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Datasheet for the decision of 18 December 2018

Case Number: T 0285/14 - 3.3.01

Application Number: 10250379.4

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Title of invention:
Pirfenidone therapy avoiding fluvoxamine

Patent Proprietor:
Intermune, Inc.

Opponent:
Sandoz AG

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - (yes)
Inventive step - (no)

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Case Number: T 0285/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 18 December 2018

Appellant: (Patent Proprietor)	Intermune, Inc. 3280 Bayshore Boulevard Brisbane, CA 94005-1021 (US)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Appellant: (Opponent)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 18 December 2013 concerning maintenance of the European Patent No. 2324831 in amended form.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 324 831 was granted with thirteen claims. Independent claim 1 reads as follows:

"1. Pirfenidone for use in treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding, contraindicating or discontinuing concomitant use of fluvoxamine."

II. The patent was opposed under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. The documents cited in the opposition and appeal proceedings included the following:

D3: US 5,310,562 A

D5: Report on the Deliberation Results by the Japanese Ministry of Health, Labour and Welfare, 16 September 2008 (Translation)

D5a: Pirfenidone/Pirespa® Tablets 200 mg product insert (October 2008), with English translation

D6: US 7,566,729 B1

D7: WO 2009/035 598 A1

D8: Drugs of Today 44(12), 887-893 (2008)

D9: FDA Preliminary Concept Paper on Drug Interaction Studies (1 October 2004)

D12: Am J Respir Crit Care Med 171, 1040-1047 (2005)

D13: Am J Respir Crit Care Med 159, 1061-1069 (1999)

D14: Pediatr Neurol 36, 293-300 (2007)

D21: Current Drug Metabolism 3, 13-37 (2002)

D28: Jpn J Clin Pharmacol Ther 31(2), 411-412 (2000)

D37: U.S. Department of Health and Human Services, FDA, CDER, CBER: "Guidance for Industry, Drug Interaction Studies" (September 2006)

D38: AAPS Journal 11(2), 300-306 (June 2009)

D40: AAPS Journal 10(2), 410-424 (June 2008)

IV. The decision under appeal is the interlocutory decision of the opposition division, announced on 7 November 2013 and posted on 18 December 2013, rejecting the patent proprietor's main request for rejection of the opposition and finding that the patent as amended in the form of auxiliary request 1 met the requirements of the EPC.

Claim 1 of auxiliary request 1 reads as follows:

"1. Pirfenidone for use in treating a patient in need of pirfenidone therapy and in need of fluvoxamine therapy, characterized in that the treating comprises avoiding, contraindicating or discontinuing concomitant use of fluvoxamine."

V. According to the decision under appeal, while the requirement of sufficiency of disclosure was met, the subject-matter of independent claims 1 and 2 as granted lacked novelty over the disclosure of each of documents D3, D5, D6, D7 and D8.

Claim 1 of auxiliary request 1 was identical to claim 1 as granted, except that it specified additionally that the patient to be treated was also in need of fluvoxamine therapy. The requirements of Article 123(2) and (3) EPC were met. The added feature was clear in defining a patient with a pathology requiring a therapy which provided the therapeutic benefit of fluvoxamine, and it established the novelty of the claimed subject-matter by defining a specific group of patients, namely

those in need of both pirfenidone and fluvoxamine therapy.

In the proceedings, two documents had been proposed as the closest prior art, namely D5 and D28. Starting from the disclosure of either document, the objective technical problem was to provide a safe treatment with pirfenidone. On the basis of the available prior-art documents, the person skilled in the art would not have expected that fluvoxamine might cause an adverse interaction with pirfenidone. The inventive step of the claimed medical use (relating to pirfenidone treatment wherein the concomitant use of fluvoxamine was avoided, contraindicated or discontinued) was therefore acknowledged.

Like claim 1, the remaining claims of auxiliary request 1 complied with the requirements of the EPC.

VI. The opponent filed an appeal against that decision, requesting that the decision under appeal be set aside and the patent be revoked.

VII. The patent proprietor filed an appeal against the rejection of its main request.

- With its reply (dated 11 September 2014) to the opponent's statement setting out the grounds of appeal, the patent proprietor submitted a main request and fifteen auxiliary requests.

- Subsequently, in response to a communication pursuant to Article 15(1) RPBA advising the parties of the board's preliminary opinion, the patent proprietor stated *inter alia* that previous auxiliary request 4 was now its new main request.

The claims of the new **main request** are identical to those of former auxiliary request 1, which was held allowable in the decision under appeal (see point IV above for the wording of claim 1).

VIII. Oral proceedings before the board took place on 18 December 2018. During the oral proceedings, the patent proprietor withdrew all its auxiliary requests.

IX. The opponent's arguments may be summarised as follows:

Opponent: Novelty

Claim 1 did not relate to a specific further medical use and therefore did not qualify as a purpose-related product claim falling under the novelty exception according to Article 54(5) EPC in combination with Article 53(c) EPC, for the following reasons:

- According to a first approach, the claim also covered non-therapeutic embodiments such as a cosmetic method for avoiding the formation of scars and wrinkles, which was mentioned, for instance, in document D3 (column 1, lines 20 to 25) as a possible application of the anti-fibrotic agent pirfenidone. Thus claim 1 had to be regarded as a mere product claim directed to pirfenidone *per se*, which was suitable for treating patients defined in claim 1.
- Assuming, in a second alternative approach, that the purpose of the treatment defined in claim 1 was purely therapeutic, it was relevant that the claim mentioned neither a disease to be treated nor any other specific therapeutic application. Since the general therapeutic treatment of patients in need of pirfenidone therapy thus addressed was not more specific in its scope than the use of pirfenidone

"in a method referred to in Article 53(c) EPC", it must be concluded that claim 1 was actually directed to a first medical use defined in the format according to Article 54(4) EPC.

With either approach, it was evident that the subject-matter of claim 1 lacked novelty over the disclosure of pre-published document D5, which related to pirfenidone and its safe and effective use in the therapeutic treatment of patients suffering from idiopathic pulmonary fibrosis.

Even assuming that claim 1 defined, at least formally, a further medical use pursuant to Article 54(5) EPC, the "characterising" technical features were not suitable for establishing novelty over the disclosure of document D5, since the claim defined neither a novel group of patients to be treated nor a new route or mode of administration, nor did it relate to a different technical effect:

- The patient group (patients in need of pirfenidone therapy and in need of fluvoxamine therapy) was not a distinct group but was fully encompassed by the patient group addressed in the prior art (patients in need of pirfenidone therapy).

- The envisaged use of pirfenidone in treating patients in need of pirfenidone therapy remained the same as in the prior art. While expressly relating to the use of the product pirfenidone, rather than proposing a novel use of that product (e.g. by defining a new route or mode of administration or dosage regimen for pirfenidone), claim 1 actually attempted to negatively define the use of another product (namely fluvoxamine) which was not itself covered by the claim. Thus it was

evident that the alleged technical effect of avoiding elevated pirfenidone exposure and potential adverse effects caused thereby was not achieved by any change in the use of pirfenidone, since the alleged effect depended exclusively on the absence of fluvoxamine.

- Since nothing else was specified in the claim but "pirfenidone therapy", pirfenidone was to be used for the same medical indications as in the prior art. The effect achieved by the treatment with pirfenidone would still be the known therapeutic benefit of pirfenidone.

- There was no connection between the physiological or pathological status of the patients and the therapeutic effect obtained: even after avoiding, contraindicating or discontinuing the concomitant use of fluvoxamine, the patients in question would still have the same status of being "in need of pirfenidone therapy and in need of fluvoxamine therapy" - they would, for example, still suffer from idiopathic pulmonary fibrosis and depressive disorder.

As a consequence, the technical features relating to the patient group and the omission of fluvoxamine could not confer novelty on the claimed subject-matter: for the purposes of novelty assessment, claim 1 had to be regarded as a mere product claim.

For the same reasons, the subject-matter of claim 1 also lacked novelty over the disclosure of prior-art documents D3, D6, D7, D12, D13 and D14, all relating to pirfenidone therapy.

Opponent: Inventive step

Document D5 was a report on deliberation results in proceedings leading to the marketing approval of pirfenidone tablets by the competent regulatory autority in Japan (PMDA). D5 disclosed that pirfenidone was metabolised by the action of five cytochrome P450 ("CYP") isoforms, namely CYP1A2, 2C9, 2C19, 2D6 and 2E1 (D5: page 25). The potential for adverse interactions of pirfenidone with other drugs was discussed. In the absence of studies investigating pharmacokinetic drug interactions, the PMDA concluded that the effect of concomitant drugs used in clinical settings needed to be evaluated (D5: page 44).

The difference between the subject-matter of claim 1 and the disclosure of document D5 was that one such concomitantly used drug, namely fluvoxamine, was specified. According to claim 1, the patient to be treated with pirfenidone was in need of fluvoxamine therapy, but the concomitant use of fluvoxamine was to be avoided, contraindicated or discontinued.
The alleged technical effect was described in the patent in suit as avoiding an adverse drug-drug interaction, or rather, avoiding a sixfold increase in exposure to pirfenidone (in terms of AUC - area under the concentration-time curve from zero to infinity) concurrent with a twofold increase in C_{max} which described said drug-drug interaction.

Since it had not, in fact, been established that any clinically relevant adverse effect would indeed result from the concurrent administration and interaction of pirfenidone and fluvoxamine, the objective technical problem should be defined as the provision of an alternative pirfenidone use, or at best, the provision

of a pirfenidone use which avoided changes in the plasma concentration of pirfenidone.

In addition to the fact that the investigation of drug-drug interactions was already envisaged in document D5, a person skilled in the art would in any case have been aware of the need to identify such interactions, in line with standard industry practice.

The background knowledge of the person skilled in the art would have included any guidelines relevant in the field of pharmacology, and in particular document D37, which was a draft industry guidance for drug interaction studies published by the FDA (the competent regulatory authority in the US) well before the priority date of the patent in suit. Since the United States were the most important pharmaceutical market in the world, the FDA documents were highly relevant for any skilled person working in the pharmaceutical field and were part of their common general knowledge.

This was corroborated by the pre-published scientific review article D40, which referred to document D37 (identical to reference (2) of D40) as "highly prescriptive" and as including "a large amount of proposed experimental detail" as well as "tables of substrates and inhibitors in common usage" (D40: page 412, left-hand column, paragraph 3). Also, the FDA's preliminary concept paper D9, published two years prior to D37 and containing much of the information also included in D37, was acknowledged in both the patent in suit (paragraph [0022]) and the corresponding passage of the application as filed, thus confirming the opponent's argument that an inventor would have consulted FDA guidance documents.

Document D37 stated the FDA's view that the metabolism of an investigational new drug should be defined, and its interactions with other drugs should be explored, during drug development. In testing such a drug for the possibility that its metabolic clearance was inhibited by interacting drugs, the selection of the potentially interacting drugs should be based on studies identifying the enzyme systems that metabolised the drug. The choice of interacting drug could then be based on known important inhibitors of the pathway under investigation. It was furthermore known that the cytochrome P450 (CYP) family of enzymes was responsible for the metabolic clearance of many drugs and that CYP inhibition, which could lead to overexposure, was a key cause of drug-drug interactions.

Thus, since pirfenidone was known from D5 to be metabolised by CYP enzymes, the person skilled in the art would have had a strong incentive to perform the appropriate drug-drug interaction assays.

Following the guidance provided in document D37 (in particular in Appendix B,) with regard to CYP-based drug-drug interaction studies, the person skilled in the art would have conducted studies with inhibitors of the CYP enzymes involved in the metabolic clearance of pirfenidone, to identify potential drug-drug interactions.

Since fluvoxamine was identified in D37 (Appendix A, Tables 2 and 6) as a strong CYP1A2 inhibitor and an inhibitor of CYP2C19 and was furthermore known from document D21 (page 32: Conclusion) to inhibit also CYP2C9 and CYP2D6, the person skilled in the art would have identified the interaction of pirfenidone and fluvoxamine by routine testing according to D37, without the exercise of inventive skill.

X. The patent proprietor's arguments may be summarised as follows:

Patent proprietor: Novelty

Article 54(5) EPC stipulated that a substance or composition for any specific therapeutic use not comprised in the state of the art was eligible for patent protection, without defining the nature of the specific use by any degree of distinctiveness.

Claim 1 met the criteria of Article 54(5) EPC, as it defined a specific medical use by a new treatment regimen applying to a specific group of patients.

The patients were those not only in need of pirfenidone therapy, but also in need of fluvoxamine therapy. A clear definition of patients in need of fluvoxamine therapy was given in paragraph [0025] of the patent in suit, which mentioned patients suffering from social anxiety disorder, obsessive compulsive disorder, depression, anxiety disorders, panic disorder and post-traumatic stress disorder as examples. Thus claim 1 related to a specific group of patients not identified in document D5, nor in the other prior-art documents cited by the opponent against novelty (namely, D3, D6, D7, D12, D13 and D14, all of which, like D5, related to pirfenidone therapy but did not mention or discuss issues relating to fluvoxamine therapy or to a potential adverse drug-drug interaction between pirfenidone and fluvoxamine).

The specific treatment regimen in relation to that group of patients involved avoiding, contraindicating or discontinuing the concomitant use of fluvoxamine, which could for instance be achieved by pirfenidone being packaged and presented to give instructions to

that effect. Such measures were not however disclosed in the prior art.

Hence, novelty was established by a new treatment regimen in relation to a specific group of patients. The wording of claim 1 was entirely appropriate for dealing with the scenario of a previously unrecognised safety issue arising in the context of pirfenidone therapy.

Patent proprietor: Inventive step

Document D5 represented the closest prior art. The technical problem to be solved could be defined as the provision of a safe pirfenidone use, reducing adverse effects during pirfenidone therapy.

The claimed invention should be regarded as a "problem invention", since it had not been recognised in the prior art that unfavourable CYP-related drug-drug interactions, in particular between pirfenidone and fluvoxamine, might occur.

In particular, document D5 taught away from that issue:

- When asked by the PMDA about the possibility of drug-drug interactions, the company applying for marketing approval stated that pirfenidone was unlikely to have pharmacokinetic interactions with other drugs, since, *inter alia*, it was metabolised not by a particular CYP isoform but by multiple isoforms and was therefore unlikely to be affected by concomitant drugs (D5: page 43, 4.(i).B).
- That response was explicitly accepted by the PMDA, which did not ask for drug-drug interaction studies involving *in vivo* testing as a prerequisite for regulatory approval, but instead merely recommended post-marketing surveillance (D5: page 44).

- Thus, D5 taught away from carrying out further investigations into potential interactions of pirfenidone and CYP-inhibiting compounds.
- The product insert for Pirespa®, the pirfenidone tablets later commercialised in Japan (i.e. the pirfenidone use authorised by the regulatory authority of D5), stated in conformity with D5 that "It is estimated that this drug is not susceptible to CYP inhibition by other drugs since multiple CYP molecules are involved in metabolism reaction" (D5a: English translation, page 4: "Metabolism").

Considering the clear direction of D5, further confirmed in D5a, the person skilled in the art would not have had any concerns over concomitant use of pirfenidone with drugs that had CYP inhibition activity. No reason for conducting further clinical trials could plausibly be derived from the available prior art, considering that similarly skilled persons from a pharmaceutical company and at a regulatory agency had decided that such trials were not necessary prior to regulatory approval.

The invention defined in claim 1 was therefore based on the identification of a new risk due to a truly unexpected drug-drug interaction.

If the content of document D37 was indeed to be regarded as common general knowledge, as argued by the opponent, then the skilled persons of the regulatory authority of D5 must have taken such knowledge into account before making their approval decision and when concluding that drug-drug interactions with pirfenidone were sufficiently unlikely to justify relying simply on post-marketing surveillance for information on any adverse events.

In any case, the approach which the person skilled in the art knowing D5 would have followed was in conformity with the approach of D37:

- As proposed in D37, the identification of the CYP enzymes involved in the metabolism of pirfenidone had already been carried out by *in vitro* testing (D5: page 25).
- According to D37 and also D38 (an article on the evaluation of drug-drug interaction potential), understanding which CYP enzyme was responsible for the metabolism of a new drug was important: interaction was likely to occur between such a drug and known inhibitors or inducers of that specific pathway if it contributed more than 25% to the total clearance of the drug (D38: page 301, left-hand column, penultimate paragraph).
- Since D5 did not identify any CYP as contributing to a major extent to the clearance of pirfenidone, the person skilled in the art would have inferred that no single CYP was a major contributor and, in line with D37 (Appendix B), would have had no reason for further investigation involving *in vivo* drug-drug interaction studies.

Prior to the application from which the patent in suit had issued, it had not been known that pirfenidone was primarily metabolised by CYP1A2. As mentioned in paragraph [0019] of the patent in suit and the corresponding passage of the application as filed, the relative contribution of CYP1A2 of approximately 48% was only established by *in vitro* experiments carried out by the inventors. On that basis, the inventors recognised, for the first time, the potential for an adverse drug-drug interaction with the strong CYP1A2

inhibitor fluvoxamine, resulting in increased exposure to pirfenidone.

XI. The appellant/patent proprietor requested that the opponent's appeal be dismissed and that the patent be maintained on the basis of the claims of the main request, previously filed as auxiliary request 4 with the letter dated 11 September 2014.

XII. The appellant/opponent requested that the decision under appeal be set aside and that European patent No. 2 324 831 be revoked.

Reasons for the Decision

1. Analysis of claim 1

1.1 Non-therapeutic indication

The purpose specified for pirfenidone in claim 1 - "for use in treating a patient in need of pirfenidone therapy and in need of fluvoxamine therapy" - is a therapeutic application within the meaning of Article 53(c) EPC. In this, the board takes the view that "treating a patient in need of pirfenidone therapy" explicitly does not cover the non-therapeutic application of pirfenidone, contrary to the opponent's first approach to the interpretation of claim 1.

1.2 Patients to be treated

According to paragraph [0024] of the patent in suit, a patient in need of pirfenidone therapy is a patient who would benefit from the administration of pirfenidone, i.e. one who is suffering from any disease or condition for which pirfenidone may be useful.

According to paragraph [0025] of the patent in suit, a patient in need of fluvoxamine therapy is a patient in need of selective serotonin reuptake inhibitor (SSRI) therapy, which includes patients suffering from social anxiety disorder, obsessive compulsive disorder, depression, anxiety disorders, panic disorder and post-traumatic stress disorder. The board understands from this that patients in need of fluvoxamine therapy are patients with a pathology requiring a therapy which provides a therapeutic benefit obtainable with fluvoxamine.

The patients according to claim 1 are defined by the overlap between these two patient groups.

The pathologies which can be treated with the antifibrotic agent pirfenidone (see paragraph [0024] of the patent in suit) would appear to be unrelated to those which can be treated with fluvoxamine.

1.3 Indication relating to first or further medical use

1.3.1 According to Article 54(4) EPC, novelty can be acknowledged with regard to a substance comprised in the state of the art, for use in a method referred to in Article 53(c) EPC, provided that its use for any such method is not comprised in the state of the art (first medical use).

1.3.2 According to Article 54(5) EPC, novelty can further be acknowledged with regard to a substance comprised in the state of the art, for any specific use in a method referred to in Article 53(c) EPC, provided that such use is not comprised in the state of the art (further medical use).

1.3.3 The opponent contended, in its second approach to the interpretation of claim 1 (see point IX above), that

the indication defined in claim 1 was the otherwise unspecified therapeutic use of pirfenidone in the treatment of patients in need of pirfenidone therapy, which was not distinguishable from a first medical use pursuant to Article 54(4) EPC.

1.3.4 However, claim 1 actually does not relate just to pirfenidone therapy, but rather to the therapeutic treatment of patients in need of both pirfenidone and fluvoxamine, restricting both the patient group (in comparison with all patients in need of pirfenidone) and the treatment options (with regard to patients in need of fluvoxamine). The board therefore considers that the indication defined in claim 1 describes a specific therapeutic use.

1.4 For these reasons, the board concludes that claim 1 relates to a further medical use in conformity with Article 54(5) EPC.

2. Novelty

2.1 Document D5 is a report on the results of a regulatory review leading to the marketing approval of pirfenidone 200 mg tablets by the competent Japanese regulatory authority PMDA (Pharmaceuticals and Medical Devices Agency). According to the conclusions reached (see D5: page 4), the data and information submitted, including data from phase III clinical studies, demonstrated the efficacy and safety of the product for use in the treatment of idiopathic pulmonary fibrosis. It was common ground that D5 therefore discloses the use of pirfenidone in treating patients in need of pirfenidone therapy.

2.2 D5 does not mention patients in need of pirfenidone therapy who are also in need of fluvoxamine therapy.

Since the pathologies involved are unrelated, there is no implicit disclosure of such patients.

2.3 The subject-matter of claim 1 is novel with regard to the disclosure of document D5, because claim 1 relates to a specific group of patients not disclosed in D5 and also defines certain restrictions to be observed with regard to their medication. The same applies to the other prior-art documents cited by the opponent against novelty (namely D3, D6, D7, D12, D13 and D14).

2.4 As a consequence, the subject-matter of claim 1 is novel within the meaning of Article 54(1), (2) and (5) EPC.

3. Inventive step

Patent in suit

3.1 The patent in suit relates to pirfenidone therapy. Pirfenidone, which has anti-fibrotic properties, had previously been approved in Japan for the treatment of idiopathic pulmonary fibrosis (see paragraphs [0002] to [0004] of the patent).

According to the patent in suit, the invention is based on the discovery of an adverse drug-drug interaction between pirfenidone and fluvoxamine, which results in reduced clearance of pirfenidone and, as a consequence, increased exposure of patients to pirfenidone.

The patent therefore seeks to avoid such potentially adverse interaction when administering pirfenidone therapy, and to that end proposes that the concomitant use of fluvoxamine should be avoided, contraindicated or discontinued (see claims 1 and 2 and paragraphs [0005], [0021], [0022] and [0027] to [0031]).

3.2 As acknowledged in paragraph [0003] of the patent, it was known from document D5 that pirfenidone had been shown to be metabolised by various isoforms of the cytochrome P450 (CYP) protein, specifically, the isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

The patent in suit (see paragraph [0019]) additionally provides the information that results of *in vitro* experiments indicated that pirfenidone was primarily metabolized by CYP1A2 (approximately 48%). It was not contested by the opponent that this was not known from the prior art.

Furthermore, the patent acknowledges that fluvoxamine was known to be a potent inhibitor of CYP1A2 and CYP2C19 (see paragraphs [0004] and [0020] citing, *inter alia*, document D21).

According to data reported in the patent in suit (see Example 1 and paragraph [0022]), co-administration of pirfenidone with fluvoxamine resulted in an average sixfold increase in exposure (AUC, or area under the curve) to pirfenidone and an average twofold increase in C_{max}, the mean maximum plasma concentration.

In that context it is mentioned (see paragraph [0022]) that FDA draft guidance (specifically, document D9) suggests that a drug-drug interaction is present when comparisons indicate twofold or greater systemic exposure for a drug when given in combination with the second drug, compared with when given alone.

Starting point in the prior art

3.3 It was common ground that document D5 was a suitable starting point for the assessment of inventive step.

3.4 As already mentioned (see point 2.1 above), document D5 discloses the use of pirfenidone in treating patients

in need of pirfenidone therapy and relates to a regulatory approval process for pirfenidone tablets completed in Japan.

According to D5 (paragraph bridging pages 25 and 26), *in vitro* assay results confirmed that several cytochrome P450 (CYP) isoforms, namely CYP1A2, 2C9, 2C19, 2D6 and 2E1, were involved in metabolising pirfenidone. D5 does not however provide any information about the relative contribution of each CYP enzyme to the metabolic clearance of pirfenidone.

In the absence of studies to evaluate pharmacokinetic interactions, the regulatory authority (PMDA) asked the company applying for regulatory approval to explain the possibility of interactions with other drugs.

The applicant company stated (see D5: page 43, third full paragraph) that pirfenidone was unlikely to have pharmacokinetic interactions with other drugs, *inter alia* because pirfenidone was metabolised not by a particular CYP isoform but by multiple isoforms and was therefore unlikely to be affected by CYP inhibition by concomitant drugs.

According to document D5, the PMDA accepted that response "at present", but considered that the effect of concomitant drugs actually used in clinical settings needed to be evaluated in post-marketing surveillance (see D5: page 44, first paragraph after the table).

Technical problem and solution

3.5 The subject-matter of claim 1 differs from the disclosure of document D5 by the technical features requiring that the concomitant use of fluvoxamine be avoided, contraindicated or discontinued in patients

receiving pirfenidone therapy who also have a pathology which might otherwise benefit from fluvoxamine therapy.

3.6 In view of the data reported in Example 1 of the patent in suit, the board recognises that the administration of fluvoxamine concomitant with the use of pirfenidone may give rise to increased exposure to pirfenidone (presumably due to reduced clearance), which may potentially present a risk of toxicity. Hence, avoiding, contraindicating or discontinuing the concomitant use of fluvoxamine in a group of patients who might otherwise incur such a risk are measures which may serve to improve the safety of pirfenidone therapy.

3.7 The objective technical problem is thus the provision of a specific ("further") safe therapeutic use of pirfenidone.

3.8 The solution to that problem is as defined in claim 1.

Obviousness of the solution

3.9 The board does not share the patent proprietor's view that the person skilled in the art, having studied document D5 and the product insert D5a, would have desisted from investigating potential drug-drug interactions of pirfenidone based on CYP inhibition. Firstly, on the basis of the information provided in documents D5 and D5a, the occurrence of relevant interactions could not have been ruled out with any certainty, and secondly, the skilled person's common general knowledge (as represented by document D37) would have provided a strong incentive for further investigation (see points 3.11 to 3.14.5 below for detail).

3.10 Hence, the board cannot agree with the patent proprietor's contention that the claimed subject-matter should be regarded as a "problem invention", since safety, including the aspect of avoiding adverse drug-drug interactions, is a general consideration in drug development, and thus the technical problem defined in point 3.7 above would have been posed by the person skilled in the art as a matter of routine.

3.11 Conclusions from D5/D5a

3.11.1 It is usually assumed that the likelihood of drug-drug interactions with inhibitors of a metabolising pathway increases when a compound has a high affinity for a single metabolising enzyme, compared with a compound with affinity for a number of different enzymes (see D38: page 301, left-hand column, penultimate paragraph). The person skilled in the art might therefore well have estimated that pirfenidone, since it was metabolised by several CYP isoforms (see point 3.4 above), was less likely to be strongly affected by CYP inhibition by concomitant drugs.

3.11.2 This view, which is expressed in both D5 and D5a, can however only be regarded as a first approach based on likelihood, which would not have conclusively ruled out the possibility that relevant CYP-related adverse drug-drug interactions might nevertheless occur. In fact, although taking the discretionary decision not to prescribe further clinical studies prior to the regulatory approval of pirfenidone 200 mg tablets, the PMDA did not rule out the possibility of drug-drug interactions, but considered that the effect of concomitant drugs needed to be evaluated at least in post-marketing surveillance.

3.12 Common general knowledge represented by document D37

Furthermore, the board considers that document D37, which is a draft guidance published and distributed for comment by the FDA, was part of the common general knowledge of the person skilled in the art. While D37 does not establish mandatory requirements for regulatory approval, it contains recommendations relevant to the industry which a person skilled in the art would not have ignored.

3.13 Teaching of D37

- Document D37 reflects the FDA's view that the metabolism of an investigational new drug should be defined during drug development and the new drug's interactions with other drugs should be explored as part of an adequate assessment of its safety and effectiveness (see D37: lines 21 to 24).

- D37 acknowledges that the cytochrome P450 (CYP) family of enzymes is known to be responsible for the metabolic clearance of many drugs and that metabolic routes of elimination can be inhibited or induced by concomitant drugs. Thus CYP inhibition by concomitant medication is a known cause of drug-drug interactions (see D37: lines 58 to 88 and Appendix B; also see D40: abstract and page 410, sentence bridging columns 1 and 2).

- In contrast to earlier approaches which focused on specific drugs likely to be co-administered, D37 takes a more general approach and recommends early screening for drug-drug interactions during drug development, in particular with regard to CYP-related interactions (see D37: lines 333 to 339).

- In testing an investigational drug for the possibility that its metabolism is inhibited by interacting drugs, the selection of the potentially interacting drugs should be based on studies identifying the enzyme systems that metabolise the investigational drug. The choice of interacting drug can then be based on known important inhibitors of the pathway under investigation (see D37: lines 398 to 404).

- *In vitro* studies can frequently serve as a screening mechanism to rule out the importance of a metabolic pathway and the drug-drug interactions that occur through this pathway, so that subsequent *in vivo* testing is unnecessary (see D37: lines 168 to 171).

- A Decision Tree for CYP-based drug-drug interaction studies is presented in Appendix B on page 24 of D37, as reproduced below (see page 24 of this decision).

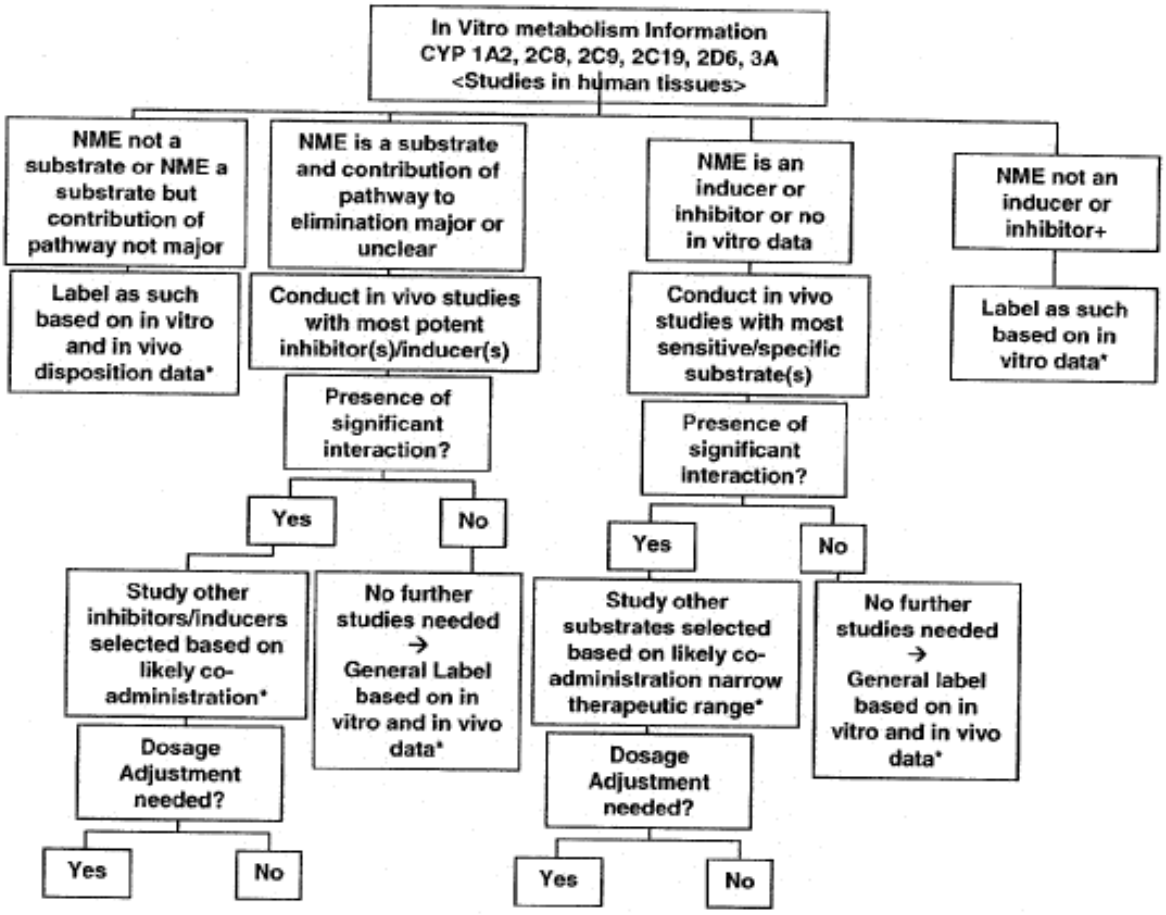
- The situation in which the drug to be investigated (also called NME or "new molecular entity" in D37) is a substrate of CYP enzymes is reflected in the first two arms (from the left) of the decision tree.

- It can be seen that in a first step (shown at the top of the decision tree), the CYP enzymes metabolising the drug are identified in *in vitro* studies.

- If the drug is a substrate of a CYP enzyme and the contribution of the pathway to its elimination is major or unclear, further testing is required (second arm of the decision tree).

Appendix B- Figures

Figure 1. CYP-Based Drug-Drug Interaction Studies — Decision Tree



NME: New molecular entity

* Additional population pharmacokinetic analysis may assist the overall evaluation.

\+ See Appendix C for criteria to determine whether an NME is an inhibitor (Appendix C-2) or an inducer (Appendix C-3) of a specific CYP enzyme; negative results from a cocktail study would preclude further evaluation to determine whether an NME is an inhibitor or an inducer of a particular CYP enzyme (see IV.C.1). (Reference: *Journal of Clinical Pharmacology*, 39:1006-1014, 1999.)

3.14 Conclusions from D37

3.14.1 The patent proprietor argued that, since document D5 did not identify any CYP enzyme as a major contributor to the metabolic elimination of pirfenidone, the person skilled in the art would have inferred that no single CYP was a major contributor and that, according to the decision tree of D37 (first arm), further tests were not required, because there was no particular risk of important drug-drug interaction. This was moreover entirely consistent with the statement made by the applicant company in document D5 (page 43).

3.14.2 The board does not reach the same conclusion. While document D5 identifies five CYP enzymes as contributors to the metabolic clearance of pirfenidone, their relative contribution is not indicated or discussed in D5. Thus there is nothing that would suggest to the reader that none of the CYP enzymes is a major contributor: information on that subject is simply not available in D5. This corresponds to the situation mentioned in the second arm of the decision tree, where the contribution of the metabolic pathway to the elimination of the drug is "either major or unclear". In that situation, document D37 recommends *in vivo* studies with potent inhibitors of the CYP enzymes involved.

3.14.3 The opponent argued that D37 clearly implied that the skilled person's next step should be the identification of any CYP enzyme(s) with a high (or "major") relative contribution to the metabolism of pirfenidone.

3.14.4 The board agrees that this would appear to be the logical next step. It was not contested that the person skilled in the art would be able to identify the relative contributions of different CYP enzymes.

In that way, the skilled person would have established by experiment that CYP1A2 was the major contributor, and would have proceeded with interaction studies involving fluvoxamine, which was the only compound listed in D37 as a strong inhibitor of CYP1A2 (see D37: Tables 6 and 2).

The second arm of the decision tree also encompasses the alternative option of conducting interaction studies with inhibitors of each relevant CYP enzyme without first identifying the relative contribution of each enzyme in the elimination of pirfenidone. Again, fluvoxamine would have been included as a potent inhibitor of CYP1A2 (also known to inhibit CYP2C19, CYP2C9 and CYP2D6; see D37: Tables 6 and 2 and paragraph [0020] of the patent).

3.14.5 Thus the person skilled in the art, proceeding according to the second arm of the decision tree, would inevitably have identified the drug-drug interaction of fluvoxamine and pirfenidone and would have arrived at the subject-matter of claim 1 without the exercise of inventive skill.

3.15 As a consequence, the subject-matter of claim 1 does not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated