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D E C I S I O N
of 3 February 2005

Case Number: T 1212/01 - 3.3.2

Application Number: 94916236.6

Publication Number: 0702555

IPC: A61K 31/505

Language of the proceedings: EN

Title of invention:
Pyrazolopyrimidinones for the treatment of impotence

Patentee:
Pfizer Limited, et al

Opponents:
VIVUS INC.
ICOS Corp.
SCHERING-PLOUGH CORPORATION
Merck Patent GmbH
Eli Lilly and Company
Ortho-McNeil Pharmaceutical, Inc.
MOCHIDA PHARMACEUTICAL CO. LTD.
Sanofi-Aventis
Bayer AG, Leverkusen Konzernverwaltung RP Patente Konzern
EISAI Co., Ltd.
Fujisawa Pharmaceutical Co., Ltd.
Tanabe Seiyaku Co., Ltd.
Bristol-Myers Squibb Company

Headword:
Pyrazolopyrimidinones for the treatment of impotence/PFIZER LIMITED ET AL

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
"Main and auxiliary requests 1 and 2 - added matter - yes"
"Auxiliary requests 3 to 5 - inventive step - no"
"Neither technical prejudice nor commercial success establishes inventive step"

Decisions cited:
T 0019/81, T 0060/82, T 0119/82, T 0104/83, T 0048/86, T 0321/87, T 0392/88, T 0601/88, T 0519/89, T 0631/89, T 0695/90, T 0453/92, T 0341/94, T 0531/95, T 0900/95, T 0452/96

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1212/01 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 3 February 2005

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 11 October 2001 revoking European patent No. 0702555 pursuant to Article 102(1) EPC.**

Composition of the Board:

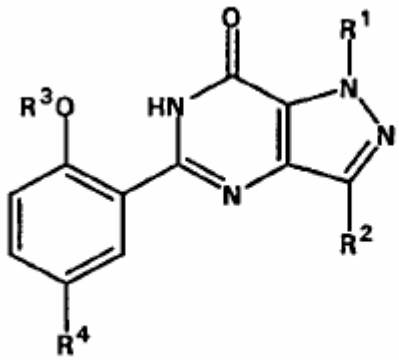
Chairman: U. Oswald
Members: J. Riolo
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 702 555 based on application No. 94 916 236.6 was granted on the basis of a set of 11 claims.

The independent claims 1 and 10 as granted read as follows:

" 1. The use of a compound of formula (I):



(I)

wherein

R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl;or C_3-C_5 cycloalkyl;
R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl;C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxyy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$;

CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-$N(R^{11})$-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;
R^7 is H or C_1-C_4 alkyl;
R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;
R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-$N(R^{12})$-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$ R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;
R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}N$)C_2-C_6 alkyl; ($R^{13}R^{14}NOC$)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;
and
R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

10. The use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity,

for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man."

II. Oppositions were filed against the granted patent by thirteen parties. The oppositions of opponents 7, 9 and 11 have been withdrawn and the remaining opponents are respondents 1, 2, 3, 4, 5, 6, 8, 10, 12 and 13 in the appeal proceedings. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step, under Article 100(b) for insufficiency of disclosure and Article 100(c) for added matter over the application as originally filed.

III. The following documents *inter alia* were cited during the opposition and appeal proceedings.

(D20) Drug Therapy, 1989, Vol. 19, No. 8, pages 102-111, I. J. Fishman "Treating Erectile Dysfunction New Approaches".

(D29) EP-A-0 463 756

(D30) The New England Journal of Medicine, 1992, Vol. 326, No.2, pages 90-94, J. Rajfer et al. "Nitric Oxide as a Mediator of Relaxation of the Corpus Cavernosum in Response to nonadrenergic, noncholinergic Neurotransmission".

(D40) Postgraduate Medicine, Vol. 93, No. 3, pages 65-72, 15 February 1993, J.E. Morley "Management of Impotence. Diagnostic, considerations and therapeutic options".

(D41) EP-A-0 526 004

(D48) Drug News and Perspectives, Vol. 6, No. 3, pages 150-156, April 1993.

(D59) Submissions made by Pfizer in the prosecution of application JP-A-7-501234, filed by Mochida Pharmaceutical Co., Ltd in its notice of opposition of 11 December 1998.

(D90) Urology, 1993, Vol. 42, No. 4, pages 468-481, Carrier et al. "Pathophysiology of Erectile Dysfunction".

(D92) JAMA The Journal of the American Medical Association, 7 July 1993, Vol. 270, No. 1, pages 83-90, "NIH Consensus Conference - Impotence".

(D100) American Family Physician, 1991, Vol. 44, No. 6, pages 2075-82, R.J. Weiss "Effects of Antihypertensive Agents on Sexual Function".

(D101) Several Pfizer press releases and in-house newsletters and various articles relating to Viagra published in the following - "Newsweek", 17 November 1997; "Wall Street Journal", 1 April 1998; "Time", 4 May 1998; "Business Week", 11 May 1998; "Chemistry in Britain", January 1999; "New Scientist", 19/26 December 1998 - 2 January 1999; "Scientific American Presents", 1999; "SCRIP", editions of 1, 20 and 22 May 1998, 3 and 5 June 1998; and "Pharma Business", editions of March/April 1999 and March/April 2000.

(D102) Spectrum Therapy Markets and Emerging Technologies, 28 March 2000, W. M. Boggs "Prospects for Erectile Dysfunction Therapies".

(D113) Expert Opinion on Therapeutic Patents, 1999, Vol. 9, No. 12, pages 1689-1696, JC Gingell et al. "Emerging pharmacological therapies for erectile dysfunction".

(D114) British Medical Journal, 19 September 1998, Vol. 317, pages 759-760, A. Gregoire "Viagra: on release".

(D115) Journal of the Formosan Medical Association, 1999, Vol. 98, No. 4, pages 233-241, T.F. Lue "Topical and Oral Agents for Erectile Dysfunction".

(D116) International Journal of Impotence Research, 1999, Vol. 11, pages 59-74, "The process of care model evaluation and treatment of erectile dysfunction".

(D133A) Annex A to the declaration of John Pryor: Int. J. Impotence Res., 1993, Vol. 5, pages 181-199, "Consensus Development Conference statement, National Institutes of Health, Impotence".

The following further documents were filed by the appellants (patent proprietors) and referred to during the appeal proceedings.

(1) British Medical Journal 1979, Vol. 2, No. 6195, pages 883-884, "Drugs and male sexual function".

(2) Fortschritte der Medizin, 1979, Vol. 97, No. 36, page 1555, D. Michel: "Impotenz durch antihypertensive Therapie?".

(3) Psychosomatics, 1980, Vol. 21, No. 3, pages 234-237, M. Hogan et al.: "Antihypertensive therapy and male sexual dysfunction".

(4) The Medical Letter on Drugs and Therapeutics, 1980, Vol. 22, No. 25, pages 108-110, "Drugs that cause sexual dysfunction".

(5) Chest, 1980, Vol. 78, No. 2, page 358, S. Ahmad: "Hydralazine and Male Impotence".

(6) Postgraduate Medicine, 1983, Vol. 73, No. 2, pages 133-135 & 138, S.A. Wartman: "Sexual side effects of antihypertensive drugs".

(7) The Medical Letter on Drugs and Therapeutics, 1983, Vol. 25, No. 641, pages 73-76, "Drugs that cause sexual dysfunction".

(8) Geriatrics, 1984, Vol. 39, No. 10, pages 63-67 & 70, K. Van Arsdalen: "Drug-induced sexual dysfunction in older men".

(9) Drug Intelligence and Clinical Pharmacy, 1984, Vol. 18, pages 113-121, J. Stevenson et al.: "Sexual dysfunction due to antihypertensive agents".

(10) Diagnosis and Treatment of Erectile Disturbances; New York, Plenum, Segraves, R.T., Schoenberg, H.W., eds, 1985, pages 23-63, R.T. Segraves et al: "Erectile Dysfunction Associated with Pharmacological Agents".

(11) Revue Médicale de Bruxelles, 1985, Vol. 6, pages 418-424, J. Mockel et al.: "les impuissances médicamenteuses".

(12) Contraception Fertilité Sexualité, 1986, Vol. 14, No. 3, pages 253-257, J. Sternon: "Les impuissances médicamenteuses".

(13) The Medical Letter on Drugs and Therapeutics, 1987, Vol. 29, No. 744, "Drugs That Cause Sexual Dysfunction".

(14) Urologic Clinics of North America, 1988, Vol. 15, No. 1, A.J. Wein et al.: "Drug-Induced Male Sexual Dysfunction".

(15) Fortschritte der Medizin, 1988, Vol. 106, No. 4, pages 61/33-63/37, B. Strauß et al.:

"Arzneimittelbedingte Hemmungen sexueller Funktionen".

(16) Hypertension 1988, Vol. 11, [Suppl. II], pages II-51 to II-55, J.D. Curb et al: "Antihypertensive Drug Side Effects in the Hypertension Detection and Follow-up Program".

(17) Contemporary management of impotence and infertility; Baltimore, Tanagho E.A., Lue T.F. and McClure R.D., eds., 1988, pages 51-54, T.F. Lue: "Pharmacology of erection and impotence".

(18) Drug Therapy, 1991, Vol. 21, pages 38-40 & 45, R. A. Galbraith: "Sexual Side Effects of Drugs".

(19) Indian Journal of Urology, 1993, Vol. 10, No. 1, pages 1-6, A. Tewari et al.: "Hypertension, Antihypertensives and Male Sexual Dysfunctions: A Review".

(20) Drug Safety, 1993, Vol. 8, No. 6, pages 414-426, G. B. Brock et al.: "Drug-Induced Male Sexual Dysfunction".

(21) Pharmacist, 1993, Vol. 18, No. 8, pages 27, 28, 30, 32, W.S. Pray: "Medications and Sexual Dysfunction".

(22) The Journal of Urology, 1989, Vol. 141, pages 546-548, J.A. Owen et al. "Topical Nitroglycerin: A Potential Treatment For Impotence".

(23) The Journal of Urology, 1980, Vol. 124, pages 925-926, R. S. Welti et al. "Treatment of intraoperative penile tumescence".

IV. By its decision pronounced on 18 July 2001 and posted on 11 October 2001, the opposition division revoked the

patent under Article 102(1) EPC because it contained added matter and did not meet the requirements of inventive step. Its principal findings were as follows.

(1) The main request (the claims as granted) was considered to be contrary to Articles 123(2) and 100(c) EPC.

(2) The auxiliary request filed during the oral proceedings, wherein granted claims 10 and 11 were deleted and claim 1 was amended by the introduction of "wherein the medicament is adapted for oral treatment", met the requirements of Articles 84, 100(b) and (c) and 123 EPC.

(3) Although the novelty of claim 1 of the auxiliary request was not challenged by any of the opponents, the claim was novel over documents (D29) and (D41) on account of the therapeutic use claimed for the compounds of formula (1), that is, the curative or prophylactic oral treatment of erectile dysfunction in a male animal.

(4) However, the subject-matter of claim 10 contravened Article 100(c) EPC, since there was no general explicit disclosure in the application as filed that cGMP PDE inhibitors could be used in the **oral** treatment of male erectile dysfunction.

(5) As to inventive step, the opposition division considered that document (D48) was the closest state of the art, that it suggested the use of PDE V_A inhibitors for the treatment of impotence and that, starting from this document, the technical problem was the provision

of new PDE V_A inhibitors for the treatment of male erectile dysfunction. The solution to this problem - that is, the oral administration of a compound within formula (1) - was obvious in the light of documents (D29) and (D41), which disclosed compounds within formula (1) having selective inhibitory activity for cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP) and which contemplated oral administration as one of the preferred routes.

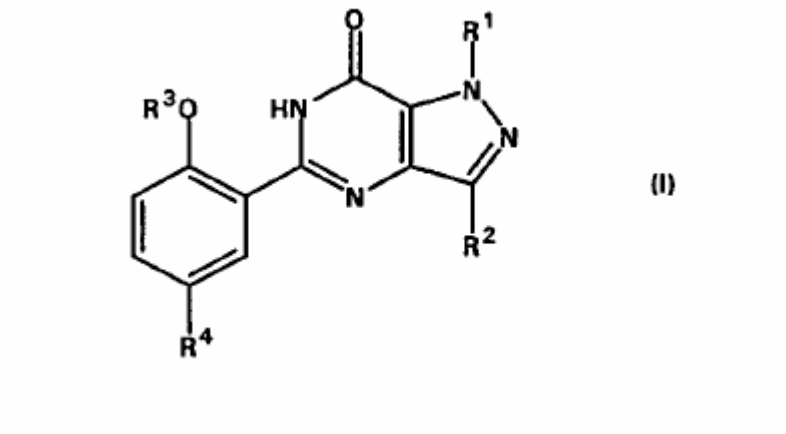
(6) The skilled person would not have been prejudiced against the use of an antihypertensive agent in the treatment of male erectile dysfunction.

(7) Accordingly, the subject-matter of claims 1 to 7 of the auxiliary request did not meet the requirement of Articles 100(a) and 56 EPC as it was obvious by reference to document (D48) in combination with documents (D41) or (D29).

V. The appellants (patent proprietors) lodged an appeal against that decision and, on 27 September 2004, filed a main request and five auxiliary requests.

(1) Independent claims 1 and 8 of the **main request** read:

"1. The use of a compound of formula (I):



(I)

wherein

R^1 is H; C_1-C_3 alkyl; C_1-C_3 perfluoroalkyl;or C_3-C_5 cycloalkyl;
R^2 is H; C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_3 perfluoroalkyl; or C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl; C_1-C_6 perfluoroalkyl; C_3-C_5 cycloalkyl;C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or $CO2R^7$; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; (hydroxy)C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxyy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; $C0_2R^7$; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino,

morpholino, 4-N(R^{11})-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;
R^7 is H or C_1-C_4 alkyl;
R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;
R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R^{12})-piperazinyl group wherein said group is optionally substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$ R^{11} is H; C_1-C_3 alkyl optionally substituted with phenyl; (hydroxy)C_2-C_3 alkyl; or C_1-C_4 alkanoyl;
R^{12} is H; C_1-C_6 alkyl; (C_1-C_3 alkoxy)C_2-C_6 alkyl; (hydroxy)C_2-C_6 alkyl; ($R^{13}R^{14}$N)C_2-C_6 alkyl; ($R^{13}R^{14}$NOC)C_1-C_6 alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$; or $C(NH)NR^{13}R^{14}$;
and
R^{13} and R^{14} are each independently H; C_1-C_4 alkyl; (C_1-C_3 alkoxy)C_2-C_4 alkyl; or (hydroxy)C_2-C_4 alkyl;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic **oral** treatment of erectile dysfunction in a male animal, including man.

8. The use of a cGMP PDE_V inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man."

(2) The **first auxiliary request** is identical to the main request save that claim 8 reads:

"8. The use of a selective cGMP-specific PDE_V inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man."

