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Datasheet for the decision of 29 April 2015

Case Number: T 1555/12 - 3.3.01

Application Number: 04002427.5

Publication Number: 1419776

IPC: A61K31/496, C07D215/22, A61P25/18

Language of the proceedings: EN

Title of invention:
Low hygroscopic aripiprazole drug substance and processes for the preparation thereof

Patent Proprietor:
Otsuka Pharmaceutical Co., Ltd.

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Aripiprazole polymorph/OTSUKA

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Admissibility of new documents (partly)
Novelty - main request (no)
Inventive step - auxiliary request 1 (no)
Inventive step - auxiliary request 2 (yes), improvement shown

Decisions cited:
G 0001/92, T 0777/08

Catchword:

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Case Number: T 1555/12 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 29 April 2015

Appellant: (Patent Proprietor)	Otsuka Pharmaceutical Co., Ltd. 9, Kanda-Tsukasacho 2-chome, Chiyoda-ku Tokyo 101-8535 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Opponent)	Teva Pharmaceutical Industries Ltd. 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 June 2012 revoking European patent No. 1419776 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: G. Seufert
L. Bühler

Summary of Facts and Submissions

I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division revoking European patent No. 1 419 776.

II. The patent as granted consists of 11 claims with claim 1 reading as follows:

"1. Anhydrous Aripiprazole Crystals C having a powder X-ray diffraction spectrum which has characteristics peaks at 2θ = 12.6°, 13.7°, 15.4°, 18.1°, 19.0°, 20.6°, 23.5° and 26.4°."

Further independent claims are directed to a process for the preparation of aripiprazole crystals according to claim 1 (claim 6), pharmaceutical compositions comprising them (claims 7 and 11), a process for the preparation of granules (claim 9) and a process for the manufacture of a pharmaceutical solid oral preparation comprising aripiprazole crystals according to claim 1 (claim 10).

III. The present decision refers to the following documents:

(1) US 5,006,528

(3) S. Aoki et al., The Fourth Japan-Korea Symposium on Separation Technology, 6-8 October 1996, Waseda University International Conference Center, Tokyo, Japan, CR. 119, pages 937-940.

(4) Experimental Report 1, dated 13 January 2011 and signed by Dr. S. Levi, filed by the respondent with the notice of opposition

(5) M. R. Caira, Topics in Current Chemistry, 1998, Vol. 198, pages 163 to 166

(6) Revised Annex 3, filed by the respondent with

the notice of opposition

(8) DSC and XRD measurements of Type 2 crystals, filed by the appellant with letter of 29 August 2011, one page

(9) Experimental Report, filed by the appellant with letter of 29 August 2011

(16) Untersuchungsbericht Aripiprazole by Professor R. Boese dated 31 May 2010, filed by the respondent with letter of 24 February 2012, three pages

(17) Annex III of document (16), Projektbericht Aripiprazole by Professor R. Boese and Dr. C. Schauerte, pages 1 to 24

(18) Experimental Report DYC3 including Annexes 1 and 2, dated 24 February 2012 and signed by Dr. J. Sterling and Dr. S. Levi, filed by the respondent with letter of 28 February 2012, eight pages

(21) Page 939 of document (3) with hand-written annotations, filed by the appellant during the oral proceedings before the opposition division, one page

(22) Enlargement of Figure b) of document (3), filed by the appellant during the oral proceedings before the opposition division, one page

(23) Experimental data on the thermal stability of Aripiprazole crystal C by S. Aoki, submitted by the appellant with statement of grounds of appeal, eight pages

(24) Experimental report on the preparation of Aripiprazole samples A-1, A-2, A-3 and B including Annex 1, by S. Aoki, filed by the appellant with the statement of grounds of appeal, twenty three pages

(25) Experimental report on Aripiprazole including Annexes by Professor J. Ulrich, dated

October 2012, one hundred and one pages

(28) ICH Harmonised Tripartite Guideline, "Specifications: Test Procedure and Acceptance Criteria For New Drug Substances and New Drug Products: Chemical Substances Q6A", Current step 4 version, dated 6 October 1999, pages i, ii, 1 to 31

(30) D. E. Braun et al., Journal of Pharmaceutical Sciences, Vol. 98, No. 6, 2009, pages 2010 to 2026

IV. Notice of opposition was filed by the respondent (opponent), requesting revocation of the patent in suit in its entirety on the grounds of lack of novelty and inventive step and added matter (Article 100(a) and (c) EPC). Insufficiency of disclosure (Article 100(b) EPC) was indicated as a ground for opposition on EPO Form 2300E, but was not substantiated.

V. The opposition division held that the claims as granted had a basis in the application as originally filed. Their subject-matter was novel over the disclosure of document (3), but did not involve an inventive step vis-à-vis aripiprazole Type 2 crystals described therein. In particular, the opposition division considered that the alleged improved thermal stability, although implied in the patent in suit, had not been experimentally demonstrated. The same applied to auxiliary requests 1 to 3 and auxiliary request 4 insofar as it was directed to compositions containing aripiprazole crystals C (hereinafter also referred to as "Form C"). The ground of insufficiency of disclosure was not considered by the opposition division, in view of the fact that it had not been substantiated in the notice of appeal.

VI. With the statement of grounds of appeal, the appellant defended the patent in suit on the basis of the claims as granted as its main request, and filed auxiliary requests 1 to 4. In addition, it filed documents (23) to (25).

Auxiliary request 1 differs from the claims as granted in that the features

- **having particular infrared absorption bands at 2939, 2804, 1680, 1375 and 780 cm-1 on the IR (KBr) spectrum,**
- **exhibiting an endothermic peak near about 150.2°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min),**
- **having a solid ^{13}C-NMR spectrum which has characteristic peaks at 32.8 ppm, 60.8 ppm, 74.9 ppm, 104.9 ppm, 152.2 ppm and 175.2 ppm"**

have been added to claim 1, and claims 2 to 5 as granted have been deleted.

Auxiliary request 2 differs from the claims as granted in that a reference to the powder X-ray diffraction spectrum according to Figure 10 has been added.

In auxiliary request 3 the features of auxiliary requests 1 and 2 have been combined.

Auxiliary request 4 differs from auxiliary request 1 in that the compound claim 1 has been deleted. The features of deleted claim 1 have been introduced into the independent claims.

VII. With letter of 2 March 2015, the respondent submitted document (30).

VIII. The appellant's arguments, as far as they concern the decisive issues, can be summarised as follows:

- Admission of document (23) and (30)

Document (23) had been submitted in direct response to the opposition division's reservations in point 37.8 of the decision under appeal. The admission of post-published evidence to show that the claimed subject-matter solved the objective technical problem was accepted practice, if the effects shown therein were at least suggested in the application as originally filed. This requirement was fulfilled, as was apparent from paragraphs [0005], [0006], [0023], [0026], [0029] and [0052] of the patent in suit, which referred to thermal stability and purity. Thermal stability was essential for obtaining Form C in high purity.

Document (30) was not prior art and had been filed at a very late stage in the proceedings without justification. It made allegations which were difficult to evaluate due to the missing experimental protocol, which were not in line with the data on file, and whose experimental evaluation was not possible without postponement of the oral proceedings.

- Novelty

Claim 1 as granted was directed to a single crystalline form of aripiprazole, namely Form C. This form was not present in the Type 2 crystals disclosed in document (3), as was apparent from the missing peak at 13.7° (2θ) in the powder X-ray diffraction (PXRD) spectrum in Figure 3 b) of document (3). The respondent's reproductions provided in documents (4)

and (18) were not true repetitions of the prior-art disclosure, because the aripiprazole starting material was not produced according to the only method known at the time. At least four differences were apparent, which, due to the potential formation of different impurities, could have a strong influence on the subsequently obtained crystalline products. If it occurred at all, the formation of Form C was random. Some peaks were even within the noise level. Documents (4) and (18) could therefore not be used as evidence that Form C was inevitably produced following the disclosure of document (3). Furthermore, even if the respondent's experiments were deemed to represent true reproductions, the conclusion that Form C was formed by the prior-art process was only possible with the knowledge of the invention, in particular the knowledge of the PXRD pattern provided in the patent. Furthermore, since the skilled person could not have separated and analysed Form C, it had not been made available by document (3).

The same arguments applied to auxiliary request 1. In addition, it was noted that no IR and ^{13}C-NMR data were provided in the respondent's experimental data.

- Inventive step

Type 2 crystals according to document (3) represented the closest prior art. This crystalline form had the disadvantage that it was prone to transformation into a different crystalline form at its production temperature. It could therefore not be obtained in high purity in a reliable manner. This problem was solved by the presently claimed crystalline Form C, which was thermally stable without changing into other crystalline forms and could therefore be consistently

obtained in high purity. Consistent quality was important, since it was known that differences in crystalline forms of a drug substance could affect the performance of the drug. In order to get marketing approval, tests as to safety and efficacy had to be provided. If a drug substance could not be produced in consistent quality, it had to be shown each time that safety and efficacy was not affected, in particular if the crystalline forms could not be separately obtained and independently characterised. The claimed solution was not obvious in view of the prior art. There was no indication in document (3) that a problem existed with the thermal stability/purity of Type 2 crystals. The transformation into a different crystalline form was only recognised after the publication of document (3) and there was certainly no hint that increasing the temperature to 140°C to 150°C would provide a pure crystalline form, let alone pure aripiprazole Form C.

IX. The respondent's arguments, as far as they concern the decisive issues, can be summarised as follows:

- Admission of documents (23) and (30)

Document (23) should not be admitted as it was an attempt to use post-published data as the sole means for establishing that the technical problem of providing a more heat-stable crystalline form had been solved. There was nothing in the application as filed from which the skilled person could derive an increased heat stability of Form C.

Document (30) had not been filed earlier, because it was not prior art. It corroborated the findings in documents (4) and (18) and explained the absence of the peak at 13.7° (2θ).

- Novelty

The heating of Type 1 crystals according to document (3) resulted in a crystalline product with all technical features, namely the PXRD peaks, of claim 1 as granted. This was shown in documents (4) and (18) and corroborated by the appellant's own experimental data in document (6). Claim 1 referred to aripiprazole with certain PXRD peaks. It was not limited to a pure product and the intensity or strength of those peaks was not relevant. The aripiprazole starting material in documents (4) and (18) was prepared using a method similar to example 1 of document (1) and differed only in some minor aspects. There was no evidence that these differences had any effect on the polymorphic transformation of aripiprazole on heating. Moreover, the presence of impurities which allegedly could have been formed and could have influenced the heating step was not plausible in view of the fact that the aripiprazole starting material was recrystallised for the preparation of Type 1 crystals.

The subject-matter of claim 1 of the auxiliary request 1 was also anticipated by document (3), since, according to the appellant, the additional features were inherent features of Form C, and Form C was inevitably formed as shown in documents (4) and (18).

- Inventive step

The post-published data in document (23) should not be considered. The problem to be solved was therefore the provision of an alternative form of aripiprazole, which was not inventive following the reasoning in decision T 777/08. Even if advantages in thermal stability and

purity were acknowledged, they were not technically meaningful and should not be taken into account for the assessment of inventive step. An increased stability at 140°C over an extended period of time was irrelevant, since it did not reflect conditions that a pharmaceutical product would be subjected to during formulation, packing or transport. Furthermore, no evidence had been provided that the pharmaceutical performance of pure Form C differed from that of Type 2 or a mixture of Form C and Type 2. There was nothing wrong with different crystalline forms being present, in particular if their ratio stayed the same. Even fluctuation mattered only if the drug performance was impaired.

The same arguments applied for auxiliary requests 1 and 2. In addition, identification of IR and ^{13}C-NMR signals was routine work for the person skilled in the art. Therefore, the subject-matter of claim 1 of auxiliary request 1, even if novel, did not involve an inventive step.

X. The appellant requested that the decision under appeal be set aside and the patent be maintained as granted or, alternatively, on the basis of one of auxiliary requests 1 to 4 filed with the statement of grounds of appeal of 15 October 2012.

The respondent requested that the appeal be dismissed.

XI. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of documents (23) and (30)

2.1 Document (23) was filed with the statement of grounds of appeal, in direct response to the decision of the opposition division revoking the patent in suit. The appellant challenged the division's findings on inventive step and filed document (23) in an attempt to address the division's objection concerning the lack of experimental evidence with respect to the alleged improved thermal stability (see point 37.8 of the decision under appeal). Although the division was of the opinion that paragraph [0023] of the patent in suit implied that aripiprazole Form C was more stable than other forms, it considered that this had not been clearly and unambiguously shown by the experimental data on which the appellant relied in this respect. In these circumstances, the board is of the opinion that the submission of document (23), filed with the statement of grounds of appeal, is an appropriate and legitimate attempt by the appellant to address the concerns raised in the decision under appeal and to further support its position with respect to inventive step.

2.2 The board also notes that it is established jurisprudence of the boards of appeal that additional advantages not themselves explicitly mentioned in the application as filed may be taken into account in support of patentability, as long as these advantages are associated with the problem initially suggested and do not alter the character of the invention.

In the present case, it is indicated in the patent in suit that Type 2 crystals of the prior art which were prepared by heating Type 1 crystals at 130 to 140°C for 15 hours cannot be obtained in high purity. Accordingly, one of the objects of the invention was the provision of a crystalline form of aripiprazole with high purity on an industrial scale with good repeatability (see paragraphs [0005], [0006], [0009] or [0026]). The appellant had already shown during the examination proceedings that Type 2 crystals were susceptible to a change in crystalline state under the conditions under which they were prepared (see document (6), cf. PXRD spectra of Type 2 crystals after heating at 8 hours with those at 20, 32 or 48 hours). Thus, in the board's opinion, the question of thermal stability is closely associated with the question of purity and therefore to the problem initially suggested. By taking the thermal stability into account the character of the invention is not altered. The board therefore sees no reason to disregard the supplementary data concerning the thermal stability provided in document (23).

2.3 Hence, the board decided to admit document (23).

2.4 Document (30) was filed by the respondent at a very late stage of the appeal proceedings (i.e. less than two months before the oral proceedings) in further support of its objection of lack of novelty of the main request. No justification for the late filing of this document was provided. In particular, no reasons were given, and none were apparent to the board, as to why this document could not have been filed with the respondent's reply to the statement of grounds of appeal, in which it challenged the opposition division's findings that the claimed subject-matter was

novel. If the objection of lack of novelty required further support, it was the respondent's obligation pursuant to Article 12(2) of the Rules of Procedure of the Boards of Appeal (RPBA) to file the necessary evidence as soon as possible in order to give the appellant a fair opportunity for a proper evaluation of any new evidence.

The board also notes that document (30) does not belong to the state of the art and is based on findings acquired after the priority date of the patent in suit. Moreover, the "conclusions" on page 2025, left column, lines 3 to 14, on which the respondent relied, are not supported by any experimental evidence and do not allow a proper verification by the appellant and the board. Admitting document (30) would have required adjournment of the oral proceedings, in order to give the appellant a fair chance to properly evaluate its teaching, scrutinise the assertions made therein and provide further experimental evidence, if considered necessary.

2.5 Hence, for reasons of procedural economy, the board decided not to admit late-filed document (30) (Article 13(1) and 13(3) RPBA).

2.6 At the oral proceedings before the board, the respondent did not maintain its objection against the admission of documents (24) and (25). The board sees no reason to disregard these documents, which were filed with the statement of grounds of appeal (Article 12(4) RPBA).

Main request

3. Understanding of claim 1

3.1 Claim 1 of the patent in suit refers to anhydrous aripiprazole crystals C with certain characteristic peaks in the PXRD spectrum (see point II above).

According to the appellant, this claim was directed to a single, highly pure crystalline form of aripiprazole. Moreover, the appellant argued that the expression "characteristic peaks" had a specific meaning in the sense that it referred only to "strong peaks".

3.2 The board disagrees with this understanding of claim 1. According to its wording, claim 1 is directed to a crystalline product of aripiprazole with certain peaks in the PXRD spectrum. It encompasses any crystalline form of aripiprazole which shows the required peaks, irrespective of whether it is a single crystalline form or a mixture of crystalline forms. The designation "crystals C" is merely a label and does not limit claim 1 in any way. Furthermore, the board concurs with the respondent that PXRD peaks are characteristic because they define a crystalline form by their presence, not by their strength or intensity. In this context, the board also notes that the patent in suit does not attribute a specific meaning, i.e. a particular strength or intensity, to the term "characteristic peaks". Moreover, as pointed out by the respondent, the eight peaks listed in claim 1 of the main request are not the eight strongest peaks in the PXRD spectrum of Form C according to Figure 10 of the patent in suit.

4. Novelty

4.1 According to the respondent, who challenged the decision of the opposition division with respect to novelty, a crystalline form of aripiprazole with PXRD

peaks according to claim 1 was inevitably obtained when preparing aripiprazole Type 2 according to the method disclosed in document (3). This method consists of heating aripiprazole Type 1 crystals at 130 to 140 °C for 15 hours (see page 938, last paragraph, lines 2 to 4). In support of its assertion, the respondent relied on documents (4) and (18).

4.2 Document (4) describes the results of five experiments in which aripiprazole Type 1 crystals were heated at 135°C or 140°C for 15 hours as described on page 938 of document (3) (see last paragraph, lines 2 to 4). The identity of Type 1 crystals was demonstrated by the PXRD spectra shown in Annex 1 of document (4). The peak pattern in these spectra tallies well with the pattern of Type 1 crystals in Figure 3 a) of document (3). The PXRD spectra of the crystalline products obtained after heating Type 1 crystals were measured, and a list of all peaks is given in table III. According to this table, all peaks of claim 1 as granted are present. Document (18) describes a further example in which aripiprazole Type 1 crystals, identified by PXRD spectrum and melting point, were heated to 140°C for 15 hours. The PXRD spectrum of the obtained crystalline product has all peaks required by claim 1 of the patent in suit (see pages 3 and 4 and Figure 1 of document (18)).

It follows from the above that a crystalline form of aripiprazole with PXRD peaks according to claim 1 is obtained when heating Type 1 crystals under the conditions described in document (3).

4.3 According to the appellant, documents (4) and (18) were not proper reproductions of the disclosure of document (3) and therefore could not serve as evidence

that the claimed aripiprazole Form C was indeed formed. In particular, it was argued that the aripiprazole starting material (i.e. the starting material for the preparation of Type 1 crystals, which, in turn, are the starting material for the heating step) in the respondent's experiments was not prepared according to the only method known at the time, which was the method disclosed in example 1 of document (1). The appellant, in line with the opposition division, argued that the observed differences could lead to the formation of impurities, which in turn could affect the properties and the subsequent reactions of the aripiprazole material thus obtained. In this context, reference was made to document (5).

4.4 The board does not agree. As pointed out by the board, the method used by the respondent, although not identical in every detail to example 1 of document (1), is nevertheless identical to the synthetic method generally disclosed in said document, namely the substitution of the halogen atom in a bromobutoxy substituted carbostyril derivative by the respective piperazine in the presence of an inorganic or organic base as dehydrohalogenating compound (see column 4, lines 7 to 39). As a consequence, the aripiprazole starting material was correctly prepared. Moreover, in order to obtain aripiprazole Type 1 crystals, the aripiprazole starting material was recrystallised (see document (4), page 2, third paragraph and document (18), page 2, first paragraph under the heading "Preparation of aripiprazole type-1 crystals"). Even assuming that the aripiprazole starting material, depending on the details of its preparation, contains (different) impurities, there is no evidence that such impurities are still present in the (recrystallised) Type 1 crystals, let alone that they have an influence

on the outcome of the subsequent heating step. In the absence of such evidence, the appellant's allegations are not persuasive.

Document (5), on which the appellant relied, states that the process of crystallisation is affected by many physical parameters, amongst them the presence of impurities, and that minor variations can tip the balance in favour of a crystalline form which is not necessarily the most stable one (see page 164, line 19 to 25). However, this very general statement does not constitute conclusive evidence that in the present case variations in the general method disclosed in document (1) lead to the formation of different impurities, that these impurities are still present after recrystallisation and that they do indeed influence the outcome of the heating process.

4.5 In order to further demonstrate that crystallisation conditions can have a strong influence on the obtained crystalline form, the appellant also relied on documents (9), (16), (17) and (25). The board fails to see the significance of these documents. They concern the preparation of aripiprazole Type 1 crystals which, depending on the crystallisation conditions, apparently differ in their hygroscopicity. These crystals have not been heated. Hence, documents (9), (16), (17) and (25) cannot be relied on as evidence that impurities in Type 1 crystals or their different hygroscopicity have any influence on the outcome of the heating process.

4.6 The board also does not share the appellant's and opposition division's view that the alleged absence of a PXRD peak at 13.7° (2θ) in Figure 3 b) of document (3) is a clear and unambiguous indication that the claimed crystalline form is not obtained.

4.7 The spectrum in Figure 3 b) is very small and of rather poor quality. It cannot be used as evidence for the absence of a peak at 13.7°(2θ), particularly in view of the fact that such a peak may be rather small (see document (4) and (18)) and could easily have disappeared during down-scaling of the original spectrum. Therefore, Figure 3 b) in document (3) cannot be used to refute the respondent's results in documents (4) and (18). The same applies to document (21), which is a copy of page 939 of document (3) supplemented by the appellant with hand-written amendments concerning the scale on the 2θ axis, which is not present in original Figure 3 b) of document (3), and to document (22), which is an "enlargement" of Figure 3 b) of document (3). In the board's opinion, an enlargement of the low quality, down-scaled spectrum is not more meaningful than the "original" spectrum (i.e. figure 3 b).

Concerning document (8), on which the appellant also relied in this context, the board notes that the peak list is incomplete. In particular, none of the peaks in the area below 16°(2θ) has been identified. No conclusion regarding the presence or absence of a peak at 13.7°(2θ) can therefore be drawn.

4.8 The appellant also argued that the peaks identified by the respondent in documents (4) and (18) were small and within the noise level and that it was only with hindsight that a skilled person could identify the crystalline Form C. Form C had therefore not been made available. The decision G 1/92 was mentioned in support.

4.9 These arguments are not convincing. Neither the purity nor the intensity or strength of the PXRD peaks are features of claim 1. As set out in point 3 above, claim 1 refers to a crystalline form of aripiprazole with certain peaks being present in the PXRD spectrum, irrespective of whether this form is a single crystalline form (i.e. a single polymorph) or a mixture. In this context, it is not relevant whether or not the skilled person was aware of the fact that some of the identifiable peaks may belong to a different polymeric form. Neither is it relevant whether or not it would have been possible for the skilled person to separate the different crystalline forms.

4.10 For the above-mentioned reasons, the board concludes that claim 1 of the main request lacks novelty within the meaning of Article 54 EPC.

Auxiliary request I

5. Understanding of claim 1

5.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that a limited number of infrared (IR) absorption bands and ^{13}C-NMR peaks and a particular melting point (endothermic peak) have been introduced (see point VI above).

5.2 The presence of certain IR absorption bands or ^{13}C-NMR peaks is not an indication of the purity of a crystalline form. Insofar as they characterise a specific crystalline form, the same signals will also be present in any mixture containing this form. Claim 1 of auxiliary request 1 is therefore not limited to a specific, highly pure crystalline form of aripiprazole as argued by the appellant (see also point 3 above).

The board also notes that there is apparently no difference between the melting point of Type 2 crystals obtained in document (3) (150 °C) and the melting point (endothermic peak) of the presently claimed crystalline form.

6. Novelty

6.1 Document (3) does not disclose IR- or ^{13}C-NMR data for Type 2 crystals. Nor has the respondent provided such data in its experiments concerning the reproduction of the disclosure of document (3) (see documents (4) or (18)). It cannot therefore be concluded with the required certainty that the crystalline form according to claim 1 of auxiliary request 1 is disclosed in document (3). In other words, although the respondent has shown that a crystalline form with all the required PXRD peaks is inevitably obtained, it has not shown that this product is without any doubt the presently claimed crystalline form.

7. Inventive step

7.1 Document (3) is considered by both parties as the closest state of the art. The board has no reason to disagree with this choice. As mentioned in point 4.1 above, this document discloses a crystalline form of aripiprazole designated as Type 2 crystals and "characterised" by an PXRD spectrum (Figure 3 b)) and a melting point. Type 2 crystals were prepared by heating Type 1 crystals at 130 to 140 °C for 15 hours. The appellant has realised - and the board has no reason to doubt the appellant's findings - that due to the thermal instability of the Type 2 crystals (see

document (6)) this method does not allow the provision of a crystalline product of consistent quality.

The board notes that document (3) also discloses a crystalline form designated as Type 1 crystals. However, taking into account the purpose of the patent in suit, namely seeking to overcome the disadvantages of Type 2 crystals, the board is of the opinion that Type 1 crystals are not a reasonable starting point for the assessment of inventive step.

7.2 In the light of document (3), the appellant defined the problem to be solved as the provision of a thermally stable crystalline form of aripiprazole which can be obtained in high purity in a reliable manner (see also paragraphs [0005], [0006] and [0009] of the patent in suit).

The proposed solution was the crystalline form according to claim 1 of the first auxiliary request.

7.3 However, as explained in point 5 above, claim 1 of the first auxiliary request is not limited to a thermally stable, highly pure crystalline form of aripiprazole (i.e. a single polymorph as argued by the appellant), but also encompasses mixtures with Type 2 crystals which are thermally instable (see document (6)), in more or less any amount.

The board is, therefore, not satisfied that the technical problem as formulated in point 7.2 above is successfully solved by the claimed subject-matter. Accordingly, the problem to be solved has to be defined in a less ambitious way as the provision of a further crystalline form of aripiprazole.

7.4 It remains to be decided whether or not the proposed solution is obvious for the skilled person.

The board concurs with the appellant that the mere provision of a crystalline form is not regarded as involving an inventive step. Investigation of whether active compounds are prone to crystalline transformation and characterisation of such crystalline forms is routine practice in the pharmaceutical industry.

According to document (3) the crystalline form characterised as Type 2 is prepared by heating Type 1 crystals at a temperature range between 130 and 140°C for 15 hours. At this temperature Type 2 crystals are apparently not stable and transform into a different crystalline form or forms (i.e. mixtures of polymorphic forms). Although the appellant was the first to report this transformation, the board is of the opinion that the same observation was within the normal skills of any person skilled in the art following the teaching of document (3). In view of regulatory requirements the skilled person would then routinely examine the conditions for this transformation and investigate the respectively obtained crystalline form(s). The mere provision of a further crystalline form, including mixtures, as the result of such routine investigations and routine experimentation does not require inventive skills.

7.5 The appellant's arguments that this identification was not possible in view of the fact that Form C was present only in small amounts, if at all, and that therefore the signals would be hidden under the signals of Type 2 crystals, is not convincing in the absence of any corroborating evidence.

7.6 For the aforementioned reasons, the board concludes that the subject-matter of claim 1 of auxiliary request 1 is not inventive, contrary to Article 56 EPC.

Auxiliary request 2

8. Amendments and novelty

8.1 Amended claim 1 is supported by the application as filed (see figure 10) and limits the subject-matter of claim 1 as granted. The requirements of Article 123(2) and (3) EPC are therefore complied with. No objection had been raised by the respondent.

8.2 The respondent also had no novelty objection to the claimed subject-matter. The board sees no reason to take a different view. It is therefore not necessary to consider this issue further.

9. Inventive step

9.1 In the light of document (3), the appellant defined the problem to be solved as the provision of a thermally stable crystalline form of aripiprazole which can be obtained in high purity in a reliable manner (see also paragraphs [0005], [0006] and [0009] of the patent in suit).

The proposed solution is the crystalline form according to claim 1 of the second auxiliary request.

9.2 In view of the available data (documents (6) and (23)), the board is satisfied that the problem has been solved. The complete PXRD spectrum in claim 1 characterises a single specific crystalline form,

contrary to claim 1 of the main request and auxiliary request 1 (see points 3.2 and 5.2 above). Unlike Type 2 crystals of document (3), the crystalline form according to claim 1 of auxiliary request 2 is stable at its production temperature and can be obtained without transformation into another crystalline form (cf. document (6), PXRD spectra of Type 2 crystals and document (23), PXRD spectra in Figures 3 to 5).

9.3 The respondent argued that document (23) should not be admitted and accordingly defined the problem to be solved as the provision of a mere alternative crystalline form.

9.4 For the reasons set out in points 2.1 and 2.2 above, the board decided to admit document (23). Moreover, in the board's judgment, documents (23) and (6) in combination show the alleged advantages of the claimed crystalline form over the Type 2 crystals. Therefore, the board sees no reason to reformulate the problem to be solved as set out in point 9.1 above.

9.5 It then remains to be decided whether or not the proposed solution was obvious in view of the prior art.

The present invention is based on the appellant's realisation that Type 2 crystals are not stable under the conditions at which they are prepared and are prone to transform into a different crystalline form. This transformation renders it difficult to prepare Type 2 crystals of constant quality in a reliable manner. As explained in point 7.4 above, the board is of the opinion that, although any skilled person applying the teaching of document (3) would have realised that a problem existed in this respect, no indication as to the technical measures necessary to solve it can be

found in document (3), which is the only available document referring to production of Type 2 crystals. In particular, it was not obvious for the skilled person that Type 1 crystals according to document (3) could be transformed into a crystalline form that, unlike Type 2 crystals, is thermally stable and can therefore be obtained in constant quality (or high purity as the appellant characterised it) in a reliable manner.

9.6 The respondent argued that even if the alleged advantage concerning the thermal stability was accepted, it was not a technically meaningful property. Aripiprazole was a drug intended to be used in a pharmaceutical composition. Nowhere during formulation, packaging, transport, use, etc. would a pharmaceutical composition be exposed to a temperature of 140 ^{o}C. The alleged thermal stability was therefore completely irrelevant and the problem to be solved entirely artificial.

9.7 However, this argument neglects the fact that the problem to be solved arose from the hitherto unrecognised thermal instability of Type 2 crystals under the conditions at which they were prepared. This affects the quality/purity of the resulting crystalline product. The fact that the product, once obtained, would never be subjected to temperature of 140 ^{o}C is of no relevance in this respect.

9.8 The respondent also argued that the presence of a different crystalline form was of no significance, particularly if the ratio between the different forms remained constant. Even fluctuation in the ratio mattered only, if it affected the safety, performance or efficacy of the drug product (see document (28), last paragraph on page 8, page 9, second and third

paragraphs and "decision tree 4" on pages 24 and 25). If this was not the case, the presence of different crystalline forms in a drug product was of no concern to the regulator. No data had been provided by the appellant showing that the safety, performance or efficacy of Type 2 crystals was in any way affected by the presence of Form C. The purity of the crystalline forms was therefore equally irrelevant for the assessment of inventive step.

9.9 The board does not agree with the respondent.

The provision of a drug substance in consistent quality/high purity is undoubtedly crucial for any drug manufacturer, since the presence of impurities - including different crystalline forms - may affect the safety, performance or efficacy of the drug substance (see document (28), page 8, last paragraph).

According to the patent in suit, Type 2 crystals of document (3) cannot be obtained in high purity in a reliable manner. They are prone to transformation into a different crystalline form under the conditions under which they were prepared (see document (6)), which results in the formation of a mixture of different crystalline forms in the process according to document (3). Indeed, the formation of such a mixture has been confirmed by the respondent's experimental evidence (see documents (4) and (18)). In contrast, the claimed crystalline form is obtained in a stable form without showing any tendency of transformation (see document (23) Figure 3 to 4). As explained in the above paragraph, this already represents a considerable advantage, since it does not require particular efforts to monitor and control the content of a different crystalline form.

Furthermore, the board is of the opinion that investigations as to whether product safety, performance or efficacy is impaired by the presence of a different crystalline form and the subsequent setting of acceptance criteria for the content/ratio of the different crystalline forms implies that these forms can be isolated and separately examined. In the present case, no information as to how the different crystalline form can be separated from Type 2 crystals is provided in document (3). Nor has it been argued, let alone shown, that such a separation can be achieved by the person skilled in the art with conventional techniques. Accordingly, no acceptance criteria can be established. It follows that if Type 2 crystals are not obtained in consistent quality - and the board has no reason to doubt this in view of their thermal instability as shown in document (6) and in the absence of any evidence to the contrary - tests have to be carried out for each batch of said crystals in order to guarantee that it is safe to use for the intended purpose. In these circumstances, the provision of a stable crystalline form in constant quality/purity - either of Type 2 or the other crystalline form (or forms) inevitably present in the crystalline product of document (3) - is undoubtedly a major advantage.

9.10 For the aforementioned reason, the board concludes that the subject-matter of claim 1 of auxiliary request 2 and by the same token that of claims 2 to 6 involves an inventive step (Article 56 EPC).

10. Since auxiliary request 2 is considered to be allowable, it is not necessary to decide on auxiliary requests 3 and 4.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the following claims and a description to be adapted thereto:

   claims No 1 to 11 of auxiliary request 2 filed with the statement of grounds of appeal of 15 October 2012.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated