross-checked with each other for consistency and when in the Board's judgment they can be considered in the absence of dispute as common general knowledge at the relevant date.

3.4.7 In that context, it is not denied that for a chemical compound different crystal forms having the same elemental composition but having different crystal packing arrangements may exist. Those forms are called polymorphs:

"Polymorphs exist when the drug substance crystallizes in different crystal packing arrangements all of which have the same elemental composition" (cf. W. J. Genck's statement (32), footnote 1).

"Polymorphs are different crystal forms of substances which are otherwise chemically identical" (cf. J. Bernstein's statement (36), point 2).

"Sometimes, materials can be chemically the same, but exist in different crystalline form. These are called polymorphs" (cf. expert report of T. M. Niemczyk (63), point 13).

"It is possible for crystals of the same chemical entity to occur in different structural forms, known as

"polymorphs" (cf. J. Van der Maas declaration (42), paragraph 4).

Therefore, the skilled reader in view of the content of the disclosure of document (1) would have concluded that the disclosed crystalline form of paroxetine methanesulfonate in document (1) was not necessarily within the claimed subject-matter since the existence of different polymorphs is not excluded.

Contrary to the Appellant's view, the more than 2400 experiments of W. J. Genck (32), which revealed only one crystalline form after having recrystallised paroxetine methanesulfonate in various solvents using a variety of techniques, cannot be relied upon, since the said experiments are not prior art and still less common general knowledge which disqualifies them from being taken into consideration for the novelty issue on the basis of document (1).

3.4.8 The Appellant argued that a comparison of limited numbers of IR peaks did not justify any conclusion as to the existence of polymorphism. A skilled person would never draw conclusions from a comparison of such two IR peaks lists but would compare full spectra instead.

The Respondent argued that the IR peak listing in Table I of document (1) could not be reconciled with the IR data referred to in Claim 1 of the patent in suit. There was, therefore, no explicit disclosure of the claimed subject-matter.

3.4.9 As stated by T. M. Niemczyk, "infrared spectroscopy is a technique which measures the frequencies of infrared light which are absorbed by a sample. The data are generally displayed as a **spectrum** (emphasis added by the Board) showing the degree to which the sample absorbs the infrared radiations over a range of frequencies generally expressed in wave numbers (having units of "$cm^{-1}$"). Spectra generally appear as a series of peaks (which can vary by height, shape and position). Infrared absorbance is affected by the nature and positioning of chemical bonds within a molecule, and, because these bonds differ in different materials, different materials absorb more or less strongly at different frequencies. As a result, different materials will have different characteristics spectra, and therefore infrared spectroscopy is used as a technique for distinguishing different materials" (cf. statement of T. M. Niemczyk (35), point 3).

3.4.10 The Board concurs with the Respondent that the infrared peak listing in Table I of document (1) could not be reconciled with the IR data referred in Claim 1 of the patent in suit. However, that does not mean that the two crystalline forms are therefore already different since the list of peaks is not limitative (cf. Claim 1: "having *inter alia*"*)*. Moreover the absence of a peak could even be due to different resolutions of the IR spectrometers used.

The Board does not deny that it is often sufficient in order to describe a new compound to disclose a list of **significant** and **characteristic** peaks rather than the full infrared spectrum (cf. statement of T. M. Niemczyk (35), points 11 and 13). However, despite a host of

declarations provided by eminent scientists, there is not the faintest indication in the present case as to what the different peaks listed mean and/or characterize: a crystal and not an amorphous compound, a non-solvated crystal, a specific polymorph or something else.

Furthermore, the Board is not convinced that the peaks listed are the relevant peaks for distinguishing polymorphs if existent. The experts of both sides seem to agree that the region of the high frequencies is, in that respect, of particular interest:

"The **spectra** of different polymorphs will frequently have some peaks which are the same and some which are different. The bonds which are frequently affected by interactions between molecules are C-H, N-H and O-H bonds, which exhibit peaks in the region from 3400 cm-1 to 2800 cm-1 (or lower if hydrogen bonded). Polymorphs frequently (but not always) have spectra which show differences in this region, although without other differences elsewhere in the spectrum, caution is needed before concluding that the different spectra come from different polymorphs" (cf. statement of T. M. Niemczyk (35), point 5) (emphasis added by the Board).

