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Datasheet for the decision of 10 January 2025

Case Number:	T 2217/21 - 3.3.02
Application Number:	10010049.4
Publication Number:	2322517
IPC:	C07D279/18, A61K31/54, A61P35/00, A61P25/28
Language of the proceedings:	EN

Title of invention:

METHODS OF CHEMICAL SYNTHESIS AND PURIFICATION OF DIAMINOPHENOTHIAZINIUM COMPOUNDS INCLUDING METHYLTHIONINIUM CHLORIDE (MTC)

Patent Proprietor:

WisTa Laboratories Ltd.

Opponents:

Provepharm Life Solutions/Provepharm
Grünecker Patent- und Rechtsanwälte
PartG mbB

Relevant legal provisions:

EPC Art. 83, 123(2)

Keyword:
Amendments
Sufficiency of disclosure
Remittal to the department of first instance

Decisions cited:
G 0007/93, T 0640/91, T 0544/12

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Case Number: T 2217/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 10 January 2025

Appellant: (Patent Proprietor)	WisTa Laboratories Ltd. 25 Bukit Batok Crescent The Elitist 06-13 Singapore 658066 (SG)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Respondent: (Opponent 1)	Provepharm Life Solutions/Provepharm Les Baronnies 22 rue Marc Donadille 13013 Marseille (FR)
Representative:	Bandpay & Greuter 11, rue Christophe Colomb 75008 Paris (FR)
Respondent: (Opponent 2)	Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstrasse 4 80802 München (DE)
Representative:	Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstraße 4 80802 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 October 2021 revoking European patent No. 2322517 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the patent proprietor (hereinafter appellant) lies from the decision of the opposition division according to which European patent 2 322 517 was revoked.

II. The following documents *inter alia* were submitted by the parties in opposition proceedings:

D32: "Test report: Reproduction of Annex C"
D35: "Test report: HPLC Analysis of a methylene blue + glycine mixture"
D65: "Experimental Report - Example of MTC"
D72: "Analysis of a mixture of methylene blue and glycine"
D73: "Attempted purification of methylene blue"
D85: Ramsay *et al.*, British journal of pharmacology (2007), vol. 152, pages 946-951
D86: Popescu *et al.*, J. Natl. Cancer Inst., vol. 59, No. 1, July 1977, pages 289-293.

III. According to the contested decision, the ground for opposition under Article 100(c) EPC did not prejudice the maintenance of the patent as granted. It was however decided that the invention defined in claim 1 of the main request was not sufficiently disclosed on the basis that the skilled person would have been unable to prepare the high purity diaminophenothiazinium compound of claim 1 with a purity as defined in claim 1.

IV. In a communication pursuant to Article 15(1) RPBA, the board *inter alia* indicated that the subject-matter of claim 1 of the main request appeared to contravene Article 123(2) EPC.

V. Oral proceedings by videoconference took place as scheduled on 10 January 2025 in the presence of the appellant and opponents 1 and 2 (hereinafter respondents 1 and 2 respectively).

VI. Requests relevant to the present decision

The appellant requested that the contested decision be set aside and that, on condition that the set of claims of auxiliary request 20 be part of the appeal proceedings, the patent be maintained on the basis of auxiliary request 20, submitted with the statement of grounds of appeal, and identical to auxiliary request 18 submitted during oral proceedings before the opposition division. In that situation, the main request and auxiliary requests 1 to 19 were withdrawn.

Respondents 1 and 2 both requested dismissal of the appeal.

Both respondents also requested that auxiliary request 20 not be admitted into appeal proceedings.

VII. For the text of claim 1 of the auxiliary request 20, reference is made to the reasons for the decision set out below.

VIII. For the relevant party submissions, reference is made to the reasons for the decision set out below.

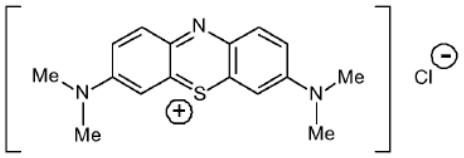
Reasons for the Decision

Auxiliary request 20

1. Admittance

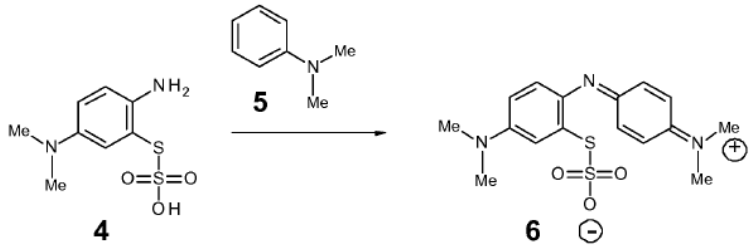
1.1 Claim 1 of auxiliary request 20 reads as follows:

1. A high purity diaminophenothiazinium compound of the following formula:



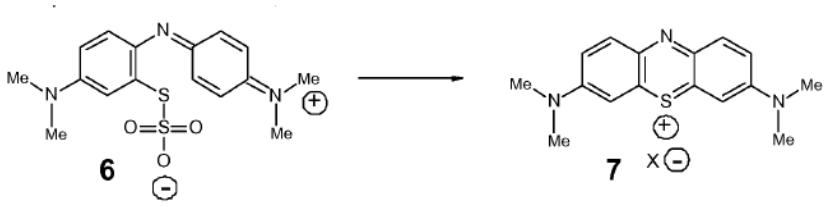
~~*wherein:*~~
wherein high purity is characterised by a purity of greater than 98% and one or more of the following:
less than 2% Azure B as impurity;
~~*less than 0.13% Methylene Violet Bernthsen (MVB) as impurity;*~~
*an elementals purity better than the European Pharmacopoeia (EP) limits of 100 µg/g Aluminium (Al), 10 µg/g Chromium (Cr), 10 µg/g Zinc (Zn), 10 µg/g Copper (Cu), 100 µg/g Iron (Fe), 10 µg/g Manganese (Mn), 10 µg/g Nickel (Ni), 10 µg/g Molybdenum (Mo), 1 µg/g Cadmium (Cd), 1 µg/g Tin (Sn) and 10 µg/g Lead (Pb) which is **obtainable** by a method of synthesis comprising the steps of, in order:*
*oxidative coupling (OC), in which a thiosulfuric acid S-{2-(amino)-3-(optionally substituted)-5-(disubstituted amino)-phenyl} ester, **4**, is oxidatively coupled to an N,N-disubstituted-3-optionally substituted-aniline, **5**, using an oxidizing agent that is or comprises Cr(VI), to give a [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally*

substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-N,N-disubstituted ammonium, ***6:***



isolation and purification of zwitterionic intermediate (IAPOZI), in which said [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-N,N-disubstituted ammonium, ***6****, is isolated and purified;*

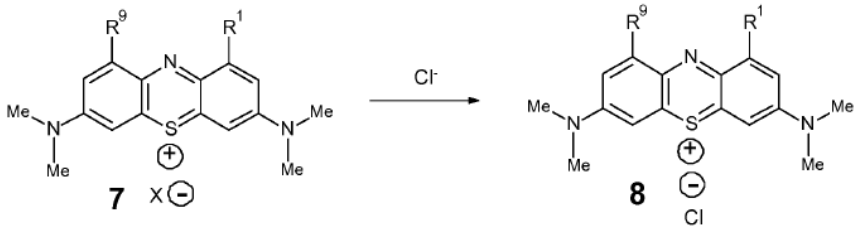
ring closure (RC), in which said isolated and purified [4-{2-(thiosulfate)-4-(disubstituted amino)-6-(optionally substituted)-phenyl-imino}-3-(optionally substituted)-cyclohexa-2,5-dienylidene]-N,N-disubstituted ammonium, ***6****, is subjected to ring closure to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt,* ***7:***



further comprising, after said ring closure (RC) step, the additional step of:

chloride salt formation (CSF), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium salt, 7, is reacted with chloride,

to give a 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, ***8:***



further comprising, after said chloride salt formation (CSF) step, the additional step of:
sulphide treatment (ST), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, ***8****, is treated with a sulphide; further comprising the subsequent additional step of:*
organic extraction (OE), in which said 3,7-bis(disubstituted-amino)-1,9-(optionally substituted)-phenothiazin-5-ium chloride salt, ***8****, in aqueous solution or suspension, is treated with (e.g., washed with) an organic solvent;*
wherein said organic solvent used in said organic extraction (OE) is dichloromethane (CH_2Cl_2, DCM)."

(strike through and underlined text denoting deletion and addition compared to claim 1 of the claims as granted)

1.2 For ease of reference, the high purity diaminophenothiazinium compound, i.e. the first compound depicted structurally in claim 1 above, is referred to in the following as "MTC", the same abbreviation used by the parties in their written submissions and during oral proceedings.

1.3 Auxiliary request 20 was submitted during oral proceedings before the opposition division as auxiliary

request 18, and was admitted into the proceedings. This request is referred to hereinafter exclusively as auxiliary request 20.

1.4 Compared to claim 1 of the main request before the opposition division (the claims as granted), claim 1 of auxiliary request 20 differs in two aspects, namely:

- the deletion of the option whereby the compound contains "less than 0.13% Methylene Violet Bernthsen (MVB) as impurity", and;

- the limitation of claim 1 to a compound obtainable by the method of synthesis of granted claim 2 (hereinafter "product-by-process features").

1.5 The opposition division decided to admit auxiliary request 20 into the proceedings on the grounds that in view of the several attacks submitted by the respondents, the appellant could not reasonably have been expected to provide all possible fall-back positions prior to oral proceedings. Furthermore, claim 1 resulted from the combination of granted claims 1 and 2 and a further straightforward deletion of one of the three alternatives pertaining to the claimed purity profile, such that its analysis did not require any particular extra effort for the parties (decision, page 16, point 6.1).

1.6 Both respondents requested that the decision of the opposition division to admit auxiliary request 20 be overturned, and that this claim request not be admitted into appeal proceedings.

1.7 The board firstly notes that in some decisions of the boards of appeal, it was held that the EPC does not provide any legal basis for excluding from appeal proceedings claim requests which were admitted by the opposition division, particularly if the contested decision was based on them. The following is based on the assumption that, contrary to these decisions, the board has discretion to overturn the opposition division's decision to admit auxiliary request 20 into the proceedings. Furthermore, it is assumed in the following that the case law developed on how boards of appeal review decisions of an opposition division not to admit a certain claim request equally applies by analogy to the review of decisions of an opposition division to admit a certain claim request.

1.8 According to this case law, the boards should overrule the way in which the opposition division exercised its discretion only if it concludes that the opposition division took its decision in accordance with the wrong principles, without taking the right principles into account or in an arbitrary or unreasonable way, thereby exceeding the proper limits of its discretion (e.g. G 7/93, reasons 2.6; T 640/91, reasons 6.3). A precondition of this case law is that an opposition division has the discretionary power to admit or not to admit a certain claim request. If no such discretion is available, the opposition division must admit the claim request in question. It is therefore decisive in the present case whether the opposition division had any discretion not to admit auxiliary request 20. A precondition for having discretion is that the request was filed late. It will therefore be examined in the following whether auxiliary request 20 was filed late.

1.9 The respondents argued that the request was late-filed because the objections it attempted to overcome had already been raised with the notices of opposition.

1.10 The board disagrees. As stated by the opposition division (point 6.1 of the decision), during opposition proceedings, there were many different objections submitted by the respondents in the context of sufficiency of disclosure. In line with the opposition division's decision, in the board's view, the appellant could not have reasonably been expected to provide, prior to the oral proceedings, all possible fall-back positions in response to all of these objections. Specifically, in view of the many objections on file, the appellant cannot have been expected to submit upfront, for example, in advance of the oral proceedings, a potentially excessive number of auxiliary requests overcoming not only each of the objections raised, but also auxiliary requests intended to deal with more than one of the sufficiency objections raised.

1.11 This conclusion does not change in view of the preliminary opinion of the opposition division accompanying the summons to oral proceedings, dated 16 February 2021, which did not give any negative conclusion on sufficiency of disclosure. More specifically, the division provided the preliminary view that some of the respondents' objections were not convincing (e.g. points 6.3.1 and 6.3.3) and, concerning the question of whether the application as filed sufficiently disclosed the synthesis and purification methods allowing the skilled person to prepare MTC, merely stated that the experimental evidence on file would need to be discussed during oral proceedings.

1.12 Aside the information that these issues would be addressed at the oral proceedings, the preliminary opinion of the opposition division gave no further indication as to which specific aspects of granted claim 1 may potentially lead to a finding of lack of sufficient disclosure, for example, in relation to the three alternative purity profiles stipulated for the claimed MTC.

1.13 There was thus no need for the appellant to file auxiliary request 20 in reply to the opposition division's preliminary opinion.

1.14 Although during oral proceedings, the evidence in question (in particular D65 and D32) was addressed, there is no indication either from the decision of the opposition division, nor from the minutes of oral proceedings, that any further information was provided by the opposition division during the oral proceedings in relation to its thinking concerning the issues underlying sufficiency of disclosure. In particular, before the submission of auxiliary request 20 during oral proceedings, there is no indication that the appellant was informed in any way of the reasons underlying the opposition division's conclusions under sufficiency of disclosure for the higher ranking requests, namely the main request and auxiliary requests 1 to 17. According to the minutes of oral proceedings (page 3, fourth and fifth paragraphs), the chairperson of the opposition division merely noted that none of these requests seemed to overcome the objection of lack of sufficiency. According to the minutes, after this conclusion was announced, the appellant was allowed to file one further request, namely present auxiliary request 20. The board

therefore sees no reason why auxiliary request 20 should have been filed during the oral proceedings at an earlier point in time than the one chosen by the appellant, or even before the oral proceedings. This request has thus not been filed late.

1.15 The filing of this request moreover constitutes a *bona fide* attempt to overcome any potential reason that at that point the appellant could assume to have led to the opposition division's negative conclusion on sufficiency of disclosure as regards the higher-ranking requests. More specifically, as stated by the appellant at oral proceedings before the board and not disputed by the respondents, the lack of product-by-process features in claim 1 as granted also formed the basis for one of the respondents' attacks under sufficiency of disclosure. Therefore, the insertion of the product-by-process features into claim 1 of auxiliary request 20 deals with this objection. In relation to the deletion of the feature whereby the compound contains "less than 0.13% Methylene Violet Bernthsen (MVB) as impurity", the board notes that a central aspect of the discussion under sufficiency of disclosure before the opposition division was that none of the processes exemplified in the patent described an MTC product having the required purity of greater than 98% and less than 0.13% of MVB as impurity. With the deletion of this feature in claim 1, the fulfilment of the requirement that the claimed compound contains less than 0.13% MVB is no longer a prerequisite for acknowledging that the invention defined in claim 1 is sufficiently disclosed.

1.16 In view of the above, the board comes the conclusion that there is no reason to set aside the opposition division's decision to admit auxiliary request 20.

1.17 Consequently, the board decided during oral proceedings not to set aside the opposition division's decision to admit auxiliary request 20 into opposition proceedings. This request therefore remains part of the appeal proceedings.

2. Amendments - 123(2) EPC

2.1 The respondents submitted that claim 1 of auxiliary request 20 failed to meet the requirements of Article 123(2) EPC.

2.2 The application for the present patent was filed pursuant to Article 76 EPC as a divisional application of earlier European application 05783989.6, published as WO 2006/032879 A2 ("parent application as filed"). The divisional application as filed comprised:

- description pages 1-95, which were identical to pages 1-95 of the parent application as filed,
- description pages 96-116, which were identical to the claims on pages 96-116 of the parent application as filed, with the exception that the heading "Claims" was replaced with the sentence "Further aspects and embodiments of the present invention are listed in the following numbered paragraphs" and the words "claim" and "claims" in said numbered paragraphs were replaced with "paragraph" and "paragraphs", respectively, and
- pages 117-122 corresponding to the claims of the divisional application.

2.3 According to the contested decision, since basis for the claims as granted (then main request) was provided by the claims of the parent application as filed,

Article 76(1) EPC was fulfilled. Furthermore, the description of the divisional application as filed was, in terms of disclosure, identical to the parent application as filed. The only difference was that the divisional application as filed included the claims of the parent application as filed, reproduced identically but as "aspects and embodiments of the invention", presented as "numbered paragraphs", rather than claims as such. Hence, the claims as granted also fulfilled the requirements of Article 123(2) EPC.

2.3.1 This conclusion was challenged by respondent 1 in appeal. It was essentially argued that the claims in the parent application as filed did not have the same function as the list of numbered paragraphs in the description of the divisional application as filed. Specifically, in the parent application as filed, it was permitted to combine claims with others claims linked by dependency, or to combine claims with passages of the description, while in the description of the divisional application as filed, this was not permitted.

2.3.2 The board does not follow the respondent's view. As stated above, the "numbered paragraphs" in the divisional application as filed are identical to the claims of the parent application as filed, also in terms of dependency. There is no reason to conclude that a particular disclosure in the claims of the parent application as filed could be combined, while the same would not apply to an identical disclosure within the description of the divisional application as filed in relation to the "numbered paragraphs".

2.3.3 Consequently, there is no difference between the basis provided by the claims of the parent application as

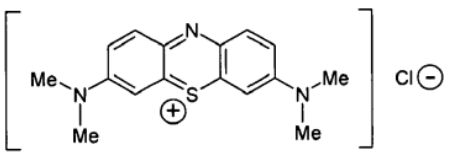
filed for the purpose of Article 76(1) EPC and the basis provided by the "numbered paragraphs" of the divisional application as filed for the purpose of Article 123(2) EPC as alleged by respondent 1. While the conclusion of the opposition division in this regard pertained to the (then) main request (claims as granted), the same applies to present auxiliary request 20.

2.3.4 For ease of reference in the following, the board refers exclusively to the parent application as filed, and the conclusions drawn under Article 76(1) EPC are considered by the board to apply equally under Article 123(2) EPC to the description of the application as filed.

2.4 Both respondents argued that claim 1 of auxiliary request 20 comprised added subject-matter.

2.4.1 This claim is based on claim 126 of the parent application as filed, which reads as follows:

"*A diaminophenothiazinium compound of the following formula (MTC) obtained by a method of synthesis according to any one of paragraphs 1 to 93; or obtained by a method of purification according to any one of paragraphs 94 to 124:*



"

2.5 Claim 1 of auxiliary request 20, set out in full above, is directed to MTC characterised by a purity of greater

than 98% and one or more of the following purity features:

- less than 2% Azure B as impurity, and
- an elementals purity better than the European Pharmacopoeia (EP) limits [defined in claim 1].

It was a matter of dispute whether these features were disclosed in the parent application as filed in combination with the further features of claim 1.

2.6 Multiple selections

2.6.1 The respondents argued that the purity features of claim 1 resulted from an arbitrary selection from multiple possible purity grades for each of said purity features, listed on pages 60-61 of the parent application as filed, without any pointer to the combinations in claim 1.

2.6.2 Specifically, the purity features of claim 1 represented:

- the selection of a purity of greater than 98% from 5 possibilities disclosed on page 60, lines 5-9 of the parent application as filed,
- the selection of less than 2% Azure B as impurity from 3 possibilities disclosed on page 60, lines 11-13 of the parent application as filed, and
- the selection of an elementals purity better than the European Pharmacopoeia (EP) limits disclosed on page 60, lines 25-27 and table 1 of the parent application as filed.

2.6.3 The board disagrees, and comes to the conclusion that claim 1 does not add subject-matter. First, the board

acknowledges that the specific combination of purity features in claim 1, namely a certain MTC purity and "one or more of" less than a certain level of Azure B and less than a certain elementals purity, does not find explicit basis in the parent application as filed. The same applies to the specific grades of these purity features provided in claim 1 in combination, namely MTC having a purity of more than 98%, less than 2% Azure B and an elementals purity better than the European Pharmacopoeia. Nevertheless, the different grades of purity and amounts of impurities set out in the parent application as filed all relate to the same embodiment, namely the compound MTC. The skilled person would thus implicitly understand that the parent application as filed focuses on MTC purity in general, and more specifically MTC having one or more of the purity features, and one or more of the grades of purity listed for each of said purity features, in combination. In this regard, the board agrees with the appellant that the application as filed comprises a pointer to **any** combination of the various purity features and grades described on page 60 of the parent application as filed. In particular, on page 59, lines 36-39, the following is stated:

"*For example, many of the methods described herein yield very high purity MTC with extremely low levels of both organic impurities (e.g., of Azure B and Methylene Violet Bernthsen (MVB)) and metal impurities (e.g., meeting or exceeding the European Pharmacopoeia limits).*"

and on page 61, lines 14-15 the following is stated:

"*All plausible and compatible combinations of the above purity grades are disclosed herein as if each*

individual combination was specifically and explicitly recited."

2.6.4 The first statement indicates that a purpose of the application as filed included the general desire to obtain high purity MTC with extremely low levels of organic and metal impurities. The second statement merely reflects the general concept underlying the application, namely the provision of higher purity MTC with lower levels of specific organic and metal impurities. Implicit in this concept, in the view of the board, is that higher purity and lower impurity levels are preferred, i.e. that the MTC obtained should be as pure as possible. "As pure as possible" is however not limited to the highest purity grade, or lowest level of impurity listed on page 60, but rather includes any achievable level of purity or impurity for each of the listed purity grades, as long as the grades in question is disclosed as one of the alternatives listed on page 60. The skilled person would therefore understand that all purity grades listed on page 60 in terms of purity of MTC or the amount of certain impurities, fall within the teaching of the application, both on an individual level, and in combination.

2.7 "High purity"

2.7.1 In a separate objection under Article 123(2) EPC, respondent 2 argued that claim 1 added subject-matter in view of the term "high purity" therein. Specifically, claim 127 of the parent application as filed (dependent on claim 126), accepted as basis for this feature according to the contested decision, did not recite the term "high purity", but rather "having a

purity of greater than 98%". Hence, claim 1 comprised added subject-matter.

2.7.2 The board disagrees. As set out in the board's communication pursuant to Article 15(1) RPBA, although present claim 1 indeed recites "high purity", this is limited to a "purity of greater than 98%" in the same way as claim 127 of the parent application as filed. Hence, no subject-matter has been added in this regard.

2.8 It follows from the above that the claims of auxiliary request 20 meet the requirements of Article 123(2) EPC.

3. Sufficiency of disclosure - Articles 100(b) and 83 EPC

3.1 Claim 1 is directed to an MTC compound characterised by a purity of greater than 98% and one or more of the following:

- less than 2% Azure B as impurity, and
- an elementals purity better than the European Pharmacopoeia (EP) limits [defined in claim 1].

3.2 The respondents submitted several arguments according to which the claimed subject-matter was not sufficiently disclosed. In the following, reference is made to the patent; it was not disputed that the information in the patent is identical to that of the application as filed.

3.3 Purity defined in claim 1 - measurement and units

3.3.1 Respondent 1 argued that the purity level of 98% in claim 1 was an undefined essential feature, since it was neither characterised by a method nor a unit of measurement. As a consequence, the skilled person was

in the dark as to the meaning of this feature. More specifically, although according to the patent, HPLC was used to assess purity (e.g. paragraph [1082]; table 2, title], this method was not appropriate for determining the claimed purity: experimental data D35 submitted by respondent 1 demonstrated that the analysis of a sample of MTC using HPLC was incompatible with the level of precision, in terms of purity, required by the criteria in claim 1. Similarly, experimental reports D72 and D73 submitted by the appellant in opposition proceedings also showed that the margin of error in measuring purity was greater than that required to accurately measure whether the requirements of claim 1 were met. The respondent concluded that the absence in the patent of a reliable method and unit for measuring purity deprived the skilled person of the promise of the invention, with the consequence that claim 1 was not sufficiently disclosed.

3.3.2 The board disagrees. The subject-matter of a patent must be sufficiently disclosed based on the patent as a whole, taking into account the common general knowledge of the skilled person. The board acknowledges that claim 1 neither refers to a method of measurement of the claimed purity, nor the unit. The board also acknowledges that the patent as a whole, although mentioning HPLC analysis as the method by which purity was determined (e.g table 2, page 51, heading), lacks information on the specific HPLC method employed, or whether other methods may be used to determine whether the claimed purity requirements are met.

3.3.3 However, even if D35, D72 and D73 were to cast doubt on whether the claimed purity levels could be reliably determined by HPLC as argued by respondent 1, the

skilled person is not limited to the determination of purity by HPLC. As stated by the opposition division in the contested decision, and as argued by the appellant in appeal, the skilled person is a chemist whose common general knowledge includes a wide variety of modern analytical tools and methods (e.g. NMR, LC-MS, etc). Given the range of analytical methods available, the skilled person reading claim 1 would expect that an accurate determination of whether a sample of MTC meets the requirements of claim 1 could be carried out, even if a certain amount of routine experimentation would be required to determine the most suitable methods of measurement. Furthermore, as stated by the appellant, since the claim is not limited by a specific method of measurement, the skilled person is free to use any technically reasonable methods to determine whether a specific MTC sample meets the claimed requirements.

3.3.4 The purity is given in claim 1 in terms of a percentage without specifying whether this percentage refers to a percentage of, e.g. weight or volume. As stated by the appellant, however, paragraph [0951] of the patent states that all percentage purities are by weight unless otherwise specified. Moreover. this unit, in the view of the board, is the standard unit used for defining purity levels, and the one which the skilled person, in the absence of any reason to construe the claim differently, would understand on reading claim 1.

3.3.5 Consequently, the respondents' objection related to the determination of the purity levels and the unit required in claim 1 is at most a clarity issue under Article 84 EPC. There is however no reason to conclude that the skilled person would be unable to carry out the invention defined in claim 1 on this basis.

3.4 Obtention of MTC with the claimed purity

3.4.1 Both respondents argued that the patent failed to provide guidance enabling the skilled person to prepare MTC meeting the purity requirements of claim 1.

3.4.2 The appellant submitted that the purified MTC product of example 17 of the patent denoted "CM-pd-378b" (page 51, paragraph [1082] and table 2) met the purity requirements of claim 1 and could be prepared by following the instructions provided in example 17.

3.4.3 The respondents argued that even assuming MTC compound CM-pd-378b reported in table 2 of the patent was according to claim 1, the description, and in particular example 17, did not disclose the preparation thereof in such a manner that it could be reproduced by the skilled person based on the information provided in the patent.

3.4.4 The board disagrees. Example 17 of the patent (page 48, line 43 - page 51, line 28) encompasses paragraphs [1052] to [1082] and table 2. Paragraphs [1052] to [1070] describe the preparation of a crude MTC product. The crude product is then purified according to paragraphs [1071] to [1081]. Specifically, three alternative crystallisation steps are described in paragraphs [1071] to [1073]. The crystallised product is then dissolved and treated with a solution of Na_2S according to paragraphs [1075] to [1077] and then extracted with dichloromethane according to paragraph [1078]. The product of the previous step is then recrystallised according to one of three alternative recrystallisation steps disclosed in paragraphs [1079] to [1081].

3.4.5 Paragraph [1082] of example 17 refers to an MTC sample prepared according to example 1, denoted "CM-pd-378", and its purification according to the methods of example 17, yielding a highly pure MTC with an organic purity of 98.53% based upon HPLC analyses. For this sample, it is stated that the purity data are described in the following table (i.e. table 2). Table 2 provides purity data for three compounds, namely Medex™, a commercial product for comparison purposes (table 2, footnote), crude CM-pd-378 mentioned in paragraph [1082], and a purified product denoted CM-pd-378b, which in view of the identical reported yield of 98.53%, is unambiguously the MTC product of paragraph [1082]. The footnote of table 2 also briefly reports on how CM-pd-378b was prepared.

3.4.6 Therefore, it is apparent that example 17 describes two ways of preparing crude MTC, namely either by the process of preparation described in example 17, paragraphs [1052] to [1070], or by way of reference to example 1 of the patent in paragraph [1082].

3.4.7 The skilled person therefore knows from paragraph [1082] of example 17 that since crude CM-pd-378 is prepared according to example 1, the preparation of crude MTC according to paragraphs [1052] to [1070] of example 17, which culminates in the preparation of "the desired MTC in solution ... ready for purification" according to paragraph [1070], is irrelevant to the preparation of the purified MTC sample CM-pd-378b.

3.4.8 Paragraph [1082] first teaches that a crude MTC sample is to be prepared according to example 1. The steps of example 1 are set out in paragraphs [1014] to [1017] of the patent. Further steps are then described in paragraph [1082] itself, namely:

- the material is crystallised using cool acid re-crystallisation as described in Example 17, and
- the material was then further purified by organic extraction and recrystallised using HCl at 25°C, also as described in Example 17.

3.4.9 The purification methods of example 17 referred to in paragraph [1082] concern paragraphs [1071] to [1081] thereof, which address the purification of crude MTC. It therefore needs to be assessed whether the preparation of CM-pd-378b described in paragraph [1082] and table 2 can be carried out following the instructions provided in these paragraphs.

3.4.10 The term "cool acid recrystallisation", i.e. the first purification step mentioned in paragraph [1082], is not explicitly mentioned in paragraphs [1071] to [1081] of example 17. However, cool acid recrystallisation is described in paragraph [0490] of the patent as "e.g. pH adjusted to about 1 using HCl, and the resulting precipitate collected". As stated above, example 17 provides 3 alternatives for the crystallisation, namely the methods of paragraphs [1071], [1072] and [1073]. As stated by the appellant and not disputed by the respondents at oral proceedings, the only method consistent with cool acid recrystallisation is that of paragraph [1073]. Hence, in relation to the crystallisation step mentioned in paragraph [1082], example 17 comprises a precise teaching.

3.4.11 Paragraph [1082] then requires further purification by organic extraction and recrystallisation using HCl at 25°C. In this regard, paragraph [1078] of example 17 discloses in detail the organic extraction with dichloromethane (DCM). In relation to the step of

"recrystallisation using HCl at 25°C", example 17 again provides three alternatives in paragraphs [1079], [1080] and [1081], only the latter of which corresponds to such a method. Hence, also in relation to the organic extraction and the recrystallisation mentioned in paragraph [1082], example 17 comprises a precise teaching.

3.4.12 Hence, example 17 provides sufficient instruction at least insofar as the purification steps mentioned in paragraph [1082] are concerned.

3.4.13 A central aspect of the respondents' arguments in relation to whether the skilled person would be capable of preparing CM-pd-378b on the basis of the information in the patent, was the argument that the instructions provided for the preparation of CM-pd-378b in paragraph [1082] were contradicted by different instructions provided for its preparation in the footnote of table 2. This footnote reads as follows:

"*CM-pd-378b: pure MTC prepared from crude MTC (CM-pd-378 treated with Na_2S and treated/washed/extracted with DCM at 10°C and then MTC recrystallised from the aqueous layer using HCl (pH 1); T = 10-25°C).*"

3.4.14 The board acknowledges that the specific instructions in the footnote differ from those provided in paragraph [1082] for the preparation of CM-pd-378b. Specifically, treatment with Na_2S mentioned in the footnote is absent from paragraph [1082], while the footnote does not disclose the first crystallisation in paragraph [1082].

3.4.15 According to the respondents, given this discrepancy between paragraphs [1082] and the footnote of table 2,

the skilled person was left in the dark as to precisely how to prepare CM-pd-378b according to the patent.

3.4.16 The board disagrees. Although paragraph [1082] and the footnote of table 2 are not the same, as stated by the appellant, they are not contradictory. In particular, the fact that treatment with Na_2S mentioned in the footnote is absent from paragraph [1082] does not mean that paragraph [1082] excludes such a treatment. Rather, it is simply not mentioned. Equally, the fact that the first crystallisation mentioned in paragraph [1082] is not mentioned in the footnote cannot be interpreted such that it is excluded from the treatment described in the footnote.

3.4.17 In the view of the board, the skilled person would not interpret paragraph [1082] and the footnote of table 2 as referring to two different, mutually inconsistent methods for preparing CM-pd-378b. Rather, it would be apparent that both descriptions must refer to the same product, namely the CM-pd-378b prepared in a purity of 98.53% according to table 2, and thus the same method of purification.

3.4.18 The board notes that paragraphs [1075] to [1077] of example 17 discloses the Na_2S treatment step of the product (i.e. of the previous step, the crystallisation), mentioned in the footnote of table 2.

3.4.19 Hence, the skilled person, realising that the Na_2S treatment step described in paragraphs [1075] to [1077] of example 17 and in the footnote of table 2 was absent from the instructions in paragraph [1082], would include this step in the preparation of CM-pd-378b. This would apply all the more so because in paragraph [1077] of example 17, the Na_2S treatment step is

explicitly taught to result in the removal of complex metals, required by claim 1 to be present in levels better than the European Pharmacopoeia.

3.4.20 Furthermore, even if the skilled person were to attempt to prepare CM-pd-378b solely following the letter of the instructions provided in paragraph [1082], thereby omitting the Na_2S treatment step, and arriving at a product not meeting the requirements of claim 1, then it would consider the reasons for the failure and, after consulting the purification steps of example 17 and/or the footnote of table 2, realise that the Na_2S treatment step described in paragraph [1075] to [1077] of example 17 would be required.

3.4.21 Similarly, in view of the instructions to carry out a first crystallisation in paragraph [1082] and the fact that such a crystallisation is carried out in [1073] of example 17, the skilled person would not omit this step, even if following the instructions in the footnote of table 2. Furthermore, even if the skilled person were to attempt to prepare CM-pd-378b solely following the letter of the instructions provided in the footnote of table 2, thereby omitting the first crystallisation step mentioned in paragraph [1082], and arriving at a product not meeting the requirements of claim 1, the reasons for failure would be considered and, after consulting paragraph [1082] and/or the specific purification steps recited in example 17, it would be realised that the first crystallisation step described in paragraph [1082] and detailed in paragraph [1073] of example 17 would be required.

3.4.22 Hence, the experimental details in the patent allow the skilled person to prepare the CM-pd-378b product of table 2, and it has not been demonstrated by the

respondents that following this method, the claimed level of purity cannot be obtained. Assuming this product is an MTC meeting the purity requirements of claim 1 (infra), the patent comprises sufficient guidance enabling the skilled person to obtain the claimed product.

3.5 Whether CM-pd-378b meets the European Pharmacopoeia limits set out in claim 1

3.5.1 The respondents also argued that the patent failed to disclose an MTC compound according to claim 1. Specifically, although CM-pd-378b described in table 2 of the patent (paragraph [1082]) was reported as having an MTC content of 98.53 % and an Azure B content of 1.29%, both falling within the scope of claim 1, the patent was silent on whether CM-pd-378b had an elementals purity better than the European Pharmacopoeia (EP) limits, as required by claim 1.

3.5.2 The board disagrees. It is acknowledged that the patent does not explicitly indicate that the elemental purity required by claim 1 is attained by CM-pd-378b. However, as stated by the appellant, the aim of the patent is *inter alia* to provide methods for preparing MTC having extremely low levels of metals (paragraph [0026]), in particular, better than the European Pharmacopoeia limits (paragraph [0952]). Furthermore, paragraph [0609] teaches that cool acid recrystallisation is particular effective at greatly reducing the metal content of the solid, while paragraph [1077] of example 17 teaches that the treatment with Na_2S removes complexed metals to provide "metal-free MTC". The product of example 17 is thus described as "metal-free highly pure MTC" (paragraph [1081]). Hence, as stated by the appellant, in particular in the absence of

evidence of the contrary, it is reasonable to interpret "metal-free" in this context as indicating that the requirement of claim 1 in this regard is met.

3.6 The examples of table 4 of the patent

3.6.1 The opponents also submitted that further examples of purified MTC disclosed in the patent in table 4 (page 53), namely products DJSP12a and DJSP13a, did not meet the requirements of claim 1 in relation to the overall purity and Azure B content. Since the methods for preparing DJSP12a and DJSP13a were indistinguishable from the method of preparation of CM-pd-378b of table 2, it followed that the patent was silent on the specific steps required to achieve the claimed purity level. Hence, the skilled person was in the dark as to the steps required to obtain MTC having the claimed purity level, and claim 1 was insufficiently disclosed.

3.6.2 The board disagrees. As stated by the appellant, the respective preparation methods disclosed in the patent for DJSP12a and DJSP13a and CM-pd-378b are different. Specifically, in the preparation of DJPS12a and DJPS13a disclosed in footnote (4) to table 4 (patent, page 54), the crude MTC product was ultimately obtained by a step of "chloride salt formation using hot NaCl". It was then "further purified by cold sodium sulphide treatment, followed by DCM wash, and then cool acidic recrystallisation."

3.6.3 In contrast, the procedure disclosed for CM-pd-378b in example 1 of the patent involves addition of sodium chloride solution to the filtrate after cooling to room temperature, with no mention of "hot NaCl", directly followed by cool acidic recrystallisation before further steps (example 17; paragraph [1082]). Hence,

the respective methods of preparation are not indistinguishable, as argued by the respondents.

3.6.4 Consequently, as submitted by the appellant, it is irrelevant that one method disclosed in the patent does not provide the claimed MTC purity, when the patent also sufficiently discloses another method for providing the claimed purity, namely the preparation of CM-pd-378b as set out above. Therefore, the fact that the method of the patent to prepared DJPS12a and DJPS13a does not yield the claimed purity does not lead to the conclusion that the claimed subject-matter is insufficiently disclosed.

3.7 Consequently, the subject-matter defined in claim 1 of auxiliary request 20 is sufficiently disclosed as required by Article 83 EPC.

3.8 Medical use claims 8-11

3.8.1 It was argued in particular by respondent 2 that the medical uses defined in claims 8-11 were not sufficiently disclosed. Specifically, in view of journal articles D85 and D86, which disclosed the intrinsic serotonin toxicity and genotoxicity of MTC as such, it was not credible that the MTC compound of claim 1 could be therapeutically effective in the same way as (less pure) MTC compositions known from the prior art, and the patent was absent any examples in this regard. Therefore, respondent 2 argued, the claimed MTC was not therapeutically effective, and the medical use claims were consequently not sufficiently disclosed.

3.8.2 The board does not find the respondent's argument convincing. Indeed, it was not disputed that the

claimed therapeutic effects of MTC were known to the skilled person before the effective date of the patent. Such uses are disclosed in the patent (e.g. paragraphs [0019] - [0023]). In view of the fact that the prior art MTC, having a lower purity than the claimed MTC, is known to possess this activity, there is no credible reason to conclude that higher purity MTC would not have the same therapeutic effects, despite the alleged toxicity. Indeed, if it is known e.g. from D85 or D86 that MTC would display toxicity at a certain dosage, the skilled person would simply work with dosage levels below this threshold. Hence, in line with the decision of the opposition division (page 14, point 5.2.2), the subject-matter defined in claims 8-11 is sufficiently disclosed.

4. Remittal - Article 111 EPC and Article 11 RPBA

4.1 In the present case, the decision of the opposition division was solely based on the grounds for opposition under Article 100(b) and (c) EPC. Since the grounds for opposition under Article 100(a) EPC are not part of the decision under appeal, these grounds also do not form the basis for appeal proceedings in accordance with Article 12 RPBA.

4.2 Consequently, having found the set of claims of auxiliary request 20 to comply with the requirements of Article 76(1), Article 123(2) and Article 83 EPC, and in the absence of any objection from the appellant or from either of the respondents, the board finds it appropriate to remit the case to the opposition division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairman:

U. Bultmann M. O. Müller

Decision electronically authenticated