Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 21 March 2023

Case Number: T 1245/19 - 3.3.07

Application Number: 11173338.2

Publication Number: 2457905

IPC: C07D279/18

Language of the proceedings: EN

Title of invention:
Methods of synthesis and/or purification of diaminophenothiazinium compounds

Patent Proprietor:
WisTa Laboratories Ltd.

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

Headword:
Methods of synthesis and/or purification of diaminophenothiazinium compounds/WisTa Laboratories Ltd.

Relevant legal provisions:
RPBA 2020 Art. 12(2), 13(2), 11
EPC Art. 76(1), 123(2), 83, 54

Keyword:
Admission of documents into the appeal proceedings
Admission of a decision of the BOA and arguments based thereon into the appeal proceedings
Main request - amendments allowable (Yes)
Main request - Sufficiency of disclsoure (Yes)
Lack of clarity does not lead to insufficiency of disclosure
Main request - Novelty (Yes)
Purity and impurity levels not inevitably reached
Remittal to the opposition division

Decisions cited:
T 2403/11, T 1085/13

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1245/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 21 March 2023

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:	Corizzi, Valérie PACT-IP 37, rue Royale 92210 Saint-Cloud (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 20 March 2019 revoking European patent No. 2457905 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	E. Duval
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

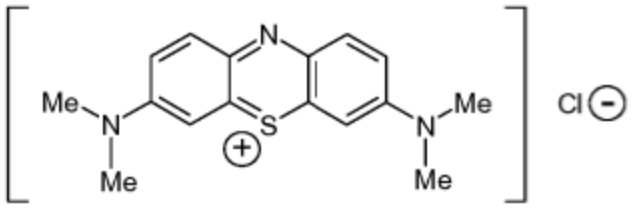
I. European patent No. 2 457 905 was granted on the basis of a set of 28 claims.

II. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division to revoke the patent. The decision was based on the main request and auxiliary requests 1-7, which were respectively the former auxiliary requests 12-19 filed with letter of 8 January 2018.

Claims 1, 17 and 18 of the main request read:

"1. A pharmaceutical composition which is a tablet or capsule comprising 20 to 300 mg of a high purity diaminophenothiazinium compound of the following formula:



;

wherein the diaminophenothiazinium compound in the composition is characterised by:
a purity of greater than 98%;

less than 1% Azure B as impurity;
less than 0.15% Azure A as impurity;
less than 0.15% Azure C as impurity; and
less than 0.05% MVB as impurity
said impurities being based on the weight of the diaminophenothiazinium compound in the composition, the composition further comprising a pharmaceutically acceptable carrier, diluent, or excipient."

"17. A high purity diaminophenothiazinium compound for use according to any one of claims 9 to 16, for use in the treatment of: a tauopathy; a disease of tau protein aggregation; Alzheimer's disease (AD); Pick's disease; Progressive Supranuclear Palsy (PSP); fronto-temporal dementia (FTD); FTD and parkinsonism linked to chromosome 17 (FTDP-17); disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC); pallido-ponto-nigral degeneration (PPND); Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD); cortico-basal degeneration (CBD); mild cognitive impairment (MCI); skin cancer; melanoma; methemoglobinemia; a viral infection; a bacterial infection; a protozoal infection; a parasitic infection; malaria; visceral leishmaniasis; African sleeping sickness; toxoplasmosis; giardiasis; Chagas' disease; Hepatitis C virus (HCV) infection; human immunodeficiency virus (HIV) infection; West Nile virus (WNV) infection; a synucleinopathy; Parkinson's disease (PD); dementia with Lewy bodies (DLB); multiple system atrophy (MSA); drug-induced parkinsonism; or pure autonomic failure (PAF)."

The subject-matter of independent claim 18 has been drafted in the form of a second medical use claim, i.e. "Use of a high purity diaminophenothiazinium compound for the manufacture of a medicament for use in the

treatment of..." and relates to the treatment of the same diseases as claim 17.

IV. According to the decision under appeal, the main request met the requirements of Article 76(1) and 123(2) EPC.

Documents D51, D55, D56 and D57 filed by opponent 01 were admitted into the opposition proceedings.

The claimed invention was sufficiently disclosed in view of the method for measuring the purity, the well-known therapeutic properties of the claimed compound (hereinafter MTC), and the reproducibility of the examples.

The opposition division considered that claim 1 lacked novelty over D1 which described a high level purity MTC, as well as a detailed method of purification leading inevitably to a compound according to the claims. Auxiliary requests 1-7 were also found to lack novelty.

V. The documents cited during the opposition proceedings included the following:
D1: WO 2006/032879
D2: WO 2008/006979
D4: European Pharmacopeia 5.4: "Methylthioninium chloride", 1 April 2006 (2006-04-01), XP055374174, pages 4218-4219
D4a: European Pharmacopeia 5.0: "Methylthioninium chloride", 2005, pages 2028-2029
D7: Test report by Provepharm
D8: HPLC Analysis of sample # MB120912, Methylene Blue Medex® by Provepharm

D10: European Pharmacopeia 8.6: "Methylthioninium chloride", 1 April 2016 (2016-04-01), XP055374139,pages 5329-5331,
D27: Comparison of the results obtained on the chromatographic purity with the HPLC methods European Pharmacopoeia v5.4 and v8.6, monograph 1132
D30: Test report, Successive recrystallizations of Crude Methylene Blue Medex (Batch n° 160612) in aqueous medium
D37: WO 2008/007074 (WO-publication of parent application)
D51: W. W. Dean et al., Journal of Chromatography, 124 (1976) 287-301
D55: R. P. Akkermans et al., J. Phys. Chem. B 1999, 103, 9987-9995
D56: Extract from the European Pharmacopoeia 5.0 (July 2004), pages 69-73
D57: Experimental Report of Dr Cocquerel and Prof. Rodriguez

VI. The patent proprietor (hereinafter the appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal dated 23 July 2019, the appellant filed a main request and 6 auxiliary requests corresponding to the main request and auxiliary requests 1-5 and 7 on file and on which the decision was based. The appellant cited decision T 1085/13 in support of its argumentation and submitted the following items of evidence:

P01: Patentee's response to the oppositions dated 8 January 2018
P02: Patentee's written submissions ahead of the oral proceedings before the opposition division, dated 30 November 2018.

VII. With a letter dated 5 December 2019, opponent 02 (hereinafter respondent 02) filed the following items of evidence:

OP01: Notice of opposition of opponent 02 of 8 May 2017
OP02: Pre-hearing submissions of opponent 02 of 30 November 2018
OP03: Print out of article dated 18 January 2019 commenting on T 1085/13.

VIII. A communication from the Board, dated 8 December 2022, was sent to the parties. In it the Board expressed its preliminary opinion that the main request met the requirements of Article 123(2) and 76(1) EPC, was sufficiently disclosed and was novel over D1.

IX. With a letter dated 18 January 2023, the respondent 01 (hereinafter respondent 01) submitted the following evidence:

A1: Analysis of a mixture of Methylene Blue and Glycine
A2: Attempted Purification of Methylene Blue
A3: EP 2 322 517 B1
A4: Decision revoking the patent EP 2 322 517 B1

X. Oral proceedings took place on 21 March 2023.

XI. The arguments of the appellant may be summarised as follows:

(a) Admission of D51, D55, D56 and D57 into the appeal proceedings

Documents D51 and D55-D57 were filed more than a year after the expiry of the opposition period. As such,

they were clearly late-filed and should not have been admitted by the opposition division.

(b) Admission of A1-A4 into the appeal proceedings

A1 and A2 had been known for more than two years and could have been filed earlier. There were furthermore no exceptional circumstances for filing new documents, since there was no unforeseeable opinion of the Board which only made comments on objections already on file in its communication, namely the uncertainty of the measurement of impurities. The documents were *prima facie* not relevant and belonged to a different file for a different context and case. A1 and A2 were in particular not related to the specific impurities which constituted the difference over D1.

(c) Main request - Amendments

The feature "said impurities being based on the weight of the diaminophenothiazinium in the composition"

The weight units were explicitly disclosed on page 69 of the parent application and the application as originally filed.

Claimed purity and impurity levels

With regard to the claimed impurities, the combination of claims from the parent application was the basis for present claim 1, and the description on page 68 was complementing this disclosure. The decision T 1442/19 was not relevant, since it related to combinations of features taken from several independent claims.

Product-by-process

With regard to the "product by process", the appellant agreed with the opposition division which had listed the relevant passages in its decision.

(d) Main request - Sufficiency of disclosure

With regard to the purity level, the skilled person could prepare the composition and the claimed compound (MTC). The determination of the purity level was part of the common general knowledge, with for instance a method based on HPLC. D27 was evidence that the preparation of the product and the determination of its purity level was possible at the filing date, even if there was a certain degree of variability to be expected with regard to the results. Moreover, the European Pharmacopoeia 5.4 was available at the filing date.

With regard to the claimed medical use, there was no reason to believe that MTC would not be useful, since its medical use was disclosed in numerous previously published documents.

(e) Main request - Novelty over D1

D1 did not disclose the claimed compound with its claimed purity level, and it was not possible to conclude that the product prepared therein would inevitably have the same characteristics; the decision of the opposition division was incompatible with decision T 1085/13. It was a matter of inventive step, not of novelty and the opponents carried the burden of proof. The teaching of D30 regarding successive crystallisations did not correspond to the disclosure

of D1. The scope of the claim was not unclear, and the application of the HPLC method of the Eur. Pharmacopoeia 8.6 would have resulted in a higher level of impurities.

XII. The arguments of the respondents may be summarised as follows:

(a) Admission of A1-A4 into the appeal proceedings

According to respondent 01, A1-A4 were filed under exceptional circumstances, since A1 and A2 had become available only after the reply to the appeal had been filed. They originated from a parallel case, where numerous documents had been cited and this explained why the documents had not been identified earlier. Hence, it was a situation comparable to one where the Board introduced a new issue into the proceedings. Moreover, the Board mentioned for the first time in its communication a possible lack of clarity of the claims, which was a new argument, thus questioning the decision of the opposition division. The documents, in particular A1 and A2, were highly relevant and their admission would not be against the principe of procedural economy, because they originated from the proprietor, who knew them well.

(b) Main request - Amendments

The feature "said impurities being based on the weight of the diaminophenothiazinium in the composition"

No basis could be found for quantities in weight. According to respondent 01, in view of the use of the expression “diaminophenothiazinium compound” which was repeated three times in claim 1 - once as “high purity

diaminophenothiazinium compound", then twice without the expression "high purity" - there was a difference between the scope of claim 1 and the teaching which follows from the description, especially with regard to the claimed quantities. The claim wording was not supported by the patent application and the application as originally filed.

Claimed purity and impurity levels

The claimed product was defined with regard to several impurity features, which constituted selections among five different lists of possible alternatives, each representing a separate embodiment. This amounted to a multiple selection of features from multiple lists. There was furthermore no specific pointer for such selection.

Product-by-process

The parent application and the divisional application only disclosed the composition in the context of "product-by-process" features and the claimed composition was a broadening of the subject-matter.

(c) Main request - Sufficiency of disclosure

According to respondent 01, there was no method disclosed for the measurement of the impurity level, and the claimed purity had to be seen as an absolute purity; respondent 01 did not agree with the opposition division which considered this to be a problem under Article 84 EPC rather than Article 83 EPC. It was not possible to determine whether something was comprised within the scope of the claims or not, and this was relevant not only for the limits of the claims, but for

the whole subject-matter claimed; the criteria defined in decision T 2403/11 with regard to essential parameters were not fulfilled. There was no method known from common general knowledge that the skilled person could have used at the filing date to fill the gaps in the disclosure. Moreover, the examples could not be reproduced, in particular in view of document D57.

According to respondent 02, the patent lacked experimental data on any of the claimed therapeutic effects thereby resulting in lack of sufficiency of disclosure of the second medical use claims 17-25 of the main request.

(d) Main request - Novelty over D1

There was no method of measurement of the purity or impurity level given in the claims, and the claims had to be evaluated in a broad sense. Since any method of measurement could be used, and since the result presented a certain variability, as shown by D27, D1 was relevant for novelty, in particular in view of example 17 and Table 2. D30 showed that successive crystallisations from a starting product close to the starting product of Table 2 of D1 would lead to the claimed compound. Moreover, the teaching of example 17 could be combined with the teaching on crystallization given on page 16 of D1.

XIII. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of main request or one of

auxiliary requests 1-6, all filed with the statement setting out the grounds of appeal dated 23 July 2019.

Respondents 01 and 02 (opponents 01 and 02) requested that the appeal be dismissed.

Respondent 01 furthermore requested that P01 and P02 not be admitted into the appeal proceedings and that documents D48-D50 and D58 be admitted in view of the assessment of inventive step. They also requested that the priority document for D2 not be admitted into the proceedings.

Respondent 02 also requested that the arguments based on decision T 1085/13 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Admission of D51 and D55-D57 into the appeal proceedings

1.1 Documents D51 and D55-D57 were filed by respondent 01 during the opposition proceedings with its letter of 20 June 2018, in response to comments and documents filed by the appellant regarding sufficiency of disclosure, and before all parties were summoned to oral proceedings. The appellant objected the admission of these documents into the opposition proceedings with its letter dated 30 November 2018, since it considered them either irrelevant to the grounds of lack of novelty, i.e *inter alia* D51 and D56, or to any ground of opposition, i.e *inter alia* document D55, while D57 repeated an experimental report already on file.

1.2 During the oral proceedings before the opposition division, the admission of specifically documents D51, D55, D56 and D57 was discussed, and it was confirmed that these documents were filed with regard to the assessment of sufficiency of disclosure. The opposition division decided to admit them, since they were filed in direct response to comments of the proprietor and since they confirmed common general knowledge or findings which had been challenged by the proprietor.

1.3 Firstly, the Board notes that documents D51 and D55-D57 have been cited in the first instance proceedings and were admitted by the opposition division. D51, D56 and D57 are furthermore cited in the decision of the opposition division in the context of sufficiency of disclosure. Accordingly, D51 and D55-D57 form part of the appeal proceedings according to Article 12(2) RPBA 2020. The Board's discretion not to admit evidence which could have been presented or was not admitted in the opposition proceedings under Article 12(4) RPBA 2007 does not apply to these documents.

1.4 In addition, in the present case, the Board does not see any deficiency in the decision of the opposition division, since it appears clear that the opposition division exercised its discretion in accordance with the right principles and not in an unreasonable way. The appellant did furthermore not give any reason in its statement of grounds of appeal why the decision of the opposition division regarding the admission of D51, D55, D56 and D57 should be overruled, and made only reference to its letter of 30 November 2019, for justifying why these documents should not have been admitted.

Hence, the Board considers that documents D51, D55, D56 and D57 form part of the appeal proceedings according to Article 12(2) RPBA 2020.

2. Admission of arguments or document OP03 based on decision T 1085/13 into the appeal proceedings

2.1 The appellant filed decision T 1085/13 with its statement of grounds of appeal and provided arguments based on this decision. The citation of jurisprudence and the submissions of arguments based thereon is not considered to fall within the ambit of Article 12 RPBA 2007 and the Board sees no reason to disregard them. Consequently, the decision T 1085/13, as well as arguments based on decision T 1085/13 form part of the appeal proceedings.

2.2 Respondent 02 filed also document OP03 with its reply to the statement of grounds of appeal. Document OP03 is an article commenting the decision T 1085/13. The filing of this document is a reaction to the citation of T 1085/13 by the appellant and can be seen as arguments relating to this decision. The document OP03 is therefore admitted into the appeal proceedings for these reasons (Article 12(4) RPBA 2007).

3. Admission of documents A1-A4 into the appeal proceedings

3.1 Documents A1-A4 were filed by respondent 01 with its letter dated 18 January 2023 in the context of the discussion on sufficiency of disclosure with regard to the method of measuring the purity.

3.2 A1 is an experimental report of an analysis of a mixture of Methylene Blue and Glycine and A2 is a

scientific article with the title "Attempted purification of methylene blue". Both documents were submitted in the opposition proceedings of the parallel case EP 2 322 517. A3 is the specification EP 2 322 517 B1 relating to a high purity methylene blue (MTC) and A4 is the decision of the opposition division revoking said patent EP 2 322 517 B1.

According to respondent 01, documents A1 and A2 show that the titration methods of the Pharmacopoeia EP5.4 (D4) lead to an error of more than 2%, and of more than 0.5% respectively, in the assessment of purity. The decision of the opposition division concerning patent EP 2 322 517 (A4) §5.2.1) considered that the purity analysis methods lead to different results but that it was a problem of clarity.

Hence, according to respondent 01, documents A1-A4 were filed in response to a comment made by the Board in its preliminary opinion pursuant Article 15(1) RPBA 2020 regarding a possible lack of clarity of the claims. Respondent 01 argued that this was a new point of view of the Board, which was to be seen as exceptional circumstances justifying the filing of documents A1-A4 which responded to that problem of clarity.

3.3 According to Article 13(2) RPBA 2020, any amendment to a party's case after notification of a summons to oral proceedings shall, in principle not be taken into account, unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned. Such exceptional circumstances might reside in objections formulated for the first time in the provisional opinion of the Board.

In the present case, the Board mentioned in its preliminary opinion in the context of the discussion of sufficiency of disclosure that "*the arguments of respondent 02 appear to relate rather to a problem falling under Article 84 EPC, but not with sufficiency of disclosure*". The Board mentioned furthermore that "*the absence of the specification of the method of measuring the purity in the claim might have a possible impact on the assessment of novelty and inventive step, in view of the variability of the purity results obtainable according to the method used, but does not lead to a insufficiency of disclosure*".

The Board cannot seen any new point raised in this context, since the same conclusions were also reached by the opposition division in its decision regarding the variability of the results of measurement of the purity, namely that "*typically, a plurality of measurement methods results in different values, even using the same method*" and "*the opposition division does also not dispute the fact that various measurement methods for purity exist or that depending on the circumstances different results may be obtained using different methods*" (cf. point 1.2.2 of the decision). The opposition division came also to the conclusion that "*the objections in this respect concern the question whether the claimed invention is correctly defined in accordance with Article 84 EPC, i.e. whether the scope of the claims is clear*".

Consequently, the point raised by the Board in its communication, and interpreted by respondent 01 as being a new point, was already discussed during the opposition proceedings and present in the decision of the opposition division, and there are therefore no

exceptional circumstances justifying the filing of new documents at such late stage of the appeal proceedings.

3.4 The other reasons given by respondent 01, namely the relevance of the documents, procedure economy and the size of the opposition file EP 2 322 517 B1, rendering it difficult to identify documents A1-A4, are neither considered relevant nor convincing by the Board.

First, the documents, in particular A1 and A2, are no more relevant that other documents already on file, such as D27 which highlights already a variability in the results of the measurement of purity of MTC, and do furthermore not relate to some specifically claimed impurities, such as in particular MVB or Azure B, which questions their relevance and adds undeniably some complexity to the case. Finally, the difficulty to identify the documents in a parallel case cannot be regarded as exceptional circumstances justifying their late filing either.

3.5 Consequently, A1-A4 are not admitted into the appeal proceedings (Article 13(2) RPBA 2020).

4. Main request - Amendments

4.1 Respondents 01 and 02 objected to the main request for lack of compliance with Articles 76(1) EPC and 123(2) EPC. Respondent 01 objects in particular to the feature "said impurities being based on the weight of the diaminophenothiazinium in the composition" in claim 1. Respondent 02 considers that the parent application as well as the divisional application only discloses the composition in the context of "product-by-process" features. Both respondents 01 and 02 consider furthermore that the subject-matter of said claim 1

regarding the claimed purity levels results from a combination from five different lists.

4.2 In addition to its objections under Article 76(1) and 123(2) EPC, respondent 01 did not agree with the opposition division in its decision that the reasoning and conclusion for Article 76(1) EPC applies for the most part also to Article 123(2) EPC.

The Board however agrees fully with the opposition division on this point and finds this objection irrelevant. The description of the application as originally filed includes indeed both the description and the claims of the parent application (publication number WO 2008/007074), and for this reason the conclusions for Article 76(1) EPC apply also to Article 123(2) EPC.

4.3 The feature "said impurities being based on the weight of the diaminophenothiazinium in the composition"

4.3.1 Page 69, line 14 of the parent application WO 2008/007074 discloses that "all percentage purities recited therein are weight/weight unless otherwise specified" and relates to the compound methylthioninium chloride (MTC) and its level of purity or presence of impurities (see page 68, line 19 to page 69, line 12). In view of this passage, it appears therefore that the feature "said impurities being based on the weight of the diaminophenothiazinium in the composition" is derivable directly and unambiguously from the parent application. Since the patent application comprises the same description with the addition of the original claims in the description, the feature is also derivable from the application as filed on the same

pages (see pages 68 line 19 to page 69 line 14 of the patent application).

4.3.2 According to respondent 01, the expression "diaminophenothiazinium compound" was repeated three times in claim 1, once as "high purity diaminophenothiazinium compound", then twice without the expression "high purity" as "diaminophenothiazinium compound in the composition". A distinction had to be made between the claimed "high purity diaminophenothiazinium compound" and the claimed "diaminophenothiazinium compound in the composition", which had an effect on the claimed purity and impurity levels, for which there was no basis in the parent or patent application.

The Board disagrees with the interpretation of the features of claim 1 by respondent 01 and agrees with the conclusion of the opposition division. A normal and sensible reading of the present claims and of the application as originally filed makes indeed clear that the purity and impurity levels recited in the application or in the parent application for the described compound correspond to the values now recited for the claimed composition and that the claimed "high purity diaminophenothiazinium compound" had to be understood as a mixture of the diaminophenothiazinium compound and its impurities. This objection raised by respondent 01 is therefore not convincing.

4.4 Claimed purity and impurity levels

4.5 Claim 1 of the main request relates to a diaminophenothiazinium compound characterized by different purity or impurity contents, namely:
1) "a purity of greater than 98% "

2) "less than 1% Azure B"
3) "less than 0.15% Azure A"
4) "less than 0.15% Azure C" and
5) "less than 0.05% MVB".

Both respondents consider that the claimed purity and impurity levels result from combinations from several lists.

4.6 Claim 83 of the parent application relates to the diaminophenothiazinium compound of the same formula as in claim 1 of the main request, which subject-matter has been combined with the subject-matter of claim 97 of the parent application which refers back *inter alia* to claim 83:

"97. A pharmaceutical tablet or capsule comprising 20 to 300 mg of a diaminophenothiazinium compound according to any of claims 82 to 96, and a pharmaceutically acceptable carrier, diluent, or excipient."

Dependent claims 84-86 relate to the purity levels of the compound while dependent claims 87-88, 89-90, 91-92 and 93-94 refer respectively to the impurity levels of Azure B, Azure A, Azure C and MVB. The same disclosure can be found in points 84-94 on page 117 of the patent application.

The specific purity feature "a purity of greater than 98%" originates from the dependent claim 85 of the parent application and constitutes a selection among three possibilities expressed in dependent claims 84 to 86, and reciting repectively purity levels of "greater than 99%", "greater than 98%" and "greater than 97%".

In the Board's view, there is however a clear pointer in the examples of the parent and patent application regarding the claimed purity level of "greater than 98%" and of "less than 1% Azure B as impurity" which constitute the minimal level of purity or maximal level of purity of Azure B impurities identified in the examples of the parent and patent application, as shown in Table 2, Table 3 and Tables 5 of pages 92 and 94. The further restriction to the subject-matter of dependent claim 89, i.e. "less than 0.15% Azure A as impurity", claim 91, i.e. "less than 0.15% Azure C as impurity" and claim 94, i.e. "less than 0.05 % MVB as impurity", constitutes also the highest claimed amounts possible of these specific impurities. For this reason alone, the subject-matter of claim 1 regarding the claimed purity and impurity levels is derivable directly and unambiguously form the parent and patent application.

4.7 Moreover, all the claimed purity or impurity levels of dependent claims 84-94 of the parent application relate and characterize the same product, namely the claimed diaminophenothiazinium compound, and cannot be considered to constitute mutually exclusive alternatives among which multiple selections were made, but must be seen rather as common dependent claims relating to the same embodiment. They indeed characterize the claimed compound at different levels of preference in a convergent way. All the features of dependent claims 84-86 relating to the purity levels of the compound and dependent claims 87-88, 89-90, 91-92 and 93-94 relating to the impurity levels of respectively Azure B, Azure A, Azure C and MVB relate to the same claimed diaminophenothiazinium compound. Under these circumstances, and considering the disclosure discussed above (see point 4.6), their

incorporation into claim 1 constitutes therefore a restriction to a specifically disclosed embodiment and not a restriction to a combination of alternative embodiments or an individualisation of subject-matter not specifically disclosed in the parent application.

4.8 The situation is in particular different from the case T 1442/19 cited by the respondents which related to the combination and selection of two specific compounds or class of compounds, namely an HIV protease inhibiting compound and cobicistat, which constituted a selection among multiple equivalents alternatives for both of the claimed compounds, without any specific pointers to this specific selection and combination.

4.9 Product-by-process

4.9.1 According to the respondents, the claimed compound was originally disclosed only by reference to its process of preparation. Since this feature is not present anymore in the pending claims, the respondents considered that this extends beyond the original disclosure.

4.9.2 The Board however fully agrees with the decision of the opposition division in that the application as a whole, including the description, may serve as basis for amending the claims, and not only the claims as filed, wherein only a limitation to the process of preparation was present. In this respect, the description makes clear that the subject-matter of the application as originally filed is not limited to the process of the application but also encompasses the product that has the defined level of purity.

Thus, several passages disclose the compound independently from its process of preparation. For instance, the description of the parent and patent application discloses on page 68, lines 11-12, "*in one embodiment, the present invention pertains to methylthionium chloride (MTC) that has a purity as defined herein*". This passage is followed on pages 68 and 69 by the levels of purity and impurity regarding the presence of inter alia Azure A, Azure B, Azure C and MVB.

Likewise, the description of the parent and patent application makes numerous references not only to the compound MTC "obtained by" or "obtainable by" a method as given, but also, alternatively, to MTC having the stated purity. For example, page 8, lines 1-4 discloses the following: "Another aspect of the invention pertains to a diaminophenothiazinium compound, as defined herein and including, for example, methylthioninium chloride (MTC), that is obtained by, or is obtainable by, a method of synthesis and/or purification as described herein and/or that has a purity as defined herein".

Consequently, the claimed diaminophenothiazinium compound is disclosed directly and unambiguously in the parent and patent application independently from its process of preparation.

4.10 The main request meets the requirements of Article 76(1) and 123(2) EPC.

5. Main request - Sufficiency of disclosure

5.1 The respondents objected that the invention was not sufficiently disclosed in view of the absence of a

method for measuring the purity, of a lack of reproducibility of the examples, and lack of data on the claimed therapeutic effects.

5.2 Method for measuring the purity

5.2.1 Claim 1 of the main request relates to a diaminophenothiazinium compound characterized by different purity or impurity contents based on the weight of the diaminophenothiazinium compound, namely "a purity of greater than 98%", "less than 1% Azure B", "less than 0.15% Azure A", "less than 0.15% Azure C" and "less than 0.05% MVB".

Neither claim 1, nor any other dependent or independent claim provides the necessary method and conditions for measuring the purity or impurity levels. Such information is neither provided in the description in paragraphs [0365] to [0384] of the specification which deal with the impurity or purity levels, corresponding to pages 68-69 of the parent or patent application. When turning to the examples, the patent refers however to HPLC methods in paragraphs [0044], [0530] and [0535] for analyzing and quantifying the purity and impurity levels. The contested patent makes also a reference to the European Pharmacopeia in paragraphs [0361], [0385]-[0394], especially to the versions 4.0 and 5.4 of the Pharmacopeia.

In the Board's view, the use of a HPLC method for determining qualitatively and quantitatively the constitution of a specific compound in terms of purity and impurity levels is a common and widely used method. The use of a HPLC method in this context does not preclude in any way the execution of the invention by those skilled in the art. This is all the more the case

since an official method for identifying MTC and its impurities is given in the European Pharmacopoeia 5.4 (cf. document D4), and this version of the Pharmacopoeia is cited several times in the description of the contested patent.

Moreover, the HPLC method used in the patent is an HPLC using a wavelength of 254 nm instead of 246 nm as indicated in the method given by the Eur. Pharmacopoeia 5.4, and it appears credible that the results of an HPLC under these conditions can identify the qualitative and quantitative presence of impurities in the same way as EP 5.4.

Hence, the Board agrees with the conclusion of the opposition on this point that the skilled person would have been able to determine the purity and impurity levels of MTC through applying an HPLC method, ultimately by applying the method of the Pharmacopoeia in force at the time when the application was filed, i.e. the European Pharmacopoeia version 5.4.

Consequently, the skilled person is in a position to determine the purity and impurity levels and to reproduce the claimed invention, and the claimed invention is sufficiently disclosed in this respect.

5.2.2 The argument of respondent 01 that the Pharmacopoeia 5.4 does not comprise any teaching as how to detect the impurities for Azure A, Azure C and MVB, but only for Azure B (Impurity A) could in particular not be followed by the Board. First, the European Pharmacopoeia version 5.4 gives the HPLC method for analysing MTC and mentions explicitly the presence of Azure B (Impurity A) and of other impurities in general, thereby identifying explicitly the possible

presence of further impurities (see D4, right-hand column). Then, the suitability of the HPLC method given in the European Pharmacopoeia version 5.4 for measuring all impurities is confirmed directly and explicitly by the experiments of D27 submitted by respondent 01 in the opposition proceedings; the measurement of the impurities by the method of the European Pharmacopoeia version 5.4 gives indeed a qualitative and quantitative result with regard to Azure A, B and C, MVB, as well as the general purity level (see D27, Tables of pages 3 and 5). In view of these experiments, this objection is not convincing.

5.2.3 The Board could also not follow respondent 01's argument that, in the absence of any method of measurement in particular in the claims, the ill-defined purity and impurity levels in claim 1 lead to insufficiency of disclosure, in view of their essential character and since these features are relevant for solving the problem addressed in the patent, as presented in decision T 2403/11.

The Board agrees that the absence of the specification of the method of measuring the purity in the claim has an impact on the clarity of the feature and of the claim, in view of the variability of the purity results obtainable according to the method used. This variability in the purity and impurity levels is indeed highlighted by the experiments D27, which presents a comparison of results obtained on the analysis of chromatographic purity with the HPLC methods of the Pharmacopoeia 5.4 and 8.6. The experiments show that the methods lead to significantly different purity or impurity values, the detected level of impurities being constantly higher when using the method of the Pharmacopoeia 8.6.

But this does not lead to a insufficiency of disclosure. The uncertainties concerning possible deviations from the results obtained by different HPLC methods do not affect the ability of those skilled in the art to prepare the claimed compound and choose an appropriate method for determining the purity and impurity levels of the claimed compound, irrespective of the fact that said method is unprecise or gives a certain variability in comparison to other methods. It is indeed not sufficient to establish a lack of clarity of the claims for establishing lack of compliance with Article 83 EPC; it is necessary to show that the lack of clarity affects the patent as a whole, i.e. not only the claims, and that it is such that the skilled person, who can avail himself of the description and his common general knowledge, is hindered from carrying out the invention, in the present case preparing the claimed compound and determining its purity and impurity levels. This is clearly not the case here. Moreover, as argued above, D27 proves that the measurement of the purity and impurity levels was possible with the European Pharmacopeia at the filing date, and that the skilled person had at least one method at his disposal for doing so.

5.3 Reproducibility of the examples

5.3.1 Respondent 01 objected that there was no reproducibility of the examples in particular in view of the experiments D57 which were not considered by the opposition division in its decision. D57 describes an attempt of reproducibility of the synthesis 1, 2 and 3 of the contested patent, which failed.

5.3.2 First, the Board wishes to mention that there is no requirement under Article 83 EPC according to which a specifically described example of a process must be exactly repeatable or reproducible. The requirements of sufficiency of disclosure are met if at least one way is clearly indicated in the patent specification enabling the skilled person to carry out the invention, and the disclosure allows the invention to be performed in the whole area claimed without undue burden, applying common general knowledge. These criteria are met since, as mentioned by the opposition division in its decision, at least the purification step of synthesis 6 of the contested patent leads in a reliable way to MTC with the desired level of purity and this embodiment was sufficient for the requirements of Article 83 EPC to be fulfilled.

5.3.3 The Board notes furthermore that the content of D57, as well as of D7, has been well discussed during the opposition proceedings and mentioned in the decision of the opposition division in this context (see point 1.2.4 of the decision of the opposition division) and the Board has the same concern as the opposition division regarding the content of these documents.

(a) D7 was filed by respondent 01 and reproduces the intermediary synthesis steps 7, 8, 1 and 2 and the synthesis 3, 4 and 9 of the contested patent. Said experiments contain however some inconsistencies and deficiencies.

The quantities used in synthesis 3 of D7 are 16 fold more than in synthesis 3 of the patent, but the final yields of MTC, namely 9.1 g in D7 and 0.51 g in the patent, do not correspond proportionally, since it should be around 8.1 g in

D7. It is also not clear to the Board why the synthesis 3 of the patent has been repeated twice in D7 in different proportions (in synthesis 3 and 4 of D7) and why the results in terms of purity are so different between the MTC obtained by synthesis 3 or 4 according to D7,as shown in the following Table 3 (cf. MTC-S3 and MTC-S4):

Sample	MTC area %	Azur B area %	AzurA area %	Azur C area %	MVB area %	Other area %
Crude MB	93.40	5.24	0.84	0.06	0.11	0.35
MTC-S3	96.90	2.75	0.11	<0.02*	<0.02*	0.24
MTC-S4	95.58	3.97	0.32	<0.02*	<0.02*	0.13

*LOD=0.02%

Table 3

The quantities used in synthesis 4 of D7 are two fold more than in synthesis 3 of the patent, and the final yield of MTC appears to correspond, namely 1.05 g of MTC in D7 while it is 0.51 g in the patent.

The quantities in synthesis 9 of D7 are missing, and synthesis 9 of D7 only follows one way of obtaining MTC.

The experiments of synthesis 5 and 6 of D7 suffer from the same deficiency as synthesis 3 and 4, namely that there are different proportional quantities than in synthesis 5 and 6 of the patent (12,44 fold more in synthesis 5 and 13.9 fold more in synthesis 6 of the patent), while the final yield is very different (9.27 g in synthesis 6 of D7, instead of 0.9 g in synthesis 6 of the patent, while it should have been around 12.5 g).

Consequently, the experiments performed in D7 and their results are questionable, and respondent 01 did not provide any explanation with regard to these points. As concluded by the opposition division in its decision, the experiments of D7 can therefore not raise serious doubts about the reproducibility of the examples of the invention.

(b) D57 has been filed by respondent 01 and tries to reproduce synthesis 1-3 of the contested patent, but fails. It is not clear to the Board why synthesis 1-3 of the patent could be repeated in D7, but not in D57.

Consequently, the Board has the same concern as the opposition division with regard to D7, while the results of D57 appear to be questionable. In any case, neither D57 nor D7 call into question the reproducibility of example 6 of the patent. As the opposition division mentioned in its decision, synthesis 6 of the patent discloses a purification step leading to MCT with the desired level of purity.

5.4 Lack of data on the claimed therapeutic effects

5.4.1 The list of diseases covered by claims 17 and 18 was objected to by respondent 02, for which, according to respondent 02, the patent in suit failed to provide experimental data and to show that the claimed medical effect was plausible, in particular with regard to the wide variety of diseases listed. Respondent 02 pointed in particular to skin cancer, melanoma, any bacterial infection, any protozoal infection, and any parasitic infection to be treated with the composition of claim 1.

5.4.2 In order for a medical indication of a known compound to be sufficiently disclosed, it is sufficient that said medical indications are already known to the skilled person at the priority date; experimental data is necessary only in the case of a new substance or a new therapeutic indication for a known substance, and a medical indication can also be generalised from the teaching or concept disclosed in the patent and the common general knowledge.

5.4.3 In the present case, the compound MTC was a well known compound at the filing date of the contested patent which gives furthermore numerous references in paragraphs [0023] to [0028] and [0567] with regard to the therapeutic applications of MTC. Moreover, document D1 relating to MTC reports the same treatment of the diseases as the contested patent; skin cancer, melanoma, bacterial infection, protozoal infection, parasitic infections, tauopathies, such as DDPAC, FTD, PPND, PNLD, etc. with the compound of claim 1 (cf. D1, page 4, line 36 to page 6, line 5; page 62, line 30 to page 63, line 10). D2 also relates to MTC and mentions its medical properties, such as *inter alia* its antiseptic, anti-infectious and antiviral properties (see D2, page 11, lines 13 to 27).

5.4.4 Consequently, the Board concurs with the decision of the opposition division that the diseases listed in claims 17 and 18 were already known to be treated with MTC. Therefore, the patent in suit does not lack disclosure in this respect.

5.5 Consequently, the main request complies with the requirements of Article 83 EPC.

6. Main request - Novelty over D1

6.1 Document D1 relates to the compound MTC and methods of preparation and purification thereof; it discloses the preparation of MTC by different methods compared to those of the contested patent (see pages 12-15 and 19-33).

Claims 128-136 of D1 relate to MTC defined by its purity or impurity grade levels, which is however higher than in claim 1 of the main request; it claims for instance at best an amount of less than 2% of Azure B and less than 0.13% of MVB.

Example 17 discloses the synthesis, treatment and recrystallisation of MTC. Several purification methods of the obtained product are given in example 17 of D1. The first method consists in adding HCl to the obtained MTC in order to reach pH 1, heating of the suspension to 65°C over 25 minutes and cooling to 20°C over 360 minutes to yield the high purity MTC (see D1, page 82, lines 24-29). Another method consists of adjusting the pH to 3.5-4.5 at 25°C and adding HCl to reach pH 1, and collection by filtration (See D1, page 82, lines 30-34). The methods appear to be comparable to the purification methods proposed in the contested patent in paragraphs [0358], [0359], [0534] or synthesis 6 in paragraph [0534], wherein however the pH and temperatures used are different, i.e *inter alia* a pH of 1.7 and a temperature of 80°C in the patent.

In this context, example 17 discloses specifically the preparation of MTC according to example 1 of D1 followed by a further crystallisation and re-crystallisation as described above. Hence, in Table 2

of Example 17, D1 discloses MTC obtained with 98.53% purity and a low level of Azure B and MVB:

Table 2
Organic Purity of Synthesized and Purified MTC as Determined by HPLC Analysis

MTC Source	MTC %	Azure B %	MVB %	Others %
Medex™	94.22	5.24	0.10	0.44
CM-pd-378	96.60	2.89	0.33	0.06
CM-pd-378b	98.53	1.29	0.14	0.04

In this example, the crude product CM-pd-378 has been specifically crystallised using cool acid-recrystallisation and the material was further purified by organic extraction and recrystallised using HCl at pH 1 and at 10-25°C, a process different from the process disclosed in the contested patent (see D1 page 83, lines 3-8). This yielded the product CM-pd-378b with an organic purity of 98.53% based upon HPLC analysis. **The product CM-pd-378b is a purified product having however an amount of impurities Azure B and MVB higher than what is claimed in claim 1 of the main request.** Given that the other impurities are in an amount of up to 0.04%, it is concluded that the amounts of the remaining claimed impurities Azure A and Azure C correspond to the claimed amounts. Since the goal of D1 is to produce MTC as pure as possible, there can be no doubt that the product of Table 2 is the product with the highest degree of purity explicitly disclosed in D1, and that the impurity levels of Azure B and MVB as claimed in claim 1 of the main request could not be reached. D1 does in any case not provide any evidence of the contrary.

D1 discloses in Table 4 further data on the purity of products synthesized and purified according to the

methods described in D1, **wherein none of the products reaches a purity level over 98% (see column MTC%):**

Table 4
Organic Purity of Synthesized and Purified MTC Determined by HPLC Analysis

MTC Source	Recrystallisation	MTC %	Azure B %	MVB %	Others %
Medex™	n/a	94.22	5.20	0.11	0.47
Urolene Blue®	n/a	94.27	5.23	0.09	0.41
NTP	n/a	94.33	5.13	0.13	0.41
DJPS12a	H_2O/HCl, pH 1	96.37	3.07	0.15	0.07
DJPS13a	H_2O/HCl, pH 1	96.85	2.73	0.15	0.27

Consequently, document D1 does not disclose directly and unambiguously the compound MTC at the purity and impurity levels of claim 1 of the main request.

6.2 One of the main arguments of the respondents, which was also the conclusion of the opposition division in its decision, is that the methods of preparation and purification disclosed in D1 would inevitably result in the production of the compound MTC in the purity level as claimed.

Lack of novelty may indeed be concluded if a prior-art disclosure describing the same compound discloses the claimed purity at least implicitly, for example by way of a method for preparing or purifying said compound, the method inevitably resulting in the purity as claimed (cf. also decision T 1085/13).

In the present case, there is no such evidence of an inevitable result in D1, neither in example 17, nor in any other part of D1.

Starting from example 17, it has to be concluded that its disclosure does not lead inevitably to the claimed purity levels, since the purification method of example

17, which is different from the purification methods of the contested patent, leads very clearly to a final compound with a higher impurity level, at least with regard to Azure B and MVB (cf. Table 2 of D1).

The respondents mentioned also the general teaching on purification methods in D1, in particular on pages 15-19 "Purification Methods", and pages 41-44 "Recrystallisation(RX)" which would lead to the claimed purity and impurity levels; the opposition division came to the same conclusion on the basis of the same passages, namely that "the use of this method on the already purified product of Table 2 would inevitably lead to a reduced amount of Azure B and MVB within the limits claimed in the patent in suit" (see decision, point 1.3). D1 discloses indeed on page 16, lines 1-13 and in claim 94 a purification method comprising 4 successive recrystallisation steps. According to document D30, such several successive re-crystallisation steps of MTC might achieve the claimed purity level, i.e. at least 4 re-crystallisations. This is proven by the following Table from D30 with the product 4S1 obtained after said 4 crystallisations and which shows the required purity and impurity levels:

		MTC m/m%	Azur B m/m %	Azur A m/m %	Azur C m/m %	MVB m/m%	Autre m/m%
Teneur corrigée / FRM@24 6nm	**BRUT**	93,58	5,45	0,33	0,13	0,06	0,45
	1S1	96,79	2,92	0,18	<0,04*	<0,02**	0,07
	2S1	97,71	2,12	0,13	0,02	<0,02**	0,02
	3S1	98,48	1,43	0,09	<0,02**	<0,02**	NA
	4S1	99,10	0,83	0,06	<0,02**	<0,02**	NA
	5S1	99,41	0,54	<0,05*	<0,02**	<0,02**	NA
	6S1	99,60	0,35	<0,05*	<0,02**	<0,02**	NA

The Board does not contest that such successive re-crystallisation disclosed in D1 leads to a MTC compound of the desired level of purity and impurity, but the passage on page 16 of D1 mentioned by the respondents is not disclosed in association with any example of D1, in particular not with the disclosure of example 17 or Table 2, since the specific methods of purification given in example 17 of D1 do not comprise several re-crystallisation steps. The successive re-crystallisation method of page 16 remains also only one alternative possible purification method among others disclosed in D1 on pages 15-19 or 41-44.

When assessing novelty, the content of a document should not be taken as a reservoir from which it would be permitted to draw characteristics belonging to distinct embodiments or disclosed distinctly one from another, to artificially create a particular embodiment which would destroy the novelty, especially with the disclosure of an example, unless the document itself suggests such a combination. Such a combination of parts of a document finds its place in the assessment of inventive step but not for novelty.

6.3 Another argument of the respondents was that the absence of any method of measuring, and of a reference to a method measuring the purity and impurity levels in claim 1 of the main request prevented a meaningful comparison with D1 and would lead to a possible absence of novelty with the choice of in particular a more accurate method. Moreover, respondent 01 also emphasized the lack of accuracy of any method of measurement and its consequence on the assessment of novelty.

The Board concurs with the respondents that the lack of indication of the measurement of the impurities has an effect on the scope of the claimed subject-matter, in particular in view of the assessment of novelty and inventive step.

The Board notes however first that **D1 suffers from the same deficiency as the contested patent, i.e. the HPLC method used therein is not defined**, so that an accurate comparison between the MTC prepared therein, such as in example 17, and the MTC of claim 1 of the main request appears in any case uncertain and it is only possible to rely on the data concretely present in D1 and in the contested patent.

Moreover, the respondents have not established that the choice of a particular measurement method for the analysis of the MTC product of example 17 of D1 would lead to a purity and impurities levels within the ranges defined in claim 1 of the main request. Such a conclusion cannot be reached based on D27, which compares the impurity levels provided by the HPLC methods given respectively in the Eur. Pharmacopeia 5.4 and 8.6 but does so on MTC products which are not those of D1.

In the Board's view, this uncertainty as to the measurement method has therefore no impact on the assessment of novelty of claim 1 of the main request over the disclosure of D1.

6.4 Consequently, claim 1 of the main request is novel over D1.

7. Remittal to the opposition division

As stated above, the main request meets the requirements of Article 76(1) EPC, Article 123(2) EPC and Article 83 EPC; moreover, the subject-matter of claim 1 of the main request is novel over D1. However, the claims of the main request have not been examined with regard to the objection of lack of novelty over D2 or inventive step by the opposition division.

Article 11 RPBA 2020 provides that the Board shall not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so. However, this provision has to be read in conjunction with Article 12(2) RPBA 2020, which provides that it is the primary object of the appeal proceedings to review the decision under appeal in a judicial manner.

This principle would not be respected if the Board were to conduct a complete examination of the grounds of opposition. Consequently, Article 11 RPBA 2020 cannot be interpreted in such a manner that it requires the Board to carry out a full examination of the application for compliance with the requirements of the EPC for which no decision of the opposition division exists yet.

Consequently, the Board considers it appropriate to exercise its discretion under Article 111(1) EPC to remit the case to the department of first instance for further prosecution.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

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

The Registrar: The Chairman:

K. Boelicke E. Duval

Decision electronically authenticated