"Accordingly, it is often the case that different polymorphs of such compounds will display IR spectra, which differ in the region that is characteristic for hydrogen bonds, i.e. between about 3500 and 2000 cm-1" (cf. expert report of J. H. Van der Maas (87), point 23).

Although all this information is later than the filing date, the Board considers in the absence of dispute by at least one of the parties to the proceedings that it is part of the accepted common general knowledge of the skilled reader (cf. point 3.4.6 above) who as a result would have been reluctant to draw any conclusion on the existence of a polymorph form for paroxetine methanesulfonate based on a list of peaks which does not include the peaks in the high frequencies region.

3.4.11 The Board has not disregarded in that context the conclusion of J. Bernstein stating: "I understand that Professor Niemczyk has concluded that the IR data presented in the Synthon patent (cf. document (1), note of the Board) for the paroxetine mesylate of Example 1 are different from the data presented in the SB patent (patent in suit, note of the Board) for the paroxetine mesylate of Example 2. Assuming that Example 1 of the Synthon patent and Example 2 of the SB patent both describe paroxetine methane sulfonate, then, based on Professor's Niemczyk's conclusion, it is my opinion that the most plausible explanation for those differences, based on the evidence I've seen, is that the paroxetine mesylate characterized by the IR data presented in the Synthon patent and the paroxetine mesylate characterized by the IR data presented in the SB patent are different crystal forms" (cf. document (36), point 13 or (65), point 63).

This statement however misses the point because it relies on the expert opinion of T. M. Niemczyk which is supported by the comparison of the complete infrared **spectra** of examples 2, 3, 12 of the patent in suit and a spectrum allegedly obtained according to Example 1 of

document (1) (cf. statement of T. M. Niemczyk, document (35), points C, D and E), namely not a comparison of the peak lists of document (1) and the patent in suit.

This is confirmed by the declaration of V. Jacewicz, an expert of the Respondent, stating that "in paragraph 5 of his November declaration, Mr Peters criticises SB's expert, Professor Niemczyk. He states that in his opinion "a scientist would never draw conclusions about polymorphism exclusively on the basis of a list of IR-peaks, instead of a spectrum". However, Mr Peters is incorrect in what he implies Professor Niemczyk did. In fact, Professor Niemczyk compared the list of characteristic IR data relating to methane sulfonate from table 1 of Synthon's PCT application, with complete IR spectra produced from SB's methane sulfonate" (cf. document (108), point 11).

Therefore, J. Bernstein relied on T. M. Niemczyk's conclusions which however were not based on a comparison of the list of table 1 in document (1) and Claim 1. The skilled reader would not have arrived at the conclusion of J. Bernstein since he only has at his disposal two fragmentary lists of peaks.

Nor can the Board accept the declaration of I. R. Lynch (cf. document (10)). It turns out from the hearings before the Danish Court (cf. document (45), page 3, paragraph 11) that the conclusions of I. R. Lynch were drawn from the comparison of the complete infrared **spectra** of examples 3 and 12 of the patent in suit with the peaks listed in the document (1) and not from the comparison of the infrared **peaks** list of examples 3 and 12 with the peaks listed in the document (1).

Nor can the Board be convinced by the statement in the expert report of T. M. Niemczyk that it is possible to "conclude from a comparison of the two peak lists that they most likely represent different crystal forms of paroxetine methanesulfonate" since in the same declaration T. M. Niemczyk states what the Board considers to be more convincing: "Whenever a chemist wants to determine whether a substance which he or she has obtained is the same as a substance characterized by a peak list, he or she would compare a spectrum of the obtained material with the peak list. If all the listed peaks are in the spectrum, then the chemist could definitely conclude that they are the same (assuming that the spectrum covers the same frequency range as the peak list). Identifying just one or some of the peaks in the spectrum, however, does not enable the chemist to reach a definitive conclusion as to the identity of the material" (cf. document (64), paragraphs 4 and 30).

Many other statements of the experts of the Appellant and Respondent converge towards the conclusion that a comparison of two limited infrared peak lists (unrelated to the C-H, N-H and O-H bonds) cannot establish a proper comparison of the crystalline form according to Example 1 of document (1) and the claimed subject-matter:

"Materials which are chemically similar will generally have similar, but distinct, IR spectra" (cf. document (35), point 5).

"A very useful way to compare two or more spectra is to overlay them on a computer screen and then expand and compare the spectra successively across small regions" (cf. document (35), point 10).

"A printed spectrum, or a digitally recorded spectrum that can be viewed on a computer screen, conveys much more information than does a listing of selected peaks" (cf. document (35), point 10).

"Polymorphs, solvates and hydrates can all be described as different crystalline form. These different crystal forms can be distinguished by analysis of their IR spectra although in some cases the differences can be subtle" (cf. document (63), point 14).

"In my experience one can only determine the existence of two polymorphs of a particular chemical compound when utilizing infrared spectroscopy by analyzing and comparing the complete infrared spectra of the respective compounds. It is, in my experience, imposible to determine that a compound does or does not exist in polymorphic forms by comparing incomplete infrared spectra of the respective compounds, or comparing incomplete lists of infrared absorption peaks of the respective compounds" (document (21), point 3).

3.4.12 It can be derived from all those experts' opinions that, firstly, even a comparison of the complete infrared spectra is not always sufficient to distinguish two polymorphs, still less a limited list of peaks. Secondly, although the region beyond 2000 $cm^{-1}$ is often characteristic, this region is absent from the infrared peaks list defined in Claim 1.

It follows from the above considerations that, in the judgment of the Board, the list of IR peaks in Claim 1 cannot distinguish a polymorph form from another one as it simply does not convey the technical information necessary for that.

3.4.13 Since document (1) discloses a crystal of paroxetine methanesulfonate and since one of the alternatives covered by Claim 1 relates *inter alia* to a crystalline form of paroxetine methanesulfonate having no further distinctive technical feature as far as it is only defined by a list of infrared peaks, it is to be concluded that the subject-matter of Claim 1 in that respect does not differ from the disclosure of document (1) (cf. G2/88 OJ EPO 1990, 93, point 7 of the reasons).

3.5 Enabling disclosure of document (1)

3.5.1 The Board does not ignore that in order to be effective, the content of the disclosure of document (1) must be sufficient to permit a person of ordinary skill to prepare the paroxetine methanesulfonate in crystalline form (cf. point 3.2 above).

It is decisive, in that respect, to determine with whom the burden of proof rests.

According to the Respondent, citing the earlier decisions T 396/89, T 793/93 and T 441/90, it was up to the Appellant to show that a compound falling within Claim 1 was the inevitable result of the "Experimental"

section and Example 1 as repeated by the person skilled in the art.

However, decisions T 396/89 and T 441/90 refer to a legal situation where the question was to establish an inevitable result when carrying into effect a prior published example which did not itself publish the alleged invention. Decision T 793/93 refers to a case where the description of the prior art is ambiguous for the skilled reader. None of this applies here.

In the present case, as stated above, the claimed crystalline form of paroxetine methanesulfonate is unambiguously disclosed by the disclosure of document (1) as understood by a skilled reader (cf. point 3.4.13 above). The inevitable result of the "Experimental" section and Example 1 is, therefore, not the proper issue.

Although such a disclosure is *a priori* enabling, it is always possible for a party to challenge it by producing evidence to the contrary.

In that respect, the well-established rule applies: each of the parties to the proceedings carries the burden of proof for the facts it alleges. In the present case, the burden of proof rests thus with the Respondent.

It remains to examine the facts and arguments provided by the Respondent in that respect.

3.5.2 Firstly, the Respondent submitted no technical arguments in support of the objection that the

disclosure in document (1) was defective but relied upon evidence submitted by him and the Appellant.

3.5.3 Regarding the evidence submitted by the Respondent, document (71) is an experimental report of E. Shapiro conducted upon the instructions of the Respondent (cf. document (69), Exh VJ1).

Four samples of paroxetine free base having a purity of 72.35%, 82,4%, 82,5% and 89,8% respectively were used. Each time 2,7 g of the sample was placed into a 50ml rotary evaporator flask, followed by absolute ethanol. The solution was treated with methanesulfonic acid (1.0 g) in absolute ethanol. The reaction was stirred then cooled to room temperature. No crystallisation occurred. The reaction flask was placed into a refrigerator at a temperature of -26°C. After 24 hours, the solvent was removed on a rotary evaporator at 80°C under reduced pressure for 0.5 hour. The four resulting products were an oil. After 2.5 months storage at 25-27°C no visible signs of crystallisation were observed (cf. document (71), points 8, 9 and 11).

3.5.4 First, the Board observes that E. Shapiro was not provided with a copy of document (1) but with a protocol established by the Respondent insisting on strict adherence to that protocol. There is no objection in principle against such an approach if the instructions are in line with the disclosure of the experiment to be repeated as understood by the person skilled in the art.

E. Shapiro used non pure paroxetine free bases. Document (1) is silent about purity. Therefore, the

choice of the Respondent who had instructed E. Shapiro to use crude paroxetine free base is not open to criticism. However, the skilled person knows from document (1) that a crystal is to be obtained and, being aware of what is common general knowledge in the art, that impurities often retard nucleation and the subsequent crystallization (cf. document (95), page 105, lines 7 to 9 and document (94), page 355, section C.I, first paragraph). Therefore, a person skilled in the art would not be surprised to encounter some difficulties upon crystallisation in such a case.

Furthermore, it was pointed out by the Appellant that the protocol remitted by the Respondent to E. Shapiro required in point 8 (following the step of placing the reaction product in the freezer at -26°C overnight) to remove the solvent on a rotary evaporator (cf. document (71), Exhibit ES 1). "Experimental" section in document (1) is more demanding in specifying that "the mixture was evaporated to dryness" (cf. page 10, line 4). Following the given instructions, the solvent in E. Shapiro's experiments was removed on a rotary evaporator at 80°C/20mbar for 0.5 hour (cf. document (71), Exhibit ES 1, Report#30, last but one paragraph).

However, M. Crimmins found, and this was not contested by the Respondent, that, having repeated E. Shapiro's conditions to evaporate the ethanol in the "Experimental" procedure (evaporation at 80°C/20mbar for 0.5 hour), 6.8% by weight of ethanol remained in the sample (cf. document (34), paragraph 54). In the Board's judgment, the mixture in E. Shapiro's conditions may well not have been sufficiently evaporated to dryness, so that a significant amount of

ethanol remained in the mixture, to be added to the other impurities already present in the mixture.

E. Shapiro following the instructions of the Respondent did not attempt to induce crystallisation after the one month storage.

The Respondent is right when observing that there was not such an indication in document (1). In the Board's judgment, the missing statement there is quite understandable since the crystallisation did occur in the disclosed "Experimental" section. However, crystallisation is a difficult art and it is well-known that when a compound is prepared for the first time in a laboratory, it is often observed that it is relatively difficult to effect crystallisation (cf. document (95), page 104). That is more scientifically explained by document (94), page 359: "For all those methods one must pay attention that the prospect of crystallisation depends unfortunately upon the amount of material (as also time) since the spontaneous nucleation is a process submitted to the Boltzmannian laws of the statistics".

This is the reason why the basic textbooks relating to crystallisation insist on the methods for inducing crystallisation in case an oil is obtained (cf. document (93), page 141 "difficulties encountered in recrystallisation").

Therefore, the person skilled in the art knowing that a crystal was to be obtained after evaporation would have applied after the sample was left one month at room temperature the usual procedures to induce

crystallisation which are without dispute within the common general knowledge of the skilled addressee (cf. documents (93), (94), (95)). For instance, the second experiment performed by L. Feringa and R. Ebens (78) (cf. point 3.5.8 below) shows that the oil started to crystallize within a few hours slowly after having scratched the sample with a spatula. Such a step is common practice (cf. document (95), page 105, line 1 or document (96), point 3.b, the latter being an expert's opinion not contested by the Respondent). In instructing E. Shapiro not to induce any crystallisation, the Respondent has not properly anticipated what a skilled addressee would have done in attempting to reproduce the "Experimental" section of document (1).

E. Shapiro, instructed by the Respondent, waited two and a half months before sending the four samples from Israel to South Africa.

Concretely, E. Shapiro was instructed on 11 August 1999 to send the four samples to L. Nassimbeni, which he did (cf. document (71), point 12). L. Nassimbeni received the samples on 27 August 1999. In the meantime, where and in which conditions the samples were stored, is not specified.

L. Nassimbeni noted that all the specimens were clear orange in colour and of a thick, viscous, consistency like toffee (cf. document (72), point 2). E. Shapiro had however noted that the samples appeared after 2.5 months as clear slightly colored, viscous homogeneous oils (cf. document (71), Exhibit ES 1, Report#30, last but one paragraph). Since neither

E. Shapiro nor L. Nassimbeni made an analysis of the samples before their dispatch and after their receipt and since the visual descriptions do not seem to fit, it cannot be excluded that the samples underwent a change in the meantime (cf. document (92), point 10).

The Board has nevertheless not disregarded the additional experiments made by L. Nassimbeni to induce crystallisation on the samples he had received from E. Shapiro (cf. document (72)). However, these attempts were made three months after their receipt on only two samples (unidentified) out of the four samples provided. Why two samples were not tested remains obscure.

The vagueness which surrounds the conditions of transfer, the state of the samples after transfer, the non identification of the samples finally tested and the absence of reasons for not having tested the two other samples and the time elapsed (more than six months), all serve to make the Board unconvinced.

Since E. Shapiro's experiments also suffer deficiencies (presence of impurities, no evaporation to dryness and no attempt to induce crystallisation within the common general knowledge), it turns out that the evidence provided by the Respondent is not relevant.

3.5.5 The Respondent also relying upon the evidence provided by the Appellant in the course of the opposition and appeal proceedings contested that the first experiments of M. Crimmins (cf. document (33)) were conducted according to the "Experimental" section of document (1). This was admitted by the Appellant who no longer relied

upon that document. Therefore, that cannot be relevant evidence in favour of the Respondent, either.

3.5.6 The Respondent did not contest that the experiments repeated by M. Crimmins were made in accordance with the "Experimental" section and Example 1 of document (1). Crystals were obtained. Those crystals had the same infrared and XRD data as defined in present Claim 1 (cf. document (34), points 21, 29 and 33).

The Respondent contended however that the starting paroxetine free base was seeded since it had been provided by the Appellant what explained the success of the experiments (cf. document (62), point 4.6.1).

The Respondent acknowledged that the NMR spectra made on a sample of the paroxetine free base by M. Crimmins did not reveal any trace of seeds but contended that those traces would certainly not be detectable by NMR analysis of the free base, or for that matter, by any other analysis of which he was aware (cf. document (62), point 4.6.2). G. Stahly added that although M. Crimmins spectra appeared to have been collected under standard conditions, even under optimized conditions, seeds of paroxetine methanesulfonate would not have been detected (cf. document (105), point 30).

In view of those statements, the Board is prone to think that in that case the presence or not of seeds would seem to be beyond any possibility of detection.

However, in view of the description of M. Crimmins's experiments reported in document (34) regarding the

seeding crystals, the Board observes that after evaporation to dryness some crystallisation had begun after about 5 days and that after standing for one month, the oil had completely crystallized to a waxy solid (cf. point 18). This statement is in line with the description of the "Experimental" section of document (1). The Board sees a first evidence of the fact that the starting paroxetine free base was not seeded in considering the declaration of P. Janning stating that in the preparation according to Example 1, the addition of a seeding crystal to the reaction mixture was not necessary, because it crystallized spontaneously. Probably seeds in the air started the crystallization (other crystallization experiments were carried out before in the same room) (cf. document (89), point 5). The Board sees additional evidence in the experiments numbered RMA.08 and RMA.09 made by J. E. Baldwin and R. M. Adlington where a crystalline product was observed at a very early stage in both the procedures probably because the laboratory had become seeded with paroxetine methanesulfonate (cf. document (73), point 82). This statement was approved by the Respondent (cf. document (67), point 33).

In view of the above, it is not credible that the crystal growth observed by M. Crimmins has necessitated one month if the paroxetine free base had been seeded. The experiment performed by M. Crimmins is strong evidence that the "Experimental" section and subsequent Example 1 of document (1) can be reproduced.

3.5.7 Upon instructions of the Appellant, R. M. Adlington under the supervision of J. E. Baldwin carried out

experiments which were intended to be repetitions of the "Experimental" section of document (1).

The experiments are numbered RMA B1p34 and RMA B1p39 (cf. document (75), Exhs. RMA-5 and RMA-6, respectively). A scheme of the various steps taken was provided by the Respondent numbered RMA.06 and RMA.07, respectively (cf. documents (61), Exhs. PMI.6 and PMI.7). The schemes were not contested by the Appellant as being incorrect.

Instructed by the protocol (cf. document (75), RMA-2), both experiments were made starting from a paroxetine free base having a purity of at least 99%. The procedure of the "Experimental" section was slavishly followed until the evaporation step which yielded in both experiments an oily foam still containing 0.6 g and 0.14 g solvent respectively. The samples were left to stand at room temperature for eleven and eight days respectively and remained an oil. Then during seven days and five days respectively, many attempts were made to induce crystallisation without success. At this time, a NMR spectrum of a sample of each oil was made. It was found that water was present in both samples. To remove water, R. M. Adlington submitted both oils to a rather long and drastic evaporating step involving in particular the evaporation on a high vacuum line [p < 0.01 mm Hg] at 80-90°C and after trituration with diethylether to yield a white solid at least partly crystalline.

Although the Board observes that the instructions contained in the "Experimental" section were not respected insofar as the oil was not left one month at

room temperature, the critical issue discussed by the parties centred on the question of whether or not the person skilled in the art would have recognised that water was present in the mixture. Water is, without dispute, a detrimental impurity when trying to produce crystals as common general knowledge shows: "It is known that impurities often retard nucleation and the subsequent crystallisation... Water, a common impurity..." (cf. document (95), page 105, lines 7 to 9 and 17).

The Respondent argued, relying upon the cross-examination of J. E. Baldwin during the UK proceedings, that it was only after this eminent scientist had recognised that the excess of methanesulfonic acid could induce the reaction of two moles of ethanol to yield ether and water that he had understood that water might be a problem (cf. document (48), pages 290 to 293 and document (74), point 11).

However, first, for the person skilled in the art, disposing of common general knowledge, it is not apparent that one molecule of ethanol condenses with another molecule of ethanol to yield diethyl ether and water under the experimental conditions. Nothing was submitted in that respect.

The Board observes furthermore that the Respondent does not adhere without some reluctance to the explanation of J. E. Baldwin. He refers to the "Baldwin's theory" (cf. document (62), point 3.4.2). It would however have been easy to leave ethanol and methane sulfonic acid at 50°C during a sufficient period of time to verify the

theory of J. E. Baldwin. Nothing was argued by any of the parties in that respect.

In the Board's judgment, there is only one fact which is beyond any dispute: there was water in both mixtures and water is detrimental to the crystallisation.

When a person skilled in the art tries to reproduce the "Experimental" section disclosed in document (1) and does not obtain the desired product, namely a crystalline solid, he would make an approximate analysis of the mixture by NMR, to verify, firstly, whether paroxetine methanesulfonate was actually obtained. Since water appears clearly at 5 ppm as a single peak on the spectrum and since water is a well-known impurity, he would as a next step try to remove it, for instance by placing the compound in a desiccator over a drying agent or by warming under reduced pressure (cf. document (95), page 105, lines 17 to 19).

Thus, although it is clear that something went wrong in the running of the experiments, the Board is not convinced that it is due to a fundamental deficiency in the "Experimental" section of document (1). In that context, it is observed that M. Crimmins in doing an NMR spectrum of the mixture of E. Shapiro did not spot any water but simply ethanol (cf. document (34), point 54).

It is irrelevant, in the Board's judgment, that R. M. Adlington obtained a white solid at least partially crystalline under rather drastic conditions not within the common general knowledge. The fact that

crystallisation occurs under those conditions does not prove that the crystallisation will fail by using normal conditions for removing water. The Respondent on whom rests the burden to show that the disclosure in document (1) is not enabling, failed in that respect.

In summary, the Balwin/Adlington team obtained in both experiments numbered RMA B1p34 and RMA B1p39 paroxetine methanesulfonate in crystalline form. The experiments were not made according to the instructions of the "Experimental" section already for the reason that the oil was not left to stand one month. The fact that the experiments only succeeded after water was removed in a rather unusual manner is not evidence that the experiments would not have succeeded when using a method to remove water within the common general knowledge of the person skilled in the art.

3.5.8 The Respondent also relied upon the experiments performed by L. Feringa and R. Ebens (51).

Document (51) is the report of L. Feringa and R. Ebens disclosing the infrared and XRD data of paroxetine methanesulfonate obtained according to "Experimental" section and Example 1 of document (1).

The method of preparation of this paroxetine methanesulfonate is disclosed in document (78) of R. Ebens as experiment 1 and also discussed in document (79) on pages 38 to 41 and in document (91) of R. Ebens.

Following the "Experimental" section, a crystalline hard material was obtained after thirty days. The crystal was used as seeding crystal according to

Example 1 resulting in the crystallisation of paroxetine methanesulfonate (cf. document (78), pages 9 and 10). The Respondent did not submit any arguments or facts liable to put in doubt that the preparation was not exactly in line with the instructions disclosed in the "Experimental" section and Example 1 of document (1).

It is true that in document (78), it is pointed out that a first experiment was discontinued since the oil was left for one month in the freezer instead of for one month at room temperature. The Board can only conclude therefrom that the experiment was not in line with the "Experimental" section and this finding does not support the Respondent's non enabling objection.

It is also true that another experiment numbered "2" conducted in parallel with experiment 1 gave an oil after one month. Two months later, the sample was scratched with a spatula and the oil started to crystallize within a few hours slowly. After one night the oil had solidified completely to a hard mass. The Respondent contended that the crystallisation was likely to have been the result of inadvertent seeding due to the former crystallisation (experiment 1). However, that allegation is not supported by any kind of evidence and is for this reason disregarded.

Therefore, the experiments of L. Feringa and R. Ebens are supporting evidence that a crystalline form of paroxetine methanesulfonate is obtained by repeating the "Experimental" and Example 1 of document (1).

3.5.9 The Respondent also relied upon the experiments performed by P. Janning reported in documents (89), (101) to (103) conducted according to the instructions set out in document (90).

From the pull-out table of P. Jannings's repeat of "Experimental" section of document (1), it appears that only one sample (Preparation A) was left to stand at room temperature at least one month. Actually, nobody opened the flask since then and the sample remained an oil. However, in the art of crystallisation, it is well-known that a failure may occur when a compound is prepared for the first time and that, under such circumstances, it is common practice to induce crystallisation by, for instance, scratching or rubbing the inside of the container with a glass rod (cf. document (95), pages 104, from the subtitle "Inducing crystallisation" to page 105, line 4). P. Janning did not and already for that reason the observed failure is not sufficient evidence that the disclosure in document (1) is not enabling.

The preparations B and C, as admitted by the Respondent, go beyond what would have been done during a routine attempt to make crystalline paroxetine methanesulfonate (cf. document (99), points 17 and 30).

3.5.10 The Respondent also relied upon the experiments performed by M. Christmann. However, the experimental report related to those experiments was never submitted. Only document (100) which gathers the correspondence between the Irish attorneys devoid of any relevant technical information and a pull-out (104) which shows that the solid was not left to stand one month at room

temperature have been provided. The submissions of the Respondent are, therefore, unsubstantiated.

3.5.11 The Respondent finally relied upon the letter of a third party received on 13 January 2004 stating that an attempt to prepare a sample of paroxetine methanesulfonate following the procedures set out in the "Experimental" section and Example 1 of document (1) was unsuccessful yielding neither paroxetine methanesulfonate nor any crystalline product. However, this allegation too is unsubstantiated.

3.6 In conclusion, none of the pieces of evidence produced by the Respondent can establish that the person skilled in the art would not have obtained paroxetine methanesulfonate in crystalline form following the instructions of the "Experimental" section and Example 1 of document (1).

3.7 Since document (1) discloses a crystalline form of paroxetine methanesulfonate within the definition of Claim 1 of the patent in suit (cf. points 3.4.12 and 3.4.13 above) and the description of the method of preparation of the said crystalline form of paroxetine methanesulfonate is sufficient to be reproduced by a skilled person (cf. point 3.6 above), Claim 1 lacks novelty for all the designating states except CY.

3.8 Since the Board can only decide on a request as a whole, the Respondent's request that the appeal be dismissed must be rejected.

4. *Article 114(2) EPC - Late-filed documents*

4.1 Regarding late-filed documents, Article 114(2) EPC allows the instances of the European Patent Office to disregard those documents which contain no more information than the documents filed on time and do not disclose matter which could change the outcome of the decision (Case Law of the Boards of Appeal of the European Patent Office 4th edition 2001, VI.F.3.1). Thus, it is within the discretion of the Board not to allow into the proceedings late-filed documents which are no more relevant than those already on file.

4.2 Documents (117), (118) and (119) reflect common general knowledge no more relevant than the documents (93), (94) and (95).

Document (116) is of no relevance at all since the experiments related thereto were not submitted to the Board.

Documents (112) and (113) being prior art in the sense of Article 54(2) EPC, they might have been only relevant for the issue of inventive step. Document (123) is not prior art (published in 2002).

Documents (111), (114) and (115) could not have changed the outcome of the decision since they are evidence in favour of the Appellant.

Document (120) is an unsubstantiated declaration.

Documents (121) and (122) raise legal and factual issues specific to the proceedings before the Board of

Appeals and Interferences of the United States Patent Office and are not relevant for the present decision.

4.3 In view of the above those documents are not admitted into the proceedings as late-filed.

*First and second auxiliary request*

5. *Article 123(2) EPC - Amendments*

5.1 The Respondent argued that the amendments, namely the deletion of "/or" and the margin of errors, i.e "± 4" and "± 0.2" respectively (cf. point XV above), found support in Example 2 of the application as filed.

5.2 However, Example 2 relates to a particular paroxetine methanesulfonate crystal product which, in addition to the infrared and XRD data mentioned in Claim 1 of the patent in suit, is characterized by a particular melting point (143-146°C) and the intensity of its XRD peaks. The subject-matter of Claim 1 covers paroxetine methanesulfonate having an indefinite melting point and an indefinite intensity for each XRD peak mentioned. Those amendments (cf. point 5.1 above) constitute, therefore, an inadmissible extension of the application as filed contrary to the requirements of Article 123(2) EPC.

Nor could the Respondent have relied on the infrared and XRD data set out in the description (cf. page 12, lines 7 to 9 and 13 to 15). Indeed, those data are intrinsically linked to a margin of error. The margin of error cannot be deleted or even changed without extending the content of the disclosure.

5.3 For the above reasons the first and second auxiliary requests are rejected.

6. None of set of claims before the Board meet the EPC requirements.

**Order**

**For these reasons it is decided that:**

1. The interventions are admissible.

2. The decision under appeal is set aside.

3. The European patent is revoked.

The Registrar: The Chairman:

N. Maslin A. Nuss