(3) The **second auxiliary request** is identical to the main request save that claim 8 reads:

"8. The use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic oral treatment of erectile dysfunction in man."

(4) The **third auxiliary request** is identical to the main request save that claim 8 has been deleted.

(5) Claim 1 of the **fourth auxiliary request** reads:

"1. The use of a compound selected from:

5- (2-ethoxy-5-morpholinoacetylphenyl)-l-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-l-methyl-3-n-propyl-l, 6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;

5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl] -1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-propyl)-1-piperazinylsulphonyl] phenyl}-l-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;

5-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl] phenyl}-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one;

and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic **oral** treatment of

erectile dysfunction in a male animal, including man."

(6) The sole claim of the **fifth auxiliary request** reads:

"1. The use of 5-[2-ethoxy-5-(4-methyl-1-piperazinyl sulphonyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H- pyrazolo[4,3-d]pyrimidin-7-one;

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic **oral** treatment of erectile dysfunction in a male animal, including man."

VI. The appellants' arguments can be summarised as follows.

(1) With respect to the opposition division's conclusion that the introduction of the feature "oral" into claim 10 could not be derived directly and unambiguously from the original application, no reason had been given to support this. The opposition division had referred to the passage in the Guidelines at Chapter C-VI, 5.4 (July 1999 edition - see now Chapter C-VI, 5.3.1 in the December 2003 edition) which uses the wording "*which is not directly and unambiguously* ***derivable***" and, in the appellants' opinion, the word "derivable" did not mean "disclosed" - the assessment of what is derivable requires an analytical reading of the original application as opposed to the opposition division's grammatical analysis.

(2) They further submitted that, even on a strictly grammatical approach, it could not be concluded that "the compounds of the present invention" meant only the compounds of formula (I). In that respect they referred to the introductory part of the original application (page 1, third paragraph) where it was mentioned that "*the efficacy of orally administrated drugs is low*" which made it clear that oral administration was a very important aspect of the invention, confirmed by the following sentences dealing with the disadvantages of other possible modes of administration.

(3) Thus, they concluded, it would have been clear to the skilled person that oral administration was shown to be the best mode of administration but, however, one which had not been arrived at previously and which would be necessary to solve the technical problem underlying the application.

(4) With respect to inventive step, in the appellants' view, document (D30), which relates to the effect of nitric oxide on the relaxation of the smooth muscle of the *corpus cavernosum*, was the closest prior art. They did not accept that document (D29) could be the closest prior art, stressing that it relates to patients with cardiovascular diseases and that impotence is a frequent side-effect of antihypertensive drugs taken for just such diseases.

However, they accepted that the result should be the same whether starting from document (D29) or from document (D30).

(5) They argued that the skilled person would not have contemplated oral administration of the compounds recited in document (D29) for treating male erectile dysfunction with a reasonable expectation of success; nor, since document (D29) does not disclose selective PDE V_A inhibitors, would the skilled person have combined document (D29) with document (D48) which is a speculative document as shown by its use of expressions such as "potential uses", "appears to be", "possible therapeutic utilities could include". Since, at the priority date, all the effective drugs were given intracavernosally, it was believed that treatment of erectile dysfunction had to be confined to the genital area in order both to be effective and to avoid side effects. There was a widespread concern about the side effects of the systemic administration of compounds, especially hypotensive agents, for treating other disorders. The appellants emphasised that, at the filing date of the patent in suit, there were no effective oral drug therapies for the treatment of sexual dysfunction.

(6) The appellants argued (with reference in particular to the documents they filed in the appeal proceedings - see paragraph III above) that the skilled person would have been prejudiced against the use of antihypertensive agents such as those disclosed in document (D29) for the treatment of impotence, since such agents (including vasodilators/smooth muscle relaxants) had repeatedly been reported to lead to male erectile dysfunction as a side effect. Such drugs were thus viewed by the scientific community at the filing date of the patent in suit as a cause of and not a treatment for impotence and, although the degree of

sexual dysfunction considered to be caused by these drugs was varied, no one group of antihypertensive drugs was exempt from this prejudice.

(7) Since antihypertensive drugs were usually given orally, the side effect of sexual dysfunction was necessarily related to the oral administration of drugs that lower blood pressure. A large number of documents were cited to demonstrate that this extended even to newer classes of antihypertensive drugs, i.e. ACE inhibitors, Ca antagonists and vasodilators which were also viewed as associated with sexual dysfunction although to a lower degree. Thus, as regards the compounds of document (D29) described as vasodilators, the appellants stressed that the skilled person would have expected that the systemic use of these would cause rather than treat impotence. In this respect they referred to documents (22) and (23) from which it was apparent that treatment of erectile dysfunction had to be confined to the genital area for reasons of effectiveness and for reducing side effects and that systemic vasodilatation results in inadequate blood supply to the penis and subsequent detumescence.

(8) The appellants contended therefore that a skilled person would beyond doubt have held such a prejudice and would have generally viewed all antihypertensives as a group of drugs that might cause sexual dysfunction. Contrary to that generally-held view, the patent had shown that PDE V inhibitors - a class of drugs that lower blood pressure - could be used effectively and orally for the treatment of male erectile dysfunction: thereby clashing with the pre-

vailing teachings in the field and overcoming a technical prejudice.

(9) Finally the appellants relied on the recognition (by awards and favourable comment) and the commercial success of Viagra, which is the brand name given by the appellants to the citrate salt of sildenafil, the product to which the patent relates. In this respect they relied on several categories of evidence. First, they pointed to various prizes awarded for Viagra including the French Prix Galien Award in 2000, the Dutch Galenus Medical Prize in 1999, the Queen's Award in the United Kingdom in 2001, and the nomination in 1999 of Viagra as a "Millennium Product", also in the United Kingdom. Evidence of these awards largely took the form of press releases from the appellants and extracts from their own internal newsletters (see document (D101), first 16 pages). Second, they referred to comments in scientific review articles which recognised Viagra as a breakthrough in the treatment of impotence including:

document (D113), page 1689, third paragraph - *"The licensing of the first extremely effective oral therapy sildenafil citrate (Viagra®) must be regarded as a major breakthrough in the treatment of erectile dysfunction"*;

document (D114), page 759, second paragraph, last sentence - *"To most sufferers a tablet treatment must have seemed too good to be true."*;

document (D115), page 233, second column - *"In 1998, the approval of oral phosphodiesterase type 5 inhibitor by the US Food and Drug Administration marked another*

revolutionary event in combating erectile dysfunction.";

and document (D116), page 60, last sentence - *"The recent advent of safe and effective oral therapy has greatly increased the number of patients seeking treatment and has significantly altered the medical management of the disorder"* (the "therapy" being identified by footnotes as the appellants' product).

Third, they argued that the coverage of Viagra, as it approached approval in the USA in Spring 1998 and since, in the general, popular science and pharmaceutical business press, as exemplified by the published articles contained in document (D101), a demonstrated the widespread notoriety it had acquired.

(10) As to commercial success, the appellants argued that sildenafil citrate (Viagra) was recognized in 1998 to be the most successful prescription drug launched by then: in the USA in 1998 more than 200,000 physicians wrote more than 7 million prescriptions for more than 50 million tablets of sildenafil for more than 3 million patients, and on 1 May 1998 IMS reported that sildenafil had taken a 94% share of all dispensed new prescriptions for erectile dysfunction products. In terms of sales and market share Viagra, first authorised in the USA on 27 March 1998, had worldwide sales of $788 million in 1988 and $1.033 billion in 1999, a 31.1% increase. This made it 34th highest selling prescription drug by worldwide sales in 1999 (up from 41st in 1998). No other drugs for the treatment of erectile dysfunction ranked in the top 500 prescription drugs by worldwide sales in 1999. Apart

from one reference to document (D102) (see page 5-1, second paragraph - *"With annual sales exceeding $1 billion, sildenafil (Pfizer's Viagra) dominated the $1.3 billion worldwide market for ED therapies in 1999."*), all the sales and market share information was set out within the appellants' letter of 16 May 2001 (see page 62, paragraphs 2 and 3).

VII. The respondents' arguments can be summarised as follows.

(1) With respect to added matter, the respondents agreed with the conclusion of the opposition division. Page 1 of the description in the application was broad enough to allow for further technical problems, such as improving intracavernosal administration or patches; and the application as originally filed, by use of the word "generally", kept open the option of all possible modes of administration, as illustrated on page 10, fifth paragraph, "*Generally, in man, oral administration of the compounds of the invention is the preferred route…*".

(2) They referred to the first response of the appellants to the notices of opposition, namely their letter of 12 November 1999, where it was written (see paragraph 15.1) "*the compounds represented by formula (I) in the Patent are pyrazolopyrimidinones (the so-called "compounds of the invention")*".

(3) They further submitted that that the introduction of the term "oral" in claim 8 was actually a disclaimer excluding all other possible modes of administration, which had been introduced in order to overcome a lack of novelty and to support inventive step, and was

therefore inadmissible. They also argued that the amendment in the same claim of "in a male animal, including man" to "in man", was not allowable, since in English the term "in man" was not limited to male humans, but included female humans as well.

(4) With respect to claim 1 of auxiliary request 3, the respondents argued that in the original application oral administration of the compounds of formula (I) was only disclosed in relation to man and not to male animals. They added moreover that claim 1 lacked clarity.

(5) With respect to inventive step, the respondents argued that it would be obvious to the skilled person, once the concept of the use of a cGMP PDE inhibitor for the treatment of impotence was disclosed (cf. document (D48)), to review the cGMP PDE V literature including documents (D29) and (D41) and to identify suitable cGMP PDE V inhibitors.

(6) The respondents did not accept that there was any technical prejudice against the oral treatment of impotence with PDE V inhibitors. Nor did they accept the commercial success argument: this could only ever be a secondary indication of inventiveness and, in the present case, there was not even adequate evidence of commercial success.

VIII. The appellants (patentees) requested that the decision under appeal be set aside and that the patent be maintained in accordance with the main request or one of the auxiliary requests 1 to 5 filed with their letter of 27 September 2004.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Main request, auxiliary requests 1 and 2: added matter

2.1 The issue of whether oral administration was disclosed in the application as filed, and thus whether Article 123(2) EPC has been contravened, arises in relation to claim 8 of all of the main and first and second auxiliary requests. In all three requests, claim 8 differs from the corresponding original claim in that *inter alia* the mode of administration has been restricted to oral administration.

2.2 The application as originally filed was, in its broadest aspect, concerned with the use of a cGMP PDE inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal (see the three last paragraphs of the description and claims 9 to 11 of the application as originally filed). Compared with that originally filed description, the use of a compound according to formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for such manufacture or treatment clearly constitutes a sub-aspect of the application. Moreover, the compounds of

formula (I) are disclosed as cGMP PDE inhibitors and oral administration has been disclosed for the compounds called "compounds of the present invention". It must thus be decided what the expression "compounds of the invention" means.

2.3 After the discussion of the prior art with its related problems, the first occurrence of "the compounds of the invention" appears on page 2, line 10 of the original application where it is mentioned that

"*The compounds of the invention are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the* ***said*** *compounds in EP-A-0463756 and EP-A-0526004, namely …*"[emphasis added].

At a first glance, the first sentence cited appears to allow both interpretations, i.e. the compounds of the present invention are those of formula (I) or are more generally inhibitors of cGMP PDE. The next sentence, however, which contains a reference to the "said compounds" can only be read as referring back to "the compounds of the invention" in the previous sentence. The second sentence also indicates that the utilities of these compounds have been disclosed in documents (D29) and (D41). Examination of those documents indicates that they clearly disclose utilities of compounds within the generic formula (I).

2.4 The description goes on to mention in the next paragraph

*"…it has now been found that **these disclosed** compounds are useful in the treatment of erectile dysfunction"* [emphasis added].

This confirms that the compounds referred to are those which were disclosed in documents (D29) and (D41), i.e. compounds of formula (I). The description continues:

*"Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. **Thus** the present invention concerns the use of a compound of formula (I)…"* [emphasis added].

Accordingly, on a reading of the application as originally filed which is both technically meaningful and grammatically correct, the only possible conclusion is that the "compounds of the invention" means compounds of formula (I).

2.5 With respect to the appellants' argument that "derivable" means more than "disclosed", it is established case law of the Boards of Appeal that the content of the application as originally filed only encompasses what is directly and unambiguously disclosed either explicitly or implicitly in the application as filed (see e.g. "Case Law of the Boards of Appeal of the EPO", 4th edition, 2001, III.A.3.3). In this context "implicit disclosure" means disclosure which any person skilled in the art would objectively consider as necessarily implied in the explicit content (e.g. in view of general scientific laws, common

general knowledge in the relevant technical field or purely logical necessity arising from the relationship of distinct portions of the application as filed).

2.6 The Board notes that the application as originally filed does indeed encompass various means of administration. On page 7, lines 22 to 28, it is mentioned that routes of administration for human use are described in documents (D29) and (D41) (EP-A-0463756 and EP-A-0526004). A close examination of these documents indicates that they mention that the compounds may for example be administrated orally, buccally or sublingually, may be injected parenterally, intravenously, intramuscularly, subcutaneously or intracoronarily (see document (D29) on page 7, lines 33 to 41), i.e. there is no limitation to oral administration. In the patent in suit itself (page 10, lines 25 to 34) the possibility of administrating the drug parenterally is expressly mentioned. Accordingly, when reading the application as originally filed, the skilled person would have not considered **oral** administration of the compounds to be mandatory.

2.7 The Board therefore cannot agree with the appellants' argument that oral administration would have been inevitably necessary in solving the technical problem underlying the application. It follows that there is neither explicit nor implicit disclosure of an oral administration of cGMP PDE V inhibitors in the application as originally filed. Accordingly, claim 8 of the main request contravenes Article 123(2) EPC.

2.8 Claim 8 of auxiliary request 1 differs from that of the main request only in that the use concerns selective

cGMP-specific PDE V inhibitors in lieu of PDE V inhibitors. The board is unable to see any support for oral administration of cGMP-specific PDE V inhibitors: both the reasons set out above in relation to the broader class of inhibitors and the conclusion hold good for the more limited class in auxiliary request 1.

2.9 Claim 8 of auxiliary request 2 differs from the main request or auxiliary request 1 only in that the use concerns cGMP PDE inhibitors. Again, and for the same reasons, the board is unable to see any support for oral administration of the more general PDE inhibitors. Therefore, the same conclusion must be reached as for the main request.

Auxiliary request 3: clarity, added matter, novelty

3.1 The oral administration of a compound is, in its broadest sense, the administration of the compound by, quite simply, taking it through the mouth. Accordingly, and contrary to the respondents' allegation, the Board sees no lack of clarity arising from an amendment, as in claim 1 of auxiliary request 3, restricting the use to oral administration in place of all modes of administration.

3.2 Also contrary to the respondents' view, the Board sees clear support for oral administration of the compounds of formula (I) in a male animal in claim 1 of auxiliary request 3 in the passage on page 2, line 30 to page 4, line 24 of the originally filed description:

"Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c.

administration. Thus the present invention concerns the use of a compound of formula (I)[…] for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man."

Accordingly, there is no unallowable selection of compounds of formula (I) which show a specific efficacy when administrated orally.

3.3 The novelty of the subject-matter of claim 1 of auxiliary request 3 was not questioned in the decision under appeal and the Board sees no objection in this respect either.

Inventive step: assessment

4.1 The patent in suit relates to a medical use of the pyrazolo[4,3-d]pyrimidin-7-one compounds of formula (1).

4.2 Document (D29) is the closest prior art. This document discloses pyrazolo[4,3-d]pyrimidin-7-one compounds of formula (I) having potent and selective cGMP PDE inhibitory activity leading to elevated cGMP levels, which in turn can give rise to beneficial platelet anti-aggregatory, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitro vasodilators (see document (D29) on page 3, lines 5 to 9). On account of this selective cGMP PDE inhibiting activity, several medical uses are proposed in this document including, among others, the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart

failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS (see document (D29) on page 3, lines 9 to 14).

4.3 Document (D29) further discloses that, for human use, the compounds of formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice, for example, they may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents (see document (D29), page 7, lines 33 to 38). The same document adds that, for instance, for administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg) and that for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day (see document (D29), page 7, lines 23 to 27). Thus, document (D29) discloses all the technical features of claim 1 of the third auxiliary request except the medical indication.

4.4 The appellants' argument against document (D29) as closest prior art was that it relates to cardiovascular diseases and that impotence was commonly viewed as a side-effect of anti-hypertensives used to treat such diseases. However, the appellants' approach is flawed: it is in effect the same approach as they adopted in relation to their alleged technical prejudice. It is well established that the closest prior art "is normally a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications ("Case Law etc", *op cit*, page 102, paragraph 3.1; see also pages 102 to 105, paragraphs 3.2 to 3.5). The determination of the closest prior art is therefore an objective and not a subjective exercise. It is made on the basis of the notional skilled man's objective comparison of the subject-matter, objectives and features of the various items of prior art leading to the identification of one such item as the closest. It is not part of this exercise to identify conclusions or opinions, be they in the form of prejudices or otherwise, about the state of the art generally; those are matters which may only arise at a later point in the assessment of inventive step.

4.5 Accordingly, as compared with document (D29) as closest prior art, the problem to be solved by the patent in suit can be seen in the provision of a further medical indication for selective cGMP PDE inhibitors. That problem is solved by the curative or prophylactic oral treatment of erectile dysfunction in a male animal. *In vitro* test methods for determining the cGMP PDE and

cAMP PDE inhibitory activities of compounds are referred to in the patent in suit. Having regard to the data provided during the opposition procedure, such as table B of document (D59) or the table on page 26 of document (D41), showing cGMP PDE inhibitory activity for representative compounds of formula (I) in combination with the recognised efficacy of one of those compounds (sildanefil) in the oral treatment of male erectile dysfunction, the Board is satisfied that the problem has been plausibly solved.

4.6 As to whether that solution entails an inventive step over the closest prior art, the Board considers that the skilled person looking to solve the problem would first consider the state of the art expressly relating to medical indications for inhibitors of the cGMP PDE enzyme. He would thus turn to document (D48) which is a review article and which discloses the therapeutic potential of PDE V_A inhibitors. He would note it is mentioned (on page 154, last paragraph of the right hand column) that smooth muscle relaxation appears to be the most promising of the potential uses of PDE V_A inhibitors, and possible therapeutic utilities could include vasodilatation, bronchodilatation, modulation of gastrointestinal motility and treatment of impotence. Accordingly, document (D48) suggests not only the same medical uses for selective cGMP PDE inhibitors as document (D29), but additionally suggests the treatment of impotence (which is synonymous with the treatment of male erectile dysfunction) as a further medical indication. Thus the disclosure of documents (D29) and (D48) would at the very least have given the skilled person an incentive to test by oral administration the efficacy of the known pyrazolo[4,3-d]pyrimidin-7-one

compounds in the treatment of male erectile dysfunction and, having done so, he would thereby have arrived at the subject-matter of claim 1 of the third auxiliary request without the exercise of inventive skill.

4.7 The appellants however presented arguments in favour of the existence of inventive step (see paragraph VI (5) above) and the Board will now consider these arguments in paragraphs 4.8 to 4.12 below.

4.8 Although it is quite correct that, as the appellants observed, document (D29) relates to patients having cardiovascular diseases and that, as a matter of fact, impotence is a frequent side-effect of taking antihypertensive drugs, document (D29) cannot be regarded as prior art relating specifically and exclusively to the treatment of cardiovascular disease. Document (D29) has to be seen as relating generally to treatments of diseases involving *inter alia* potentiation of the effects of endothelium derived relaxing factor (EDRF) (see paragraph 4.2 above), which plays an important role in the mechanism of erectile dysfunction in a male animal (see document (D30)).

4.9 In document (D29),the phosphodiesterase activity is determined as follows. The PDE enzymes are isolated from rabbit platelets and rat kidney, essentially by the method of W.J. Thompson et al. (Biochem., 1971 10, 311). The calcium/calmodulin (Ca/Cam)-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes are obtained from rabbit platelets whilst, of the four major PDE enzymes of the rat kidney, the Ca/CAM-dependent cGMP PDE (fraction I) is isolated. Assays are performed using a modification of the "batch" method of

W.J. Thompson and M.M. Appleman (Biochem., 1979, 18, 5228). The results from these tests show that the compounds of the present invention are potent and selective inhibitors of both cGMP PDEs. This can only be understood in that the compounds of formula (I) of document (D29) are disclosed having both inhibitory activity on both PDE I and PDE V.

4.10 Document (D48) is entitled "Phosphodiesterase V_A Inhibitors". Treatment of impotence has also been suggested for PDE V_A inhibitors. Document (D48) describes briefly the isoforms of the cGMP-specific PDE isoenzyme (PDE V). It explains that the cGMP-specific PDE isoenzyme family consists of several members, or isoforms, including PDE V_A, PDE V_B and PDE V_C. It goes on to mention that PDE V_B and PDE V_C have properties similar to those of PDE V_A , but are exclusively located in the retina, while PDE V_A is found in lungs, platelets and in various smooth muscle types. As the calcium/calmodulin (Ca/Cam)-independent cGMP PDE enzyme is obtained from rabbit platelets in document (D29), it is clear that it corresponds to PDE V_A.

4.11 Document (D29) does not mention selective PDE V inhibitors and does not disclose whether the compounds have an inhibitory activity on PDE I rather than on PDE V. Document (D48) discusses specifically the activity of the PDE V_A inhibitors with reference to zaprinast which is a selective PDE V_A inhibitor. However, the teaching of document (D48) with respect to the potential therapeutic uses of PDE V_A inhibitors should not be restricted to selective PDE V_A inhibitors, such as zaprinast, but should also include non-selective PDE V_A inhibitors, albeit with potential associated side

effects. Moreover, document (D48) in figure 2 (page 153) exemplifies some PDE V_A inhibitors which are not selective, such as papaverine (also see table IV of document (D48)).

4.12 It is correct that, as the appellants argued, document (D48) contains expressions, such as "potential uses", "appears to be", and "possible therapeutic utilities could include". Such expressions could, depending on the context in which they are used, be seen as evidence of a speculative approach on the part of a document's author. However, the context shows this is not the case with document (D48). This document is a review article which brings together the teaching of a number of previously published scientific articles, including document (D30) (the appellants' candidate as the closest prior art) and suggests the course of future developments in the field. That the language used in making such suggestions should be cautious is wholly unsurprising. In as much as such documents are not reporting actual new developments, they necessarily contain an inherent element of speculation, but this does not mean a skilled person would automatically assume such suggestions are not to be seriously contemplated. On the contrary, suggestions based on a review of most or all of the known art could be seen as of greater value than one individual researcher's statement of his own further plans.

4.13 Accordingly, the appellants' arguments - that the relevance of document (D29) is limited to cardiovascular disease, that it does not disclose compounds having selective PDE V_A inhibitory activity, that document (D48) is speculative, and that the

skilled person would not have combined those two documents - must fail. The appellants' remaining arguments, based on technical prejudice or commercial success, must also fail.

Technical prejudice

5.1 The following represents a good working definition of a technical prejudice and how such a prejudice is to be established:

"According to the case law of the boards of appeal (see T 119/82 (OJ 1984, 217) and T 48/86), inventiveness can sometimes be established by demonstrating that a known prejudice, i.e. a widely held but incorrect opinion of a technical fact, has been overcome. In such cases, the burden is on the patentee (or patent applicant) to demonstrate, for example by reference to suitable technical literature, that the alleged prejudice really existed (T 60/82, T 631/89, T 695/90). A prejudice in any particular field relates to an opinion or preconceived idea widely or universally held by experts in that field. The existence of such prejudice is normally demonstrated by reference to the literature or to encyclopaedias published before the priority date. The prejudice must have existed at the priority date, any prejudice which might have developed later is of no concern in the judgment of inventive step (T 341/94, T 531/95 and T 452/96). Generally speaking, prejudice ***cannot*** *be demonstrated by a statement in a single patent specification, since the technical information in a patent specification or scientific article might be based on special premises or on the personal view of the author. However, this principle does not apply to*

explanations in a standard work or textbook representing common expert knowledge in the field concerned (T 19/81 (OJ 1982, 51), T 104/83, T 321/87, T 392/88, T 601/88, T 519/89, T 453/92, T 900/95)." ("Case Law etc", *op cit*, page 134; emphasis as in the original.)

5.2 In the present case the appellants relied on some thirty scientific articles in order to demonstrate the existence of a technical prejudice. However, the contents of such a selection from the prior art cannot be considered *per se* as creating a technical prejudice against oral treatment of male erectile dysfunction. Such a prejudice can only be established by proving that, in relation to the technical solution, a relatively widespread error or misapprehension about the technical invention existed among skilled workers in the relevant field before the priority date of the patent in suit. As the summary quoted above indicates, the prejudice must be widely or universally held by experts in the relevant field. This is not the situation in the present case for the following reasons.

5.3 The appellants argued that these documents support the general view - which is at the centre of the alleged prejudice - that drugs lowering blood pressure are a cause of impotence rather than a form of treatment for that condition. This argument was constructed as follows:

(i) cGMP PDE V inhibitors were known to be smooth muscle relaxants and consequently thought to be useful as vasodilators and antihypertensive agents;

(ii) vasodilators and antihypertensive agents were known to cause rather than to treat impotence;

(iii) since antihypertensive agents were usually administered orally, the side-effect of impotence was associated with that method of administration;

(iv) further, to avoid such side-effects the prior art indicated treatment had to be confined to the genital area;

(v) thus the existing knowledge of both treatments and their systemic administration taught away from the systemic administration of a cGMP PDE inhibitor for treating erectile dysfunction.

The alleged prejudice was thus presented as, in effect, two prejudices - against the use of antihypertensive agents, including vasodilators, in the treatment of impotence; and against the use of oral (systemic) administration of a treatment for impotence.

5.4 The Board notes that, although the documents relied on by the appellants relate to various classes of anti-hypertensive medications, none of them relate to PDE inhibitors. The antihypertensive agents referred to in documents (D20), (D90), (D100) and (1) to (21) can be classified into seven groups:

– diuretics such as thiazides, (chlorothiazide, hydrochlorothiazide), bendrofluazide, furosemide, ethacrynic acid, triamterene, spironolactone and chlorthalidone;

- sympatholytic agents (peripherally or centrally acting) such as guanethidine, bethanidine, clonidine, methyldopa, reserpine, guanabenz, guanoclor, guanfacin, guanadrel, guanoxan, guanoclor and debrisoquine;

- alpha-adrenergic blocking agents (alpha blockers) such as phenoxybenzamine, phentolamine, prazosin, terazosin and indoramin;

- beta-adrenergic blocking agents (beta blockers), such as propranolol, metoprolol, oxprenolol, pindolol, atenolol, labetalol, timolol and nadolol;

- vasodilators such as hydralazine, minoxidil, prazosin and adelpman;

- angiotensin-converting enzyme (ACE) inhibitors such as captopril, enalapril and lisinopril;

- calcium channel blockers such as verapramil, diltiazem, nifedipin, nicardipine and nefedipene.

The skilled reader might deduce from the cited documents that certain antihypertensive agents such as clonidine, methyldopa and guanethidine may cause impotence in a relatively high percentage of patients. However, those documents offer no evidence permitting any extrapolation of that deduction to **all** the agents in even one of the seven classes of antihypertensives listed above.

5.5 The appellants argued (see page 48 of their letter of 24 July 2003) that the basic teaching of document (2) was that all effective antihypertensive agents that inhibit the sympathicus can in some way have an adverse effect on sexual potency. Document (2) in fact discloses that, at its publication date (1979), all effective antihypertensive drugs were known to contain centrally acting substances (such as clonidine, methyldopa or reserpine) or ganglion blockers (such as trimethaphan) or sympathetic nerve terminal agents (such as guanethidine) or receptor antagonists (such as alpha or beta adrenergic blockers). Thus, it could be concluded that, in 1979, antihypertensive drugs were associated with the cause rather than with the treatment of erectile dysfunction.

5.6 However, since 1979 new antihypertensive drugs with new mechanisms of action have been made available. For example, page 27 of document (14), published in 1988, mentions that

"Antihypertensive agents that have not been reported to cause male sexual dysfunction include minoxidil (Loniten), angiotensin-converting-enzyme inhibitors such as captopril (Capoten) and enalapril (Vasotec) and calcium channel blockers such as verapamil (Calan; others)"

and similarly document (18), published in 1991, says at page 40

"It is worth noting that angiotensin converting enzyme inhibitors such as captopril and enalapril are noted for their lack of sexual side effect".

The appellants contend (see their letter of 24 July 2003 at page 59) that these statements derive from document (13) (published in 1987) where such a statement was based only on the assumption, unsupported by any experimental data, that antihypertensive drugs generally thought not to cause sexual dysfunction included the ACE inhibitors captopril and enapril, calcium-channel blockers such as verapamil, and the arteriolar dilator hydralazine (apresoline). Document (13) is certainly cited in support of the statements in documents (14) and (18) and the relevant passage in document (13) is part of a summary paragraph unrelated to any research results or other publication. However, it must be observed that this is true of almost all the text of document (13) which is a summary occupying only seven paragraphs covering less than one and a half pages, so to characterise any one sentence as an unsupported assumption is misleading. The value of document (13) was clearly intended to be its table entitled "Some Reports of Sexual Dysfunction" which lists a number of drugs with their reported side-effects and the references to such reports.

5.7 It is of course impossible for the Board to establish the correctness or otherwise of the statements made in the various documents relied on by the appellants. All the Board can do - and all it needs to do - is to take these statements into account in assessing whether or not, on the evidence put forward by the appellants, a technical prejudice at the priority date has been established. What the documents referred to in the previous two paragraphs show is that one view held in 1979 differed from a later view which had appeared by

1987 and was still current in 1988 and 1991, the priority date of the patent in suit being 9 June 1993. That summary is sufficient to show that document (2) is no basis for the alleged prejudice.

5.8 The appellants further contended that, since PDE V inhibitors and ACE inhibitors belong to completely different classes of compounds, the lack of side effects observed for ACE inhibitors could not be extrapolated to PDE V inhibitors. It is indeed a matter of fact that ACE inhibitors work against a system modulating a hormonal cascade whereas the effect of PDE V inhibitors is specifically directed to the effect of relaxation of blood vessels. However, this neither establishes nor even supports a technical prejudice: all it establishes is that, while it was known that some antihypertensives did cause impotence, it was also known that others with different mechanisms of action did not.

5.9 Turning to the appellants' submissions directed specifically to vasodilators (for example, the compounds of document (D29), the closest prior art), it is beyond dispute that impotence had been reported in some hypertensive patients receiving hydralazine therapy, hydralazine being a recognised vasodilator. However, no direct relationship had been established between the vasodilatory effect and impotence. On the contrary, there are several suggestions, in the documents relied on by the appellants, that hydralazine may have a central sympatholytic effect as well (see document (5), penultimate paragraph; document (10), page 33, first paragraph; and document (14), page 26, right-hand column). Furthermore, throughout the cited

documents it appears that vasodilators, such as minoxidil or hydralazine are considered to have a relatively minimal impotence-inducing effect (see document (15), page 34/62; document (19), page 4; and document (20), page 420, bottom of the left-hand column).

5.10 The Board also notes that document (D48) mentions that smooth muscle relaxation appears to be the most promising of the potential uses of PDE V_A inhibitors and possible utilities could include vasodilation (see the sentence bridging pages 154 and 155). However, in the same sentence the utilities proposed also include treatment of impotence from which it is clear that the authors of that document were not subject to any technical prejudice against the use of a vasodilator in the treatment of impotence. It should be also be remembered in this context that document (D48) is a review article, in other words a paper written with knowledge of most or all of the then current literature, and that it was published in April 1993 i.e. one month before the priority date. The absence of any prejudice in that document is strong evidence that no such prejudice as that alleged existed at the priority date. The Board also notes that, with respect to the systemic administration of a vasodilator, document (D40) mentions (see page 71) that a number of oral agents have been reported to have some success in the management of impotence including pentoxifylline (Trendal) (400 mg three times a day) for early vascular impotence.

5.11 As regards the alleged prejudice against oral (systemic) administration, the appellants argued that the skilled person would have assumed that the concentration of tissue in the penis was likely to be so high that, in order to achieve an effect, oral doses would necessarily have to be very large. Furthermore, because cAMP and cGMP are to be found all over the body, to give a PDE inhibitor systemically in large doses would be highly likely to lead to undesirable side effects, including falling blood pressure.

5.12 The starting point in considering this issue is an awareness of what those in the art thought of oral administration of treatments for male erectile dysfunction at the priority date. There is no room for doubt that at that time a high priority in the search for any new treatment was that it should be administered orally: this was considered to be the ideal form of treatment. The vast majority of clinicians had recognised the disadvantage of penile injection therapy and the desirability of having an oral preparation. The oral route of administration is generally the most convenient and most acceptable to a patient for any drug. It enables the patient to manage easily and in the safest way possible the treatment of his particular disorder. It is suitable for acute, chronic or prophylactic treatment. With respect to the treatment of erectile dysfunction, oral administration of a medicament was generally recognised as being the obvious goal to aim for since it would overcome the unpleasant and potentially hazardous procedures associated with intracavernosal injections into the penis. The skilled person would have made it a priority,

in the search for a new treatment for male erectile dysfunction, to develop an orally active drug.

5.13 Evidence for this can be found in the statement prepared and published in documents (D92) and (D133A) as a result of the Consensus Development Conference on Impotence held on 7-9 December 1992 by the National Institutes of Health ("NIH") in the USA held. Under the heading "What are the needs for future research?", it is stated:

"*Development of new therapies, including pharmacologic agents, and with emphasis on oral agents, that may address the cause of male erectile dysfunction which greater specificity*" (see document (D133A), page 194; document (D92), page 89, right-hand column).

The NIH Consensus Conference also considered the known injectable agents papaverine, phentolamine and prostaglandin E_1 (see document (D133A), page 190, under the heading "Intracavernosal Injection Therapy"). The existence of such injection treatments clearly did not hinder the panel which prepared the statement from thinking of the need for an oral therapy for impotence. Although the paper was published in July 1993, the conference took place in December 1992. This supports the view that, at the priority date of the patent, there did not exist any technical prejudice against an orally-administrated impotence treatment.

Commercial success and scientific awards

6.1 Commercial success and similar arguments can only ever be secondary *indicia* of inventiveness, which are

usually only of importance in cases where an objective evaluation of the prior art has not provided a clear answer. In such cases, secondary *indicia* may show that an inventive step is involved (see generally, "Case Law etc", *op cit*, pages 133 to 134, paragraph 7.1 and pages 136 to 137, paragraph 7.5). Since in the present case the claimed subject-matter merely follows plainly and logically from the prior art, secondary *indicia* cannot assist in the assessment of inventive step. However, since the parties' arguments in this area were developed at some length, particularly during the oral proceedings, the Board considers it appropriate to make certain observations.

6.2 The principal difficulties faced by the appellants' arguments in this area lie with the nature of their evidence (summarised in paragraph VI (9) and (10) above). To establish commercial success as an *indicia* of inventive step requires two evidentiary steps - first, to show that there has been commercial success and, second, to show that such success results from the claimed invention and not from one or more other causes.

6.3 That Viagra, the brand name of sildenafil citrate, has been the subject of various awards and praise in various journals has been shown by the press releases and press cuttings filed as document (D101). While the press releases are those of the appellants themselves, and the press articles may well have been prompted by such releases, there is no objection *per se* to such use of a party's own material provided, as the Board accepts is the case here, the content is correct - after allowing for the almost usual self-congratulation found in such announcements, there can be no doubt that

the prizes referred to were awarded and the laudatory articles were published.

6.4 Indeed, the respondents did not challenge the existence of such "prizes and praises". They did however question exactly what such "prizes and praises" related to and the Board shares that scepticism. The prizes would be significant if awarded by persons who understand patent law for the unobvious nature of the technical contribution to the art made by the claimed invention. If however the prizes were awarded for the product's life-enhancing nature, or for the appellants' high standard of research, or for a high level of sales, then, for all that any of those reasons might well be prize-worthy, the prizes can have no significance in the context of inventive step. The evidence does not establish that the "prizes and praises" resulted from the claimed inventive step. To take one example, the appellants' own documents - their press release and "Pfizer World Café" newsletter both of 27 November 2000 (both in document (D101) - respectively describe the Prix Galien, awarded in 2000 to Viagra, as:

"the highest accolade for research and development in the biomedical industry"

and as recognition of

"the dedicated teamwork that underpins pharmaceutical innovation...also a tribute to how the drug has revolutionized the treatment of erectile dysfunction, not only by offering the first oral therapy, but by bringing this sensitive topic into the open, making it easier for patients to seek medical advice."

Thus the appellants themselves ascribe that prize to no fewer than four reasons - research and development effort, corporate teamwork, the first oral therapy for erectile dysfunction, and making advice on that condition easier to obtain. Only the third of those reasons comes anywhere near the nature of the invention - if the appellants claim three other reasons for such a prize, how can the Board accept it was in fact awarded for the technical nature of the alleged invention?

6.5 Similarly, the laudatory comments on Viagra in scientific review articles offer an ambiguity, or even multiplicity, of reasons for their praise. Thus, while document (D113) says (page 1689, third paragraph)

"The licensing of the first extremely effective oral therapy sildenafil citrate (Viagra®) must be regarded as a major breakthrough in the treatment of erectile dysfunction."

the whole paragraph reads:

"As knowledge of the pharmacology and physiology of the erectile process has advance, new pharmacological approaches to treatment have emerged. The licensing of the first extremely effective oral therapy sildenafil citrate (Viagra®) must be regarded as a major breakthrough in the treatment of erectile dysfunction. It will open the door for future research and development of huge potential."

So, according to this review article, while sildenafil was a "major breakthrough", it was one of a number of emerging approaches to treatment, and at least one reason for being a breakthrough was the further research it would induce. While the article does explain the drug's mechanism, its "breakthrough" status is not ascribed solely or even primarily to the claimed invention. The same can be said of the other such documents relied on. Thus the statement in document (D114) (page 759, second paragraph, last sentence)

"To most sufferers a tablet treatment must have seemed too good to be true."

is preceded by the following

"The popular interest in Viagra (sildenafil) is not solely the result of media hype and the drug's association with sex: the demand for treatment has been enormous. Since its launch in the United States in March it has become the fastest selling drug ever. The demand is being met by prescription in the United States and globally through the internet and on the street, which in Europe precedes its licensing for prescription by doctors.
The level of demand was predictable, given a prevalence of erectile dysfunction of over 50% in men aged 50-70, and the unacceptability, poor effectiveness, or unavailability of existing treatments, such as implants, intracavernosal injection, intraurethral pellets, vacuum devices, and sex therapy. To most sufferers a tablet treatment must have seemed too good to be true."

Thus, while they clearly acknowledge the commercial success of Viagra, the introductory paragraphs of this document also tells the reader that success is at least partly due to media hype, to an association with sex, and to the drawbacks of prior art products.

The epithet "revolutionary" applied to the approval of Viagra in document (D115) (page 233, second column) is immediately preceded by the use of "breakthrough" for a previous development:

"The introduction of intracavernous injection therapy in 1982 was a ***major breakthrough*** *in the pharmacologic treatment of erectile dysfunction. In 1998, the approval of oral phosphodiesterase type 5 inhibitor by the US Food and Drug Administration marked another* ***revolutionary*** *event in combating erectile dysfunction."* (emphasis added)

The comment relied on in document (D116) (page 60, last sentence):

"The recent advent of safe and effective oral therapy has greatly increased the number of patients seeking treatment and has significantly altered the medical management of the disorder" (the "therapy" being identified by footnotes as the appellants' product)

in fact ascribes Viagra's success to subsequent medico-social events rather than to the claimed invention.

All the documents just referred to supply some description of the mechanism employed in the appellants' product as sold and all make clear that, as

the first such product capable of oral administration, it has significant advantages. However, as demonstrated above, these documents also offer a variety of reasons for Viagra's success and none of them ascribes that success, either exclusively or even primarily, to the nature of the claimed invention.

6.6 Similarly, the appellants relied on the notoriety acquired by Viagra and the respondents did not deny this. The Board can add that evidence of such notoriety is almost unnecessary - Viagra as a product is so well-known to the public (indeed, for a pharmaceutical product quite remarkably well-known beyond its users) that the Board would if asked have taken judicial notice of such notoriety. But again there is no evidence that such notoriety resulted from the exact nature of the claimed invention - it might equally possibly have resulted from massive advertising and/or pubic relations campaigns. The press articles relied on by the appellants do not, unlike, the specialist reviews considered above, all contain a description of the drug mechanism but those that do also fail to ascribe Viagra's success even primarily to that. Indeed, almost as one might expect, the less specialist press offers further reasons, less closely related to the product's content, for its success - for example, a large pent-up demand created by widespread publicity (SCRIP, 1 May 1998, page 20), the appellants' preparation of large-scale manufacture while the product was still being tested (Business Week, 11 May 1998, page 97), and Viagra's role as a "life-enhancing" drug (*ibid*, cover and Pharma Business, March/April 2000, page 60 *et seq*).

6.7 Similar observations can be made in relation to the remaining category of such "success" evidence - volume of sales (see paragraph VI (10) above). While, as mentioned below, there is no real comparative data, there is little doubt that the early sales of Viagra were very substantial. However, there is no evidence to demonstrate whether the level of sales was due to the technical advance claimed for the product or to advertising or other publicity, or any of the other reasons already mentioned, or indeed yet others. Moreover, in the case of the appellants' sales evidence, there are two further problems. First, the information supplied was simply provided in written arguments filed by the appellants' representatives. It is of course the role of representatives to present the evidence of others and not to give evidence themselves. Second, when presenting evidence of commercial success in the form of sales figures (whether by market share or money value or units sold or, in the case of pharmaceuticals, prescriptions written or dispensed) the figure for one year is of little if any value, however high that figure may be. Only some comparison can make such evidence meaningful and the comparison must be such as to show at least a *prima facie* case of success - such as a comparison between sales of prior art products and patented products, or between the patentee's sales before and after manufacture in accordance with the invention. A prudent patentee will also provide parallel information relating to advertising and similar expenditure to anticipate the argument that such activities could explain the growth in sales. All such information is typically available from each year's auditing process and, if filed with an appropriate certificate from the patentee's auditors,

is likely to be conclusive in itself (there will of course still remain the need to prove a nexus between success and the invention).

6.8 To summarise, the appellants' case on commercial success consists of a considerable volume of their press releases, specialist and general press articles, and sales data all of which suggests (rightly) that Viagra has been successful. However, rather than actually link that success to the claimed invention, the appellants simply argue that such a link must exist. Yet, as the previous paragraphs show, even a cursory examination of the evidence does not bear this out. The requirement for a demonstrated nexus between the facts relied on and the claimed inventive step is missing. That Viagra has been successful is beyond question: whether that success has anything to do with the patent in suit is a question which remains unanswered. There is therefore no relevant conclusion which can be drawn as to the alleged secondary *indicia*, let alone any conclusion which could play a role in the assessment of inventive step.

Auxiliary requests 4 and 5

7.1 As claim 1 of these auxiliary requests is directed to individual compounds specifically disclosed in document (D29), both the reasons and the conclusion as to inventive step set out above in relation to auxiliary request 3 hold good for these requests as well. For example, compound 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, the use of

which is claimed in both auxiliary requests 4 and 5, is disclosed in example 12 of document (D29).

7.2 The appellants argued that sildenafil - i.e. compound 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one - has a unique pharmacological profile compared to other PDE V inhibitors. They referred more specifically to the data given in their letter of 22 June 2001 (see paragraph 7) and outlined the outstanding dose/plasma concentration response of sildenafil compared with other PDE V inhibitors. However, the submission that the use of the compound of example 12 of document (D29) not only led to an oral agent for treating male erectile dysfunction but also resulted in an outstanding pharmacological profile cannot lead to a different conclusion. Since, for the reasons already given, the skilled person would have envisaged the use of the compound of example 12 of document (D29) without the exercise of any inventive ingenuity, any additional advantage, even if unexpected, could only be considered as a gratis effect which would inevitably have resulted from the non-inventive activity.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald