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D E C I S I O N
of 28 October 1998

Case Number: T 0158/96 - 3.3.2

Application Number: 90311797.6

Publication Number: 0429189

IPC: A61K 31/135

Language of the proceedings: EN

Title of invention:
A method of treating anxiety-related disorders using sertraline

Applicant:
Pfizer Inc.

Opponent:
-

Headword:
Obsessive-compulsive-disorder/PFIZER

Relevant legal provisions:
EPC Art. 54(1)

Keyword:
"Novelty (yes): no possibility of deriving the claimed therapeutic application from the information available that clinical trials are in progress"

Decisions cited:
-

Catchword:
The information in a citation that a medicament is undergoing a clinical phase evaluation for a specific therapeutic application is not prejudicial to the novelty of a claim directed to the same therapeutic application of the same medicament if such information is plausibly contradicted by the circumstances and if the content of said citation does not allow any conclusion to be drawn with regard to the actual existence of a therapeutic effect or any pharmacological effect which directly and unambiguously underlies the claimed therapeutic application.

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Case Number: T 0158/96 - 3.2.2

D E C I S I O N
of the Technical Board of Appeal 3.2.2
of 28 October 1998

Appellant: Pfizer Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 25 August 1995 refusing European patent application No. 90 311 797.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: C. Germinario
M. B. Günzel

Summary of Facts and Submissions

I. European patent application No. 90 311 797.6 (publication No. 0 429 189) was refused by the examining division under Article 97(1) EPC on the ground of lack of novelty of the subject-matter of claim 1. The decision was taken on the basis of claims 1 and 2 filed with a letter dated 26 July 1994 and reading as follows:

"1. *The use of the compound (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to treat or prevent obsessive-compulsive disorder.*

2. *Use as claimed in claim 1 where the compound or salt thereof is administered in a dose of from 50 to 500 mg per day.*"

II. The following documents cited during the examination procedure are relevant for the present decision:

(5) The Journal of Neuropsychiatry and Clinical Neurosciences, Vol. 1, No. 3, Summer 1989, pages 253 to 262

(7) Psychiatric Developments, 1, (1989) pages 1 to 18.

III. It was the examining division's judgment that the use of the compound at issue (commonly named "sertraline") for the treatment of obsessive-convulsive disorder (OCD) was known from document (5).

The examining division specifically relied on table 4 of document (5), which showed that in 1989 sertraline was undergoing clinical phase II trials for obsessive-compulsive disorder.

The examining division argued that clinical phase II tests represented a stage of drug experimentation preceded by various proofs of activity *in vitro* as well as on animals. Therefore the information conveyed by (5) was that sertraline had already been submitted to the complete pre-clinical experimentation necessary to start clinical testing and had already proved useful for treating OCD.

The examining division emphasised that it was common practice to accept any pharmacological test, even at its earlier stage, as the disclosure of a medical use, as long as this test was commonly accepted as an indication of a potential therapeutic utility. In its view, this was the type of data that necessarily preceded phase II clinical trials.

IV. The appellant lodged an appeal against this decision, requesting a refund of the appeal fee because of a procedural violation of Rule 68(2) EPC and oral proceedings. Oral proceedings were held on 28 October 1998.

The appellant argued that, before phase II clinical trials, drug efficacy in treating a disease was not yet established and that, in the United States, the showing of efficacy in humans was not a prerequisite for conducting phase II clinical studies on a particular drug. Declarations by Montgomery, Hollander and Grant N. Ko, were produced. The clinical efficacy testing was, on the contrary, conducted in phase II and III studies. Therefore, even at the end of the phase II

stage, the efficacy of sertraline in treating OCD had not been finally established and no conclusions could be drawn. In fact, a large proportion of drugs entering phase I and phase II studies did not proceed to phase III at all.

For this reason, the efficacy of sertraline in the treatment of OCD remained an undisclosed effect hidden within the teaching in (5), and as such it could not be regarded as made available to the public.

V. The rapporteur issued a preliminary communication in which he emphasised that the decisive point was not whether the efficacy in humans of sertraline had already been conclusively established in all its clinical aspects when it was undergoing clinical phase II trials, but whether during any of the earlier phases, ie the preclinical studies and the clinical phase I trials, the novel therapeutic activity, or any other effect able to point directly to this therapeutic activity, had already been identified, whether or not its observed efficacy would have been sufficient to justify a practical application.

VI. In reply to the official communication and during the oral proceedings, the appellant submitted affidavits by Rasmussen and Brumfield. Attached to the latter, the following documents were also produced:

1. "Information for Sponsor-Investigators Submitting Investigational New Drug Application (IND's)" issued by the Centre for Drug Evaluation and Research of the US Food and Drug Administration (FDA) and including a heading entitled "Draft Summarisation", relating to Title 21, part 312 of the Code of Federal Regulations.

2. The official text of Section 312.21 of Title 21 of the Code of Federal Regulations. Section 312.21 of Title 21 provides definitions of clinical phases I, II and III of an investigation of a new drug.

At the oral proceedings, the appellant further explained that no animal model suitable for evaluating the efficacy of a substance in treating OCD was available by 1989, and, for these reasons, the pre-clinical studies of sertraline were simply aimed at evaluating the different aspects of toxicity and metabolism.

Moreover, while it was exceptionally possible in certain disease areas that some data relating to the efficacy of a new drug under investigation could be obtained during clinical phase I, this was certainly not the case of sertraline in the treatment of OCD.

VII. The appellant requested that the decision of the examining division be set aside and the patent be granted on the basis of claims 1 and 2 filed with the letter dated 26 July 1994, pages 1 to 4 of the description also filed with the letter dated 26 July 1994 and pages 5 and 6 of the description as originally filed.

The appellant also requested reimbursement of the appeal fee.

Reasons for the Decision

1. The appeal is admissible.

2. Amended claims 1 and 2 are disclosed in claim 10 and on page 3, lines 18 to 21 of the original application respectively. Therefore they meet the requirements of Article 123(2) EPC.

3. *Novelty*

3.1 Claim 1 is directed to the second or subsequent therapeutic application of sertraline, or a pharmaceutically acceptable salt thereof, said therapeutic application being the treatment or prevention of obsessive-compulsive disorder.

This claim belongs to the family of use claims protecting the use of a given substance for the manufacture of a medicament for obtaining a therapeutic effect in the treatment of a disease.

Therefore, the present claim 1 is to be construed as implicitly including the functional technical feature that *sertraline*, when formulated into a medicament and administered to patients, achieves a therapeutic effect or any pharmacological effect which directly and unambiguously underlies the claimed therapeutic application.

For the purpose of assessing novelty, it thus has to be examined whether or not the same therapeutic effect has been shown in the prior art documents.

3.2 The sole point addressed by the examining division in the decision under appeal is the novelty of the claimed subject-matter in relation to the prior document (5).

This piece of literature describes the clinical utility of pharmacological agents that act on serotonin receptors. The part relevant to the present case is the section entitled "Serotonin-Uptake Blockers" (pages 258 to 260), in which attention is focused on a series of selective 5-HT (ie serotonin) uptake blockers including sertraline. As illustrated in Table 4 on page 259, these compounds were, by 1989, at varying stages of clinical evaluation. The table reports that sertraline (Pfizer) was undergoing clinical phase III trials for depression and clinical phase II trials for obsessive-compulsive disorder.

3.3 As explained in the first paragraph under the heading "Serotonin-Uptake Blockers" (page 258), drugs that block the transport back of the released serotonin (5-HT) into the presynaptic terminals potentiate the action of 5-HT and, as reported, alleviate a variety of clinical disorders such as depression, panic attacks, obsessive-compulsive disorders and obesity. Following this introductory paragraph, the document reports three sections specifically addressed to depression, panic disorder and OCD (pages 258 to 260). Sertraline is cited in the first section, in relation to depression, as being the most potent inhibitor of the 5-HT uptake relative to norepinephrine in rat brain, and as being as effective in treating major depressive disorders as standard tricyclics. However, no reference at all to sertraline is to be found in the section addressed to obsessive-compulsive disorder or in any other part of the document. Thus, the skilled reader of document (5) could not find any textual support, explanation or confirmation of the information conveyed by table 4 in relation to sertraline for the indication obsessive-

compulsive disorder. Under these circumstances, the novelty-destroying effect of this document, alleged by the examining division, is confined and limited to the teaching explicitly or implicitly derivable from table 4.

3.4 The only explicit teaching derivable from table 4 is that sertraline, by 1989, was being submitted to phase II trials for the indication obsessive-compulsive disorder. Neither the table nor any other part of the document reports the results of any such phase II investigation in progress.

3.4.1 The description of clinical phase I, II and III investigations, the targets and the models to be used are given in Section 312.21 of Title 21 of the Code of Federal Regulations released by the US FDA, relative to Investigational New Drug Applications (IND's). The text of this part of the Code of Federal Regulations was produced by the appellant.

According to the aforementioned Section 312.21, phase II includes controlled clinical studies conducted in patients with the disease or condition under study for the purpose of evaluating the effectiveness of the drug for a particular indication.

Although one of the targets of phase II is indeed that of evaluating the effectiveness of the drug, thus whether or nor the drug exhibits the alleged therapeutic activity in patients, the answer to this question could not be predicted by the skilled reader, as document (5) lacks any anticipation of a preliminary positive or negative outcome of phase II trials. Only the successful approval of the drug in the subsequent phase evaluation, namely phase III, would imply an implicit positive answer.

For this reason the skilled person, reading in table 4 that sertraline was undergoing phase II trials for OCD, had no means of concluding from this information, reliably and beyond mere speculation, that the drug finally proved, during this phase, any therapeutic effect potentially useful in the treatment of OCD. In fact, as the appellant reiterated, and as a matter of common general knowledge, many candidate drugs submitted to phase I and II evaluation do not proceed to phase III studies at all.

3.5 Table 4 also imparts an implicit teaching to the skilled reader. In fact, in order to be approved for clinical phase II trials, the tested substance must have complied with all the requirements of the previous clinical phase I and pre-clinical investigation. Therefore, the therapeutic efficacy of sertraline in the treatment of OCD or any other effect indicating therapeutic efficacy may have been observed already during these preliminary studies.

For this reason, if the person skilled in the field of psychiatry, faced with the information that sertraline was undergoing phase II trials for OCD as disclosed in table 4 of document (5), was in a position to conclude with the required certainty that the anti-OCD activity of sertraline, or any other pharmacological effect, ie indisputably underlying such a therapeutic application, had already been shown or proven during phase I trials or during the pre-clinical experimentation, then the teaching of document (5) would have to be regarded as prejudicial to the novelty of the claimed subject-matter.

3.5.1 According to Section 312.21 of Title 21 of the Code of Federal Regulations, clinical phase I studies are designed to determine the metabolism, the structure-activity relationship, the pharmacokinetic and pharmacological effects of the drug in humans, the side effects associated with increasing doses and, only if possible, to gain early evidence of effectiveness.

Thus, proving the existence of therapeutic effectiveness in the treatment of OCD was not a mandatory requirement of the phase I investigation which had to be met before submitting sertraline to the subsequent phase study. This is also confirmed by the fact that, according to the Code of Federal Regulations, phase I is not necessarily conducted on patients, but may be conducted on normal volunteers. Therefore, the reader of (5) could not conclude that a therapeutic effect had already been proven or observed during phase I investigation.

3.5.2 Although the direct evidence of a therapeutic effect was not to be expected from the phase I trials in the present case, the skilled reader knew that such evidence could possibly also be derived from the results of previous investigations, such as those concerning the pharmacokinetic and the pharmacological properties of a substance. It is indeed not exceptional that a pharmacological effect observed in an early investigation may directly and unambiguously reflect a therapeutic effect, thus underlying a therapeutic application. For this reason, it is not unusual for an early shown pharmacological effect to be accepted, for the purpose of patent protection, as sufficient proof of a therapeutic application. Yet this is not a general or absolute rule.

At the priority date of the European application, sertraline was known to be a selective serotonin re-uptake inhibitor. By blocking the transport back of serotonin into the presynaptic terminals, sertraline potentiates the action of serotonin [see (5), page 258 "Serotonin-uptake blockers"]. As is well-known to those skilled in the art, serotonin is a neurotransmitter exhibiting a multiplicity of physiological activities. No evidence is on record showing that, before the priority date of the European application, a clear and accepted relationship between these physiological activities and the many psychiatric disorders and diseases (ranging from depression to anxiety) allegedly affected by the potentiation or the depression of the serotoninergic neurotransmission had finally been established. Thus, the skilled reader of (5) had no means of concluding with the required certainty that any evidence of a therapeutic effect in relation to OCD could have been produced by the results of the pharmacological studies carried out in clinical phase I.

3.6 As underlined in the decision under appeal, clinical trials are generally preceded by pre-clinical studies in animals.

The examining division held that the information conveyed by document (5) was that sertraline had already undergone the complete pre-clinical phase experimentation, in animals, including the pre-clinical activity tests showing the utility of sertraline for treating OCD. It also stressed that, for the purposes of patent disclosure, it was common practice to accept any pharmacological test as the disclosure of a medical use, as long as this test was commonly accepted as an indicator of potential therapeutic utility, and this was the type of data that had to precede phase II clinical trials.

3.6.1 The board does not share the examining division's conclusion in the present case. For a prior-art document to be recognised as prejudicial to the novelty of a claimed subject-matter, the information conveyed by this document cannot be interpreted on the basis of rules, which, though normally valid, do not necessarily apply to the specific situation and therefore may lead to speculative conclusions.

3.6.2 In fact, given the level of knowledge on OCD available in 1989, as illustrated in the documents on record and in the affidavits and declarations produced during the proceedings, the person skilled in the field of psychiatry had no reasonable ground for expecting the pre-clinical evaluation of sertraline to include any "activity-test showing the utility of the substance in the treatment of OCD", and still less for expecting any pharmacological test to exist that was "commonly accepted" as an indicator of the potential therapeutic utility in the treatment of OCD.

As argued by the appellant (see Montgomery statutory declaration, point 8), OCD is a complex behavioural disorder involving both obsessions and compulsions, which only relatively recently has been operationally defined to allow testing of a homogeneous population. Accordingly, it was only after December 1989 that it was possible to develop a consensus on how to study potential anti-obsession drugs.

This picture is confirmed by document (7), which describes the level of knowledge on obsessive-compulsive disorders in 1989.

It is reported under the heading "Treatment Effects" (page 6) that "Until recently, psycho-pharmacologic interventions in OCD were thought to be largely ineffective. Little evidence was available to document

reductions in obsession, compulsion, or phobic avoidance in response to pharmacological treatment. In part, this reflected methodological problems adversely affecting treatment outcome studies in OCD including small sample size, non-standardized diagnoses, lack of valid and reliable assessment procedures, inadequate control groups, and the presence of intercurrent diagnoses, particularly major depression".

As further indicated by the appellant, the evaluation of a potential anti-OCD effect was rendered even more difficult by the fact, also confirmed by (7), page 11, third paragraph, that the anti-OCD effect often appeared late, without reaching its peak until 3 to 5 months had passed.

The board is, therefore, convinced that the skilled person, faced with the teaching in table 4, and conscious of all the difficulties and problems still found in 1989 in assessing drug-effectiveness in treating OCD, even in human patients, would not realistically have concluded that evidence of sertraline effectiveness had already been produced by the pre-clinical studies in animals.

Under these specific circumstances, the board recognises as plausible the appellant's arguments, though not confirmed by documents, that experimentation in animals was not indicative of any therapeutic effectiveness of sertraline for OCD since no animal model for OCD actually existed, but was simply intended to prove the lack of any form of toxicity and to gain early knowledge about the metabolism of the substance.

In view of the foregoing, the board's judgment is that the conclusion of the examining division that the subject-matter of claims 1 and 2 lacks novelty over the teaching of document (5) is not justified.

4. Although, by virtue of Article 111(1) EPC, the board may exercise any power within the competence of the department responsible for the decision appealed, in the present case the board considers it appropriate to remit the case to the first instance for further prosecution of the examination. In fact, important patentability aspects still need to be addressed by the examining division.

The board notes that the patent application includes no example or evidence substantiating the novel therapeutic effect of sertraline underlying the present invention. Nor was any evidence of the alleged effect produced during the proceedings before the examining division or during the appeal proceedings. Whether this situation implies a deficiency which may still be remedied with the submission of evidence, or whether it has inescapable substantive consequences with regard to the clarity of the claims, the repeatability of the invention or the inventive step involved in the claimed subject-matter are questions that need to be discussed in the first place before the examining division.

5. Reimbursement of the appeal fee was also requested by the appellant, on the ground that no reason for the rejection of claim 2 was stated in the decision, which amounted, in the appellant's view, to a substantial procedural violation of Rule 68(2) EPC.

The board emphasises that all the claims belonging to one set of claims form an indivisible unit representing the appellant's request. Even if only one of the claims fails to meet the requirements of the EPC, the whole set of claims is to be rejected, regardless of whether the remaining claims might be patentable if claimed separately. It is in fact the responsibility of the appellant to formulate or to amend the claims in such a way that the whole set of claims may be acknowledged as

patentable. In the judgment of the examining division, the subject-matter of claim 1 did not meet the requirements of Articles 52(1) and 54 EPC. The examining division was therefore not obliged to examine claim 2 and to give further reasons in relation to this claim.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution.

3. The reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

P. Martorana U. Oswald