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Datasheet for the decision of 1 February 2017

Case Number:	T 0488/16 - 3.3.01
Application Number:	00922102.9
Publication Number:	1169038
IPC:	A61K31/426, C07C237/40, C07D213/81, C07D213/82, C07D231/38, C07D233/90, C07D239/42, C07D263/48, C07D277/56, C07D409/12, C07D417/12
Language of the proceedings:	EN

Title of invention:
CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

Patent Proprietor:
Bristol-Myers Squibb Holdings Ireland

Opponents:
Isenbruck Bösl Hörschler LLP
APOTEX INC.
Actavis Group PTC ehf
Generics [UK] Limited

Headword:
Dasatinib/BRISTOL-MYERS SQUIB

Relevant legal provisions:
EPC Art. 56, 112(1)(a)

Keyword:
Inventive step - (no)
No plausible solution of the technical problem
Solution to less ambitiously defined problem obvious
Referral to the Enlarged Board of Appeal - (no)

Decisions cited:
T 0022/82, T 0939/92, T 0320/01, T 0715/03, T 0604/04, T 1329/04, T 1336/04, T 0433/05, T 0578/06, T 0536/07, T 1642/07, T 0716/08, T 0108/09, T 1043/10, T 0210/11, T 1677/11, T 0428/12, T 0863/12

Catchword:

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European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0488/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 1 February 2017

Appellant: (Patent Proprietor)	Wolter, Thomas; Thalhammer, Wolfgang Bristol-Myers Squibb Holdings Ireland Hinterbergstrasse 16 6312 Steinhausen (CH)
Representative:	Reitstötter Kinzebach Patentanwälte Postfach 86 06 49 81633 München (DE)
Respondent 1: (Opponent 1)	Isenbruck Bösl Hörschler LLP Seckenheimer Landstrasse 4 68163 Mannheim (DE)
Representative:	Jacobi, Markus Alexander; Ruttekolk, Ivo Robert Isenbruck Bösl Hörschler LLP Eastsite One Seckenheimer Landstrasse 4 68163 Mannheim (DE)
Respondent 2: (Opponent 2)	APOTEX INC. 150 Signet Drive Toronto, Ontario M9L 1T9 (CA)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Respondent 3: (Opponent 3)	Actavis Group PTC ehf Reykjavikurvegi 76-78 220 Hafnarfjördur (IS)

Representative:
Cooke, Richard Spencer
Elkington and Fife LLP
Thavies Inn House
3-4 Holborn Circus
London EC1N 2HA (GB)

Respondent 4:
(Opponent 4)
Generics [UK] Limited
(trading as Mylan)
Albany Gate
Darkes Lane
Potters Bar
Hertfordshire EN6 1AG (GB)

Representative:
Clarke, Lionel Paul
Gill Jennings & Every LLP
The Broadgate Tower
20 Primrose Street
London EC2A 2ES (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 9 February 2016 revoking European patent No. 1169038 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. The patent proprietor (appellant) lodged an appeal against the decision of the opposition division revoking the European patent No. 1 169 038.

II. The present decision refers to the following documents:

(1) EP 0 928 790
(2) EP 0 275 312
(7) J. L. Buchanan *et al.*, Bioorganic & Medicinal Chemistry Letters, Vol. 9, 1999, pages 2353 to 2358
(9) L. J. Lombardo *et al.*, Journal of Medicinal Chemistry, Vol. 47, 2004, pages 6658 to 6661
(10) J. Wityak *et al.*, Bioorganic & Medicinal Chemistry Letters, Vol. 13, 2003, pages 4007 to 4010
(34) L. M. Strawn, L. K. Shawver, Expert Opinion on Investigational Drugs, Vol. 7, No. 4, 1998, pages 553 to 573
(35) WO 99/21845
(36) Declaration of Professor D. Alessi, dated 16 May 2016 plus annexed documents DA1 to DA10, submitted by the appellant with letter of 20 May 2016
(37) Declaration of Professor K. Parang, dated 5 November 2016 plus annexed document KP1, submitted by the appellant with letter of 20 May 2016
(38) Affidavit of Dr. J. Barrish, dated 22 December 2016, submitted by the appellant with letter of 23 December 2016

III. Notices of opposition were filed by opponents 1 to 4 (respondents 1 to 4) requesting revocation of the

patent in suit in its entirety on the grounds of lack of novelty and inventive step, insufficiency of disclosure and added matter (Article 100(a), (b) and (c) EPC).

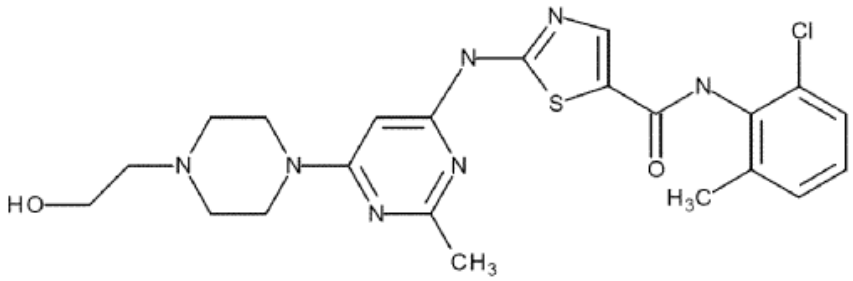
IV. The decision of the opposition division was based on a main request and first and second auxiliary requests.

The opposition division decided that the subject-matter of the main request was not sufficiently disclosed because it had not been plausibly demonstrated at the filing date that the compounds of the invention were protein tyrosine kinase inhibitors suitable for the claimed use, i. e. the treatment of cancer. According to the opposition division, this lack of disclosure could not be remedied by post-published evidence. The first auxiliary request was held to contravene Article 123(3) EPC. The second auxiliary request was considered to comply with Articles 123(2) and (3) and 83 EPC. Its subject matter was considered to be novel, but not inventive. In its assessment of inventive step, the opposition division did not take the post-published evidence into account and defined the problem to be solved as the provision of alternative low molecular compounds. The proposed solution was considered to be a mere enrichment of the pool of organic compounds, which was not considered to be inventive over the compounds disclosed in any of the documents (1), (2), (7) or (35).

V. With the statement of grounds of appeal, the appellant defended the maintenance of the patent in suit on the basis of a single request (main request), which was identical to the second auxiliary request underlying the decision under appeal. In addition, it submitted documents (36) and (37).

The only claim of the main request reads as follows:

"1. The compound of formula:



or salts thereof."

VI. In their replies to the statement of grounds of appeal, respondents 1, 3 and 4 maintained their objections of lack of inventive step. Respondent 1 raised additional objections under Articles 123(2) and 84 EPC against the amended description of the patent in suit. Respondent 4 raised an objection under Article 123(2) EPC against the amendment and "salts thereof" in the only claim of the main request. Respondent 2 did not reply to the statement of grounds of appeal.

VII. Third party observations filed by the European Federation of Pharmaceutical Industries and associations (EFPIA) were received on 12 October 2016.

VIII. With letter of 23 December 2016, the appellant submitted document (38).

IX. With letter of 5 January 2017, respondent 2 informed the board that it would not attend the oral proceedings scheduled for 1 February 2017.

X. At the oral proceedings before the board, the appellant filed a request for referral to the Enlarged Board of Appeal pursuant to Article 112(1)(a) EPC consisting of the following questions:

"1) Can the question of whether a technical problem is plausibly solved be answered without having regard to the prior art?

2) Is the lack of data in the application as filed a sufficient reason for denying plausibility? Is the answer different in the absence of evidence of a substantiated doubt?

3) In *inter partes* proceedings, if the patent has a clear teaching of a technical effect, is the burden of proof on the opponent to formulate substantiated doubts regarding that teaching?

4) If 2) is answered in the affirmative, does the lack of data in a prior art document disqualify that document as relevant prior art?"

XI. The arguments provided by the appellant as far as they relate to the decisive issues of the present decision can be summarised as follows:

- Admission of documents (36) and (37)

These documents were filed at the earliest possible opportunity as a *bona fide* reaction to the opposition division's surprising decision to disregard the post-published evidence, contrary to its preliminary opinion. Their filing was expedient and relevant for the assessment of what the application conveyed to the

skilled person, in particular whether the technical effect relied on had been made plausible at the filing date of the application. They also addressed the opposition division's objection regarding the alleged lack of a pharmacophore, an issue that had not been addressed before.

- Post-published evidence

The technical effect, namely the PTK inhibitory activity was clearly taught in the application as filed. There was positive information in the application in the form of a summary statement on page 50 that this effect had been achieved and that the problem the application purports to solve was solved. It was also clearly taught that dasatinib was found active as a PTK inhibitor in one or more of the assays mentioned in the application. Documents (9) and (10), in particular document (9), merely confirmed the technical teaching conveyed by the application. Further evidence in this respect could be found in document (38).

PTKs were drug targets for the treatment of immunological and oncological disorders which was confirmed by documents (34) and (36). The assays described in the application as filed were well-known and reliable to ascertain PTK inhibitory activity as confirmed in document (36). The inhibition of some PTK members would produce useful results. For a compound to be a PTK inhibitor and thereby solve the technical problem underlying the invention it was sufficient if the compound inhibited one of those members. This was clearly the case for dasatinib.

Even without any numerical data, the application conveyed to the skilled reader that dasatinib belonged to a clearly emerging group of compounds with favourable, more potent PTK inhibitory activity and thus solved the technical problem underlying the application. This was confirmed by Professor Parang in document (37).

The statement on page 50 was sufficient evidence that dasatinib plausibly solved the technical problem underlying the invention, which could easily be verified. No absolute proof was required. The skilled person would have understood this statement as a summary of the outcome of experiments actually carried out, which was confirmed by documents (36) and (37). It was not necessary to include data or experimental proof in the application, as this was not required by the EPC. There were also no *a priori* reasons to doubt the information in the application and no evidence or reason to assume the contrary existed. In the absence of such doubts, the assumption prevailed that the problem was solved. The burden of proof rested on the opponents or the opposition division to establish doubts to discredit plausibility. This was confirmed by the Case Law of the Boards of Appeal and National decisions of EPC states and the United States, which were consistent with EPO Case Law.

- Inventive step

Document (7) was the closest state of the art. It described 2,4-disubstituted thiazoles as novel class of Src inhibitors. Src was a member of the preferred kinase family targeted by the application (see page 39, lines 11 to 15). The distinguishing feature was the striking structural difference between the compounds of

document (7) and dasatinib. A comparison of results from table 1 of document (7) and table 2 of document (9) revealed that dasatinib was a much better Src PTK inhibitor than the compounds of document (7). The problem was therefore the provision of an improved PTK inhibitor and this problem was solved by dasatinib.

This solution was not obvious from document (7), which was concerned with the design of peptide analogues. No pointers were given in that document which would have motivated the skilled person to make the modifications required to arrive at dasatinib. Nor was the present solution obvious from any of the documents (1), (2) or (35), either alone or in combination with document (7). None of the former documents was concerned with the provision of PTK inhibitors. The cyclin-dependent kinase referred to in document (35) belonged to a different class of kinases, namely serine/threonine kinases. Furthermore, the compounds disclosed in documents (1), (2) or (35) were structurally different and had mandatory features not present in dasatinib. In particular, they had a substituent in position 4 of the thiazole ring, which was abandoned in the application (see page 13, lines 16 to 30) and which improved the activity (see document (38)). As was explained in document (37), the application conveyed an evolution in the direction of compounds with improved activity. Dasatinib was a member of this emerging group. It was not an arbitrary selected compound. This was also apparent from the improvement in solubility for compounds of the higher numbered examples, which included dasatinib. Dasatinib was a unique chemical compound with properties which made it particularly suitable for the treatment of cancer.

- Referral to the Enlarged Board of Appeal

The referral of the four questions was necessary and appropriate in the present case, particularly for the clarification of such an important issue as plausibility. Finding the mere lack of data relevant in the absence of any substantiated doubts was clearly inconsistent with the Case Law of the Boards of Appeal. The consequences of lack of data in the prior art would also need clarification.

XII. The arguments provided by the respondents as far as they relate to the decisive issues of the present decision can be summarised as follows:

- Admission of documents (36) and (37)

These documents should not be admitted pursuant to Article 12(4) RPBA. They were late filed and addressed issues, such as lack of enablement and lack of experimental evidence, which were raised early on in the opposition proceedings. There was no shift in argumentation and no new facts were relied on in the decision under appeal, which could justify the filing of these documents. Furthermore, the title page of both documents referred to third party observations from 6 June 2010 indicating that these submissions might have been considered for some time.

- Post-published evidence

The documents (9) and (10) should not be taken into account for the assessment of inventive step, since they were not supplementary evidence (cf. T 1329/04), but showed for the first time that the technical problem the application purports to solve was indeed

solved. For dasatinib the first disclosure going beyond speculation was provided in document (9).

The assessment of inventive step was to be made at the filing date of the patent. The application must make it at least plausible that it solved the problem it purports to solve. This was presently not the case. The application disclosed an extremely wide range of compounds allegedly useful as protein tyrosine kinase (hereinafter PTK) inhibitors. This was for the sheer breadth *a priori* implausible taking into account that for drugs structural modifications were *a priori* expected to disturb the pharmacological activity in the absence of an established correlation between structure and function. Furthermore, many different PTKs existed and it was not expected that a suitable compound would inhibit all of them. Although certain assays were suggested which could be conducted to establish the alleged inhibitory activity, no experimental results at all were provided for any compound in any assay. Nor had any threshold level for activity been given.

The statement on page 50 of the application was a mere assertion, which in the absence of any data was not sufficient to render the teaching of the application plausible. To argue plausibility there must be verifiable evidence, in the form of experimental data or a structure-activity relationship that made the activity plausible. The statement on page 50 was also not correct because, according to the appellant's post-published evidence, certain compounds of the examples in the application were inactive.

Dasatinib was disclosed in the application, but no preference for this compound was apparent. As for any other compound, no data was provided in the application

demonstrating that it had any PTK inhibitory activity suitable for the treatment of any disease or disorder associated therewith. In particular, no information with regard to the selective inhibition of PTKs associated with cancer was provided. This information was for the first time provided in the post-published document (9).

Documents (36) and (37) were not pertinent for the issue of plausibility. Even if the assays disclosed in the application were reliable tools for identifying the PTK inhibitory activity, as explained by Professor Alessi in document (36), this did not demonstrate that the tests had been carried out for any compound disclosed in the application or that useful results had been obtained. No convincing explanation was provided by Professor Alessi as to why the skilled reader in the absence of any verifiable evidence would simply accept the statement on page 50. Professor Parang's conclusion in document (37) with respect to a progression through the examples of the application and the emergence of a best working group, which included dasatinib, was fundamentally flawed in the absence of any experimental data. The examples were merely a list of compounds, from which a number of different pharmacophores was discernible. None was identified as preferred over any other.

Document (38) was irrelevant for the issue of what was plausible for the skilled person, because it concerned information only available to the patentee. It also contained no activity data, in particular from before the application was filed.

Concerning the present issue of plausibility, the Case Law of the EPO was settled. The Case Law from foreign

jurisdictions was not relevant. It was also not in contradiction with the EPO Case Law.

- Inventive step

Each of the documents (1), (2), (7) and (35) could serve as the closest state of the art. The distinguishing feature was the particular structure of dasatinib. Since the technical effect relied on had not been made plausible in the application, in particular not for dasatinib, post-published evidence could not be used and the problem to be solved was merely the provision of a further compound. The mere provision of a compound without any particular activity did not solve any problem and amounted to a mere enrichment of chemistry, which did not involve an inventive step. Arbitrary compounds were all equally obvious.

The alleged improvements in solubility should not be considered, since there was no comparison with the prior art.

- Referral to the Enlarged Board of Appeal

There was no need for a referral. What was plausibly disclosed in an application could not be answered in general, but depended on the facts and circumstances of a case. The questions were irrelevant for the case at hand and also had answers. Question 1 could be answered in the affirmative, as it concerned the subjective problem as defined in the patent in suit. Questions 2 and 4 were case dependent and had to be answered by the board taking into account all the facts and circumstances of the specific case. Question 3 was an artificial problem, since there was no clear teaching of a technical effect in the present case.

XIII. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed with the statements of grounds of appeal. It also requested the referral of four questions, submitted at the oral proceedings before the board (see point X above), to the Enlarged Board of Appeal.

XIV. Respondent 1 requested that the appeal be dismissed. It requested further that documents (36) and (37) and the accompanying documents DA1 to DA10 and KP1 not be admitted into the proceedings.

Respondent 3 requested that the appeal be dismissed. As an auxiliary measure, it requested that the case be remitted to the opposition division, if the board were to define the problem to be solved more ambitiously than the decision under appeal.

Respondent 4 requested that the appeal be dismissed.

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

Reasons for the Decision

1. The appeal is admissible.

2. As communicated in advance to the board (see point IX above), respondent 2, who did not submit any comments or observations with regard to the substantive issues, did not attend the oral proceedings before the board, to which it had been duly summoned. The board decided

to continue the proceedings pursuant to Rule 115(2) EPC and Article 15(3) RPBA.

3. Admission of documents (36), (37) and (38)

3.1 Documents (36) and (37) were filed with the statement of grounds of appeal in direct response to the opposition division's decision revoking the patent. In the decision under appeal, the opposition division was of the opinion that the technical effect relied on by the appellant had not been plausibly demonstrated at the filing date. Furthermore, it criticised the lack of an identifiable pharmacophore. As a consequence, contrary to the opposition division's initial indication in its preliminary opinion, the post-published evidence was not taken into account and inventive step was not acknowledged.

The appellant challenged the opposition division's findings and addressed these key issues in its statement of grounds of appeal, in particular the concern as to the lack of an identifiable pharmacophore. Documents (36) and (37), dealing with the question of what the application conveyed to the skilled reader, were filed in support of the appellant's position that the opposition division erred in its assessment of what was plausibly disclosed in the application, and consequently in its assessment of inventive step. In these circumstances, the board is of the opinion that the submission of these documents with the statement of grounds of appeal is an appropriate and legitimate attempt by the appellant to address the objections raised in the decision under appeal and to further support its position with respect to plausibility and inventive step.

The argument of respondent 1 that these declarations might have been considered much earlier and could therefore have been filed at a much earlier state is not convincing. The title page of both documents makes reference to such data as the patent, application and appeal number. It identifies the patentee and the opponents and, in this context, also mentions third party observations. In the board's opinion this reference is not an indication that the present declarations were a late reaction to these third party observations, which for some unknown reasons were not filed before.

3.2 Hence, the board decided to admit documents (36) and (37) into the proceedings.

3.3 Document (38) was filed about one month before the oral proceedings took place. None of the respondents raised an objection to its introduction into the proceedings. Nor did the board see any reason to reject this document. Consequently, document (38) was admitted into the proceedings.

4. Post-published documents

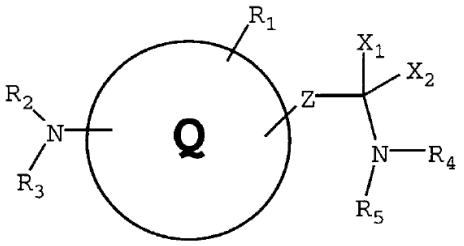
4.1 Documents (9) and (10), in particular document (9), on which the appellant relied as evidence that the presently claimed compound dasatinib showed protein tyrosine kinase (PTK) inhibitory activity and was therefore suitable in the treatment of disorders associated therewith, particularly cancer, were filed more than three years after the filing date of the patent in suit (document (9) in December 2004 (on the Internet in July 2004); document (10) in November 2003). In the decision under appeal, the opposition division decided not to take these documents into

account on the grounds that the alleged activity had not been made plausible at the effective date of the patent in suit and that the post-published documents were the first disclosure going beyond speculation. This decision was challenged by the appellant, who continued to rely on these documents as confirmation for a plausible disclosure of dasatinib as PTK inhibitor.

4.2 It is established jurisprudence of the boards of appeal that the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. Post-published evidence in support that the claimed subject-matter solves the technical problem the patent in suit purports to solve may be taken into consideration, if it is already plausible from the disclosure of the patent that the problem is indeed solved (see Case Law of the Boards of Appeal, 8th edition, I.D.4.6; T 1329/04, point 12 of the Reasons; T 1043/10, point 12 or the Reasons).

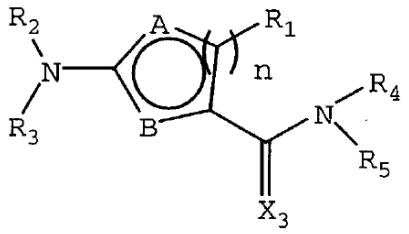
Thus, for post-published evidence to be taken into account, it is necessary to establish whether or not the asserted activity has been made sufficiently plausible for dasatinib at the effective date of the patent in suit. Basis for this assessment is the application as filed and the common general knowledge of the person skilled in the art at the filing date.

4.3 The application is directed to an extremely broadly defined group of compounds of the following generic formula I:



I

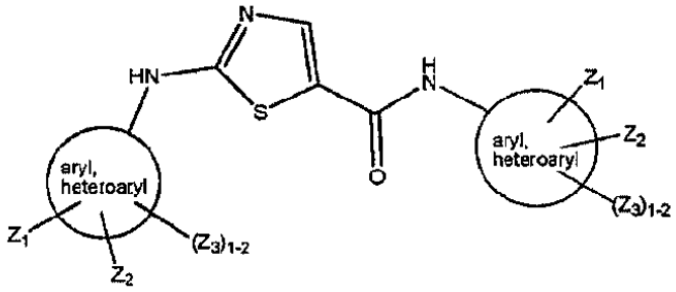
Q is an aryl ring or a 5- or 6-membered heteroaryl ring (see page 3, lines 5 to 14); the variables are defined on page 3, line 10 to page 8, line 7. Furthermore, a subgroup is defined having the following general formula II:



II

were A is carbon or nitrogen, B is nitrogen, oxygen and sulfur, X is oxygen and sulfur and the other variables are defined as for formula I (see page 8, lines 8 to 18).

Preferred compounds of formula I are defined on page 13, line 16 to page 14, line 2, where Q is thiazole, Z is a single bond and R_2 and R_4 are hydrogen. Taking into account, the more preferred definitions of the variables R_1, X_1, X_2, R_3 and R_5, the information on pages 13 and 14 translates into the following formula



The application also discloses 580 compounds falling within the scope of general formula I, including dasatinib (see example 455).

4.4 On page 39, line 10 to page 43, line 25, the application describes a number of PTKs, which are potential targets of the claimed compounds, and the diseases or disorders associated therewith. Particular types of kinases, which are listed in this context are the non-receptor kinases Lck, Fyn, Lyn, Src, Yes, Hck, Fgr and Blk, which belong to the Src-family (page 39, lines 10 to 15) or the receptor kinases HER1 and HER2, which belong to the epidermal growth family (see page 42, line 30 to page 43, line 3 and page 1, lines 20 to 21). Other types of receptor and non-receptor tyrosine kinase families are mentioned on page 1, lines 18 to 24. As is apparent from pages 39 to 43, inhibition of specific protein tyrosine kinases are associated with specific disorders, for example Lck inhibitors are of value in the treatment of T-cell mediated diseases, such as arthritis, multiple sclerosis, lupus, transplant rejection delayed-type of hypersensitivity, certain types of cancer, etc; Hck and Fgr are important in the Fc gamma receptor response and are considered valuable in the treatment of inflammatory bowel disease or autoimmune glomerulonephritis; Lyn and Src are important in the Fc epsilon response and are of value in the treatment of

asthma or allergic disorders; HER1 and HER2 can be used in the treatment of proliferative treatments, such as psoriasis and certain types of cancer.

4.5 On page 50, line 4 to page 53, line 18, the application refers to assays "which can be employed in ascertaining the degree of activity of a compound ("test compound") as PTK inhibitor" (see page 49, lines 29 to 30). The assays are generically described and refer to the "protein kinase of interest" and the "test compound" or "compounds of interest" to be assayed. No further details are provided in this respect. Nor are any results, for example IC or K_i values, provided. Indeed, there is no evidence at all in the application as filed that shows that any of the compounds falling within the scope of formula I, let alone dasatinib, is active as an inhibitor for any of the specific protein tyrosine kinases, except a mere assertion on page 50, lines 1 to 2 with reads that "Compounds described in the following Examples have been tested in one or more of these assays and have shown activity." No further information is provided. No individual values or range of values are given. No information as to whether the observed "activity" is suitable for the intended use, i. e. the treatment of a number of diseases and disorders, is provided. In the board's judgement, a mere verbal statement that "compounds have been found active" in the absence of any verifiable technical evidence is not sufficient to render it credible that the technical problem the application purports to solve, namely providing PTK inhibitors to treat disorders or diseases associated therewith, is indeed solved, in particular in the present case, where the invention is directed to a very broadly defined class of compounds encompassing millions of structurally rather different candidates with unknown properties,

where even the examples show a broad structural variation and where it is inherently unlikely for any skilled person that all of the compounds of the invention or at least a substantial amount of them will exhibit the alleged PTK inhibitory activity.

In the present case, there is also no evidence on file showing that, at the date of filing, the skilled person was in the possession of common general knowledge which, even in the absence of data, made it plausible that the compounds of the invention, in particular dasatinib, could be expected to show PTK inhibitory activity. The appellant's argument that a number of structurally different compounds are known as PTK inhibitors and are in clinical trials or near clinical development (see document (34), point 3 on pages 559 to page 565) is not pertinent in this context, as no conclusion with regard to PTK inhibitory activity of dasatinib can be drawn from this knowledge in the absence of any correlation between structural features and function.

Even if the board were to accept the assertion on page 50 of the application as filed as an indication that some tests had been carried out, no information is provided as to which of the structurally rather different compounds had been tested and in which assay, in particular whether any of the tests included dasatinib. In this context, the board would like to emphasise that it does not accept the appellant's contention that the passage on page 50 is to be read in the sense that all compounds of the examples had been tested. As pointed out by the respondents, such a reading also appears to be in conflict with the appellant's post-published evidence according to which certain compounds of the examples were inactive at a

specific concentration. In this context, the board notes that in document (38), Mr Barrish, one of the inventors, refers to a review of the results of the assays performed before the patent was filed, which showed that these specific compounds were tested and found active in "one or more PTK assays" (see points 20 and 21). Irrespective of fact that document (38) can not be relied on for the purpose of what has been made plausible by the application (see point 4.7 below), no evidence was provided in support of this assertion. Nor are any results concerning the performance of dasatinib provided in document (38).

4.6 In support of its position that the claimed effect had been made plausible for the skilled reader, the appellant relied on the declarations of Professor Alessi and Professor Parang (documents (36) and (37)).

4.6.1 As a preliminary remark, the board would like to point out that the opinion of highly skilled experts on how a disclosure of a document is to be understood does not reflect the view of the notional skilled addressee, who is a person of ordinary skills aware of what is common general knowledge in the art at the relevant date. Experts give evidence based on their professional experience and expertise which is not common general and will have an influence on their way of reading the disclosure of a document. Since the assessment of the disclosure from the point of view of the skilled person does not normally call for special technical knowledge or experience, expert evidence on this matter will not be pertinent. Such evidence is only necessary when the board does not consider itself in a position to decide upon a matter without technical assistance. As the board includes two technically qualified members such cases will be rare and will only occur in special

circumstances. Finally, opinions by party experts are subject to the free evaluation by the board. It is therefore the adequate substantiation and persuasiveness of the experts' propositions that matter rather than the mere fact that they are presented as an expert opinion which is a means of evidence within the meaning of Article 117(1) EPC.

4.6.2 In his declaration, Professor Alessi mainly comments on the suitability and reliability of the assays referred to in the application for measuring the effectiveness of kinase inhibition (see paragraphs 13 to 27 of document (36)). This is not contested by the board. However, the board fails to see the significance of Professor Alessi's observations, in particular since they do not provide an explanation as to why the skilled reader would simply accept the assertion on page 50 of the application without question. In the board's opinion, the skilled reader can be expected to react in a way common to all persons skilled in the art, which means that any acceptance as to whether or not a particular assertion is correct must be based on verifiable facts, be it information provided in the patent application or available to the skilled person as common general knowledge. In the present case, no such verifiable facts exist. The situation is further aggravated taking into account that, contrary to the appellant's view, the skilled person is not in a position to readily verify the assertion on page 50 in the absence of any detailed information as to the conditions under which the assays are to be carried out. As is apparent from point 4.5 above (see last paragraph), whether or not a compound is "active" apparently also depends on its concentration.

4.6.3 In his declaration, Professor Parang mainly reviewed the examples in the application, which in his opinion indicated to the skilled person a progression through a research program. Starting from early hit compounds, such as example 1, successive variants were synthesised to improve those compounds. Professor Parang identified in the first 129 examples three groups of thiazole compounds (see document (37), page 5, Figures 1, 2 and 3). From example 376 onwards, he identified a further common core structure with a 2-chloro 6-methyl-phenyl group at the carboxamide in position 5 of the thiazole ring (see Figure 4 on page 6 of document (37)). According to Professor Parang, the continued re-use of this common structure meant that a useful pharmacophore had been identified and the additional work embodied in the subsequent examples was to fine tune and optimise the physicochemical properties, particularly the solubility of the compounds. Dasatinib was one of the compounds that re-use the aforementioned common structure. It also fell into the preferred group of compounds as described on page 13 to 14 of the application which lent additional support to it being a PTK inhibitor.

4.6.4 The board agrees with Professor Parang insofar as it is possible to group compounds from the examples together which share a common structural moiety, such as a methyl substituted thiazole ring as illustrated in Figure 2 of the declaration, a 2,4,6 trimethylphenyl groups at the carboxamide in position 5 of the thiazole ring as illustrated in Figure 3, or a 2-chloro 6-methyl phenyl at the carboxamide in position 5 of the thiazole ring as illustrated in Figure 4. Other groups are also apparent, for example, compounds without a thiazole ring (see examples 368 to 375), compounds with a 2-chloro 6-methyl phenyl at the carboxamide in position 5

of the thiazole ring but no aryl or heteroaryl group at the nitrogen in position 2 as in Figure 4 (see examples 322 to 362), compounds without a 2,4,6-trimethylphenyl group or a 2-chloro 6-methyl phenyl group as illustrated in Figures 3 and 4 (see examples 410 to 427 or 521 to 526, 539 to 551). Indeed, no moiety is apparent which is common to all examples.

However, in the complete absence of any data, no conclusion can be drawn as to whether or not the examples reflect a progression in the direction of improved PTK inhibitory activity. Nor is any conclusion possible as to whether or not a suitable pharmacophore reflected by the formula in Figure 4 of Professor Parang's declaration, which includes dasatinib, had indeed been found at the filing date of the application.

4.6.5 In summary, neither Professor Alessi's nor Professor Parang's declaration can support the appellant's view that the alleged activity had been made plausible for dasatinib at the time of filing.

4.7 Document (38), on which the appellant also relied, is not relevant in answering the question whether the application made it plausible for the skilled person that dasatinib showed PTK inhibitory activity, since it refers to knowledge which was not available to the skilled person at the filing date. Furthermore, although this document refers to results, which had been obtained before the filing date of the patent in suit, none of these results were included in this document or were ever provided in the proceedings before the EPO, in particular not for dasatinib.

4.8 The appellant also argued that the EPC does not require experimental proof. A summary statement as provided on page 50, lines 1 to 2 was sufficient to meet the low plausibility threshold, which was satisfied in the absence of any substantiated doubts. No absolute proof was required and there was no legal basis to provide any raw data. As the threshold test had been met, the post-published evidence which merely confirmed the PTK inhibitory activity of dasatinib should be taken into account.

4.9 The board agrees with the appellant insofar as it is not always required to include experimental data or results in an application (see T 578/06, point 13 of the Reasons). It is however a *conditio sine qua non* that it is shown that the technical problem underlying the invention was at least plausibly solved at the filing date. If, as in the present case, the nature of the invention is such that it relies on a technical effect, which is neither self-evident nor predictable or based on a conclusive theoretical concept, at least some technical evidence is required to show that a technical problem has indeed been solved. In the board's judgement, it is not acceptable to draw up a generic formula, which covers millions of compounds, vaguely indicate an "activity" against PTKs and leave it to the imagination of the skilled reader or to future investigations to establish which compound inhibits which kinase and is therefore suitable to treat the respective diseases associated therewith. In this context, the board notes that it has been acknowledged by the appellant that the skilled person would not expect that each compound would be active against all kinases. The board would also like to emphasise that in the present case the issue is not the absence of any *in vivo* data or clinical data, but

rather the absence of any verifiable data with regard to the asserted technical effect.

Furthermore, contrary to the appellant's assertion, the post-published document (9) - the only document which refers to dasatinib - does not merely confirm the technical effect, but rather discloses a specific PTK profile, which identifies dasatinib as an inhibitor with potent anti-tumour activity (see table 2 on page 6660). No such disclosure is present in the application as filed.

4.10 With regard to the appellant's argument that the burden of proof was on the respondents to show that the application did not solve the technical problem it purports to solve, the board notes the following:

In the present case, no decision is required as to whether there exists, as argued by the appellant, a presumption that a granted patent solves the technical problem it purports to solve. The respondents (opponents), starting from the disclosure in the application as filed, have provided technically sound and persuasive arguments as to why the alleged effect had not been made plausible, which raises doubts as to whether the technical problem had been solved at the filing date, in particular by dasatinib. Thus, even if the burden was on the opponents to raise substantiated doubts, they discharged of it. It then rests on the appellant who continues to rely on the alleged effect to counter-argue and to rebut these doubts.

4.11 In support of its case, the appellant also made extensive reference to the Case Law of the Boards of Appeal. In particular, it relied to a number of decisions in which the boards have taken post-published

evidence into account, for example T 428/12, 1677/11, T 715/03 (erroneously referred to as T 517/03), T 1642/07 or T 210/11.

4.12 In the board's judgement these decisions cannot support the appellant's case.

4.12.1 In decision T 428/12, the application as filed, contrary to the present case, contained a significant amount of activity data showing that certain substituents could vary considerably with practically no influence on the activity. Based on an assessment of this technical data, it was the board's view that it had been made plausible that the compounds of a claimed subgroup actually showed the required activity and thus provided a solution to the problem (see point 5.5.3 of the Reason). The post-published evidence was not even considered (see point 5.6 of the Reasons).

4.12.2 In decision T 1677/11, the claimed compound belonged to a well-known class of gastric acid secretion inhibitors. This was uncontested and the board saw no reason why, in the absence of any arguments to this effect, it should be *a priori* implausible that the salt provided an improved therapeutic profile (see fourth paragraph in point 9.5.1 of the Reasons).

4.12.3 In decision T 715/03 it was already known in the prior art that a compound of the application (e. g. the known atypical neuroleptic ziprasidone) underwent a clinical trial on efficacy and tolerability on patients with Tourette syndrome and that this study was near completion. The post-published evidence referred to this particular study and the author of the prior art document and inventor of the application, confirmed that he was already aware of positive results of the

study announced by himself as nearing completion. The board accepted these specific circumstances as an indication for the plausibility of the statement made in the application with respect to the suitability of the compounds disclosed therein, in particular ziprasidone, for the treatment of Tourette syndrome (see point 2.4.2 of the Reasons).

4.12.4 In decision T 1642/07 and T 210/11 the boards had no doubts that it was at least plausible that the alleged improvements (i. e. improved anti-tumour activity of a known anti-tumour agents with a chemotherapeutic agent; increased bioavailability of specific nano-particles) were obtained. In the present case, as set out in points 4.5, 4.6, 4.8 and 4.9 above, there are indeed such doubts.

Furthermore, unlike in T 1642/07, where the board viewed the post-published evidence as being a mere confirmation of the technical effect already made plausible based on a convincing theoretical explanation in the application as filed this is presently not the case (see point 4.9 above).

4.13 The appellant also argued that the situation in decision T 1329/04, on which the opposition division relied in the decision under appeal, was significantly different to the present application.

4.14 The board does not share the appellant's view that the factual situation in decision T 1329/04 differs to such an extent that it is not applicable in the present case. In that decision the key issue was whether it was plausible that the claimed polypeptide GDF-9 belonged to the TGF-β superfamily and therefore exhibited the functions contributed to members of this family. The

board held that this was not the case as there was no evidence at all that GDF-9 played a role similar to that of TGF-β (see point 9 of the Reason). Furthermore, it lacked the consensus region common to all family members, which even in the absence of evidence as to it role, could identify it as a member (see point 3 of the Reasons).

In the present case, there is also no evidence provided on the date of filing that dasatinib is a suitably active PTK inhibitor, let alone an inhibitor for PTKs associated with the treatment of cancer, such as Src or Abl kinase, the latter is not even mentioned in the application as filed. Structural similarity of small molecules does not necessarily imply similar function. Their activity is in general unpredictable and even minor structural changes can disrupt activity. No established structure-activity relationship exists, which, in the complete absence of any verifiable data in the application, would make it plausible that dasatinib is a PTK inhibitor.

4.15 Additional decisions were cited by the appellant to further illustrate the situation which was meant to be addressed by T 1329/04 (for example T 536/07, T 604/04, T 108/09, T 863/12, T 716/08 T 578/06, T 433/05 or T 1336/04). The appellant argued that according to these decisions there must be *prima facie* serious doubts as to the suitability of the claimed invention to solve the technical problem. In the present case, the board concurs with the respondents that such doubts existed (see points 4.5, 4.6, 4.8 and 4.9 above). The board also notes that in the majority of these cases there was sufficient evidence in the application as filed which made it at least plausible that the technical problem was solved, such as screening

examples in combination with general knowledge (T 716/08, points 17 to 24 of the Reasons), structural similarity to known members of a particular family (T 1336/04, point 9 of the Reasons or T 604/04, point 6 of the Reasons) or at least a plausible theoretical concept (T 433/05, improving *in vivo* stability of known peptides via coupling to a long living blood component; T 108/09 use of a known second-line agent in the treatment of breast cancer as a third-line agent for the same disease).

4.16 The appellant also referred to national decisions of EPC states and the United States, which in its opinion are consistent with EPO Case Law. As explained above (see points 4.12 to 4.15), the board sees no conflict in the present case with the EPO Case Law. For the sake of argument, it is noted that this applies also with regard to the decisions of national courts relied on by the appellant. In the following, the board wishes to briefly comment on these decisions although they are not legally binding on the Boards of Appeal and thus not immediately relevant to the present case.

4.16.1 The case "Human Genome Sciences v Eli Lilly [2011] UKSC 51" was a biotechnology case, where the plausibility for a pharmacological effect of the claimed Neutrokine-α polypeptide rested on the fact that it was a member of a known super family and could be expected to exhibit similar functions. As explained above in the context of decision T 1329/04 (see point 4.14), in the present case, no such established correlation between structure and function exists.

4.16.2 Concerning the case "Generics (UK) Ltd t/a Mylan v Yeda Res and Dev Co Ltd [2013] EXCA Civ 925", the board notes that paragraph [49] of that decision, on which

the appellant relied, explicitly states in points (v) and (vi) that "A technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step" and "Later evidence may be adduced to support a technical effect made plausible by the specification". In the present case, it is the board's position that the claimed effect had not been made plausible for dasatinib at the filing date.

4.16.3 In the decision "Actavis v Eli Lilly [2015] EWHC 3294" the High Court viewed plausibility as a threshold test which is satisfied by a credible disclosure. The board considers that in the present case, this threshold has not been met. In the context of this High Court decision, the appellant also referred to the importance of the claim type and the breadth of the claims to the assessment of plausibility. In particular, the appellant referred to the statement that "Generally, it is likely to be easier, as a matter of fact, to show plausibility for a claim of narrow scope, for example a single drug for a single disease, than for a claim of wide scope, for example a class of drugs for multiple diseases". This statement has to be seen in the context of the case underlying the UK High Court decision, which was concerned with the use of tomoxetine in the treatment of attention-deficit/hyperactivity disorder, i. e. a single use for a single disease. In the present case, the application as filed was concerned with an extremely broadly defined group of compounds for a plethora of disorders based on the inhibition of different types of PTKs associated with the treatment of different diseases or disorders. This is a completely different situation, irrespective of the fact that the present main request is now limited to a single compound.

4.17 The position on the issue of plausibility under Dutch law appears to be very much aligned to the Case Law of the Boards of Appeal. In particular, it is considered that the application must at least make it plausible that the technical problem is solved ("Court of Appeal of the Hague in BMS v Yew Tree Taxol), that post-published evidence may be taken into account to supplement and support a credible disclosure ("Court of Appeal of the Hague in Angiotech v. Sahajanand - Taxol coated stents"), that clinical trials are not required ("Court of Appeal of the Hague Glaxo v. Pharmachemie - Ondansetron"), and that in vitro tests may be sufficient ("Court of Appeal in the Hague in Lilly V. Ratiopharm - Olanzapine"). None of this is contested by the board. However, in the present case, it is the board's judgement that, based on the nature of the invention and the lack of experimental evidence, it had not been credibly shown at the filing date of the patent in suit that dasatinib was a successful PTK inhibitor suitable for the treatment of cancer.

4.18 The United States decisions cited by the appellant are based on national law unrelated to the EPC. Nevertheless, the board cannot discern a conflicting approach, since one of the key issues considered in these decisions was whether or not there were, on the basis of the facts and evidence on file, reasons for the skilled person to doubt the asserted utility. Based on the facts and evidence of the present case, the board concludes that such doubts exist. The board also notes that the second case ("Federal Circuit in Eli Lilly and Company, Plaintiff-Appellant, v. Actavis Elizabeth LLC) apparently concerned the same or a similar case as the UK decision (see 4.16.3 above), in which a single compound was considered to be suitable

in the treatment of a specific disorder. As explained in point 4.16.3 above, in the present case, the situation is entirely different.

4.19 For the reasons set out above, the board concurs with the opposition division and the respondents that the post-published documents (9) and (10) are the first disclosure showing that at least for certain thiazole, in particular dasatinib, the purported technical problem has actually been solved. In accordance with established case law, these documents are therefore not taken into consideration in the assessment of inventive step.

5. Inventive step (Article 56 EPC)

5.1 Claim 1 of the sole request is directed to a single compound, namely dasatinib (see point V above). According to the appellant, it has PTK inhibitory activity and can be used to treat disorders associated therewith, particularly cancer.

5.2 In the decision under appeal, the opposition division considered each of the documents (1), (2), (7) or (35) as a suitable starting point for the assessment of inventive step (see page 15, last paragraph, page 16, first paragraph or page 17, first paragraph). The appellant identified document (7) as the closest prior art, while the respondents either agreed with the opposition division (respondents 3 and 4) or preferred documents (1), (2) or (35) (respondent 1).

In these circumstances, the board considers it justified to start the assessment of inventive step with document (7).

5.3 This document describes the structure-based design and synthesis of 2,4-disubstituted thiazoles as a novel class of Src inhibitors. Src is a protein tyrosine kinase implicated as a potential target for the therapeutic intervention for osteoporosis and breast cancer (see abstract) and belongs to the target kinases of the patent in suit. The thiazoles of document (7) differ from dasatinib in that they are disubstituted in position 2 and 4 of the thiazole ring, rather than 2 and 5, and that the two substituents are structurally markedly different from those of dasatinib (cf. compound 3 on page 2354 and compound 3a/3b on pages 2355 and 2356).

5.4 At the oral proceedings before the board, the appellant argued that dasatinib showed a clear improvement in PTK inhibitory activity compared to the compounds disclosed in document (7). According to the appellant, this was apparent by comparing the IC values in table 2 of document (7), which were in the micro molar range, with the value given in document (9), which was 0.5 nmol for Src (see table 2, second entry). Accordingly, the appellant formulated the problem as the provision of an improved PTK inhibitor and considered it solved by the compound dasatinib.

5.5 The board does not agree.

The patent in suit does not contain any evidence that the problem as formulated by the appellant has been successfully solved. There is no evidence at all that any compound of the examples, let alone dasatinib, had been tested for Src inhibitory activity and is thus useful for the treatment associated therewith, in particular cancer. Furthermore, the post-published document (9), on which the appellant relied as evidence

for the PTK inhibitory activity of dasatinib, cannot be taken into consideration, for the reasons set out in detail in point 4 above. The same applies to document (38). The board also notes that this document does not contain any evidence as to the assays, which had actually been carried out with dasatinib or the results that had been achieved. It merely repeats the same general assertion as the patent in suit on page 25, line 41 to 42 and the application on page 50, lines 1 to 2 (see points 16 and 17 of document (38)). The board therefore concurs with the opposition division and the respondents that the effect on which the appellant relied (i. e. any PTK inhibitory activity) cannot be taken into account in formulating the technical problem.

Nor can the alleged improvement in solubility be taken into account, as there is no comparison with the prior art in this respect which could demonstrate such an improvement. The appellant compared the solubility of dasatinib (illustrated by the HPLC retention time) with the solubility of other examples in the patent in suit, none of which belongs to the prior art.

5.6 It follows from the above that the problem to be solved has to be defined in a less ambitious way, namely as the provision of a further chemical compound.

5.7 According to the jurisprudence of the boards of appeal, a chemical compound is not patentable merely because it potentially enriches chemistry and structural, since originality has no intrinsic value or significance for the assessment of inventive step as long as it does not manifest itself in a valuable property in the widest sense, an effect or an increase in the potency of an effect (see T 22/82, OJ EPO 1982, 341, point 6 of the

Reasons, T 939/92, OJ EPO 1996, 309, point 2.5.1 of the Reasons, T 320/01, point 3.2.4 of the Reasons). In other words, the mere provision of a chemical compound capable of being synthesised, which was not contested, and not showing any effect does not require inventive ingenuity. The structural uniqueness of dasatinib alone cannot therefore support an inventive step.

5.8 The appellant's additional arguments in favour of an inventive step were focused on the PTK inhibitory activity of dasatinib (see point XI above). They are, however, not pertinent in a situation where this effect could not be acknowledged and the problem to be solved was merely the provision of further chemical compound.

5.9 Relying on document (37), the appellant also re-emphasised that dasatinib was not an arbitrarily selected compound, but belonged to an evolving group of compounds (cf. figure 4 of document (37)), which the skilled person would clearly recognise as being qualitatively better than the earlier groups of compounds, even without providing any numerical results.

The board does not agree. As explained above (see point 4.6.4) in the absence of any data provided in the application with regard to PTK inhibitory activity of the compounds of the application, or similar information available to the skilled person as common general knowledge, no such evolution or development, let alone any selectivity for PTKs which are associated with the treatment of cancer, is apparent. If on the other hand improvements in solubility were to be accepted as an indication of preference, this would not suggest any preference for dasatinib, which is one of the poorer performing examples in the group of

compounds disclosed on page 110 to 111 of the patent in suit (cf. page 156 to 158 of the application as filed).

5.10 For the aforementioned reasons, the board concludes that the appellant's main and sole request lacks inventive step (Article 56 EPC).

5.11 Since the board did not define the problem to be solved differently from the opposition division in the decision under appeal, it was not necessary to decide on respondent 3's request for remittal.

5.12 Third party observations supporting the appellant's view have been filed by EFPIA (see point VII above). The observations are essentially identical to the arguments provided by the appellant and have been addressed in points 4 and 5 above, including the decision cited by EFPIA in support of its case.

6. Referral to the Enlarged Board of Appeal

6.1 Article 112(1) EPC stipulates that the Boards of Appeal shall, during proceedings on a case following a request from a party to the appeal refer any question to the Enlarged Board of Appeal, if it considers that a decision is required in order to ensure uniform application of the law, or if a point of law of fundamental importance arises.

6.2 The board is of the opinion that the questions proposed by the appellant (see point X above) do not satisfy these prerequisites. The questions are mainly concerned with whether or not the technical effect on which the invention was based has been made plausible and can therefore be considered for the assessment of inventive step. They are primarily technical questions to be

answered by the board taking into account the facts and evidence of the present case. The board also concurs with the respondents that the question of whether an invention is plausible cannot be answered in general, as this assessment depends upon the individual circumstances, namely the nature of the invention, the disclosure of the specification and common general knowledge.

The questions also do not relate to the uniform application of the law as the board does not take any view of the law different to established case law of the boards of appeal. The board's conclusions are not in conflict with established case law as implied by the appellant, but have been reached by applying established principles to the specific circumstances of the present case.

6.3 The request for referral to the Enlarged Board of Appeal is therefore rejected.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The request for referral to the Enlarged Board of Appeal is rejected.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated