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Datasheet for the decision of 18 January 2024

Case Number: T 0147/22 - 3.3.07

Application Number: 13749171.8

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Language of the proceedings: EN

Title of invention:
ORAL ADMINISTRABLE PHARMACEUTICAL COMPOSITION

Patent Proprietor:
Taiho Pharmaceutical Co., Ltd.

Opponent:
Teva Pharmaceutical Industries Ltd

Headword:
TAS-102 formulation/TAIHO

Relevant legal provisions:
EPC 1973 Art. 113(1), 84, 123(2), 56
RPBA 2020 Art. 11, 12(4)

Keyword:

Substantial procedural violation - (no)
Remittal - (no)
Amended claims - admitted (yes) - clarity (yes) - added subject-matter (no)
Inventive step - (yes)

Decisions cited:

T 0472/88, T 1621/16

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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 0147/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 January 2024

Appellant: (Patent Proprietor)	Taiho Pharmaceutical Co., Ltd. 1-27, Kandanishiki-cho Chiyoda-ku, Tokyo 101-8444 (JP)
Representative:	Blodig, Wolfgang Wächtershäuser & Hartz Patentanwaltspartnerschaft mbB Weinstrasse 8 80333 München (DE)
Respondent: (Opponent)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 November 2021 revoking European patent No. 2815753 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	Y. Podbielski

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision revoking European patent No. 2815753. The decision was based on the patent as granted and the claims of eight auxiliary requests.

II. The following documents are referred to in the present decision:

D1 EP 1849470A1

D2 Appellant's letter to the examining division dated 21 December 2015

D3 H.A. Lieberman et al., Pharmaceutical Dosage Forms - Tablets, vol. 1, 2nd edition, 1989, 93-110 and 173-177

D7 Additional comparative tests dated 15 April 2020

D8 R.C. Rowe et al., Handbook of Pharmaceutical Excipients, 6th edition, 2009, 129-133

III. In the decision under appeal, the opposition division concluded, among other things, that the subject-matter of the patent as granted did not involve an inventive step starting from D1 as the closest prior art. Auxiliary requests 1 to 4, 7 and 8 added subject-matter, auxiliary request 5 lacked clarity, and auxiliary request 6 was not admitted.

IV. The patent proprietor (appellant) filed an appeal against the decision. With its statement of grounds of appeal, the appellant filed eleven sets of claims as its main request and auxiliary requests 1 to 10.

Auxiliary request 4 had two claims, which read as follows:

"*1. An orally administrable pharmaceutical composition consisting essentially of*

(a) α,α,α-trifluorothymidine and 5-chloro-6-(2-iminopyrrolidine-1-yl)methyl-2,4(1H,3H)-pyrimidine dione hydrochloride as active ingredients at a molar ratio of 1:05,

(b) a sugar having a critical relative humidity of 85% or more at 25°C as an excipient, wherein the sugar having a critical relative humidity of 85% or more at 25°C is one or more selected from lactose, sucrose, mannitol, and erythritol,

(c) a disintegrating agent which is partly pregelatinized starch, and

(d) additives selected from excipients other than the sugar having a critical relative humidity of 85% or more at 25°C,
0.001 to 5% by mass in the total composition of a binder selected from hydroxypropyl cellulose, hypromellose, and polyvinyl alcohol,
0.001 to 3% by mass in the total composition of a lubricant selected from hydrogenated oils, sucrose fatty acid esters, and stearic acid,
flavoring agents,
colorants, and
taste-masking agents,

wherein the content of the sugar having a critical relative humidity of 85% or more at 25°C is 3.6 parts by mass or more based on 1 part by mass of α,α,α-trifluorothymidine,

wherein the proportion of the sugar having a critical relative humidity of 85% or more at 25°C is 90% by mass or more in the total excipient,

wherein the content of the disintegrating agent is from 3 to 7% by mass in the total amount of the pharmaceutical composition, and
wherein the pharmaceutical composition is in a formulation form of a granule, a compression-molded product, or a mixture."

"*2. An orally administrable pharmaceutical formulation comprising the orally administrable composition according to claim 1, wherein the composition is coated.*"

The compounds α,α,α-trifluorothymidine and 5-chloro-6-(2-iminopyrrolidine-1-yl)methyl-2,4(1H,3H)-pyrimidine dione hydrochloride are also referred to in the patent as "FTD" and "TPI", respectively. The combination of FTD and TPI at a molar ratio of 1:0.5 is known as "TAS-102" (patent, paragraphs [0002] and [0003]).

The binder hypromellose is also known as hydroxypropylmethylcellulose.

V. The Board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion on the case.

VI. During the oral proceedings before the Board, the appellant withdrew the main request and auxiliary requests 1 to 3. At the end of the oral proceedings, the Board announced its decision.

VII. The appellant's arguments relevant to the present decision can be summarised as follows.

Procedural violation and remittal

The opposition division committed a substantial procedural violation which justified remitting the case and reimbursing the appeal fee. The decision was based on an added-matter objection that had been discussed for the first time at the oral proceedings before the opposition division. The appellant was taken by surprise and could not respond properly. Furthermore, by basing their decision on added subject-matter, the opposition division conveniently precluded discussion of other grounds for opposition in relation to lower ranking auxiliary requests. Moreover, point 11.3.2 of the decision cited T 472/88 for the first time.

Admittance of auxiliary request 4

Auxiliary request 4 derived from auxiliary request 5, which was filed during the oral proceedings before the opposition division and was admitted. Claim 1 of auxiliary request 4 had been amended to correct the definition of component (d) and make clear that binder, lubricant, flavouring agents, colourants and taste-masking agents were additives other than excipients. A basis for the amendment could be found in paragraphs [0003] and [0017] of the application as filed. The amendment addressed added-matter and clarity issues raised in point 11.3.1 of the decision. It did not change the appellant's case and streamlined the proceedings.

Clarity - claim 1 of auxiliary request 4

The expression "consisting essentially of" was accepted in practice before the EPO and, in general, it was not considered unclear. The aim of the expression was to prevent infringers from circumventing a claim directed to a composition by adding compounds that have no effect. In accordance with the established case law, "consisting essentially of" in claim 1 meant that ingredients not cited in the claim could be present only if they did not materially affect the essential characteristics of the composition. As taught in the patent, the essential characteristic of the composition was the chemical stability of TAS-102. Therefore, it was clear that only ingredients that did not affect the stability of TAS-102 could be present in addition to those explicitly mentioned. Claim 1 allowed only a limited number of additional ingredients and in limited amounts.

With respect to the functional definition of the ingredients (binder, lubricant, etc.), they were well-known ingredients in pharmaceutical formulations. The artificial situations put forward by the respondent and the intention of the formulator were irrelevant. The function of a compound in a composition had to be assessed on the basis of the function that the skilled person would assign to it in the composition under consideration.

The fact that component (d) allowed the addition of excipients other than the sugars of component (b) did not render claim 1 unclear. Furthermore, contrary to the respondent's view, the amount of excipients according to component (d) was limited because the

sugar of component (b) constituted at least 90% by mass of the total excipient.

Amendments - claim 1 of auxiliary request 4

The combination of features in claim 1 was directly and unambiguously disclosed in the application as filed. The primary basis lay in the claims as filed.

Partly pregelatinised starch was selected from among the preferred disintegrating agents in claim 6. Its concentration range was limited to the most preferred option, disclosed on page 9, line 4.

The additives of component (d) could be found on page 10, lines 12 to 16. The concentration ranges of binder and lubricant were disclosed on page 11, lines 1 to 6.

The feature that the sugar in component (b) constituted 90% or more by mass of the total excipient was on page 10, line 3. This was the most preferred range allowing the presence of other excipients. It included the most preferred upper limit, 100% by mass, which was also the most preferred embodiment.

The limitation "consisting essentially of" did not involve a selection. It was directly and unambiguously derivable from the passage on page 10, lines 7 to 10.

Inventive step - claim 1 of auxiliary request 4

The composition of claim 1 was inventive over the closest prior art, represented by Formulation Example 1 in D1. The function of each ingredient in Formulation Example 1 was not clear and could vary depending on

whether D1 or common general knowledge was considered. Lactose could be an excipient, disintegrant or diluent. Cornstarch could be a disintegrant or diluent. Crystalline cellulose could be an excipient, a disintegrant, an absorbent, a suspending agent or a diluent. Talc could be a lubricant, diluent and glidant. Only the functions of hydroxypropylmethylcellulose and magnesium stearate were clear, namely binder and lubricant, repectively.

The composition of claim 1 differed from Formulation Example 1 in several features:

- the composition consisted essentially of components (a) to (d),
- the content of component (b) was 3.6 parts by mass or more based on 1 part by mass of FTD,
- the disintegrating agent was partly pregelatinised starch, present in an amount of 3 to 7% by mass of the total composition,
- the amount of binder did not exceed 5% by mass in the total composition,
- the lubricant was selected from hydrogenated oils, sucrose fatty acid esters and stearic acid.

The comparative tests in Tables 1, 2 and 6 of the patent demonstrated that TAS-102 was particularly stable in the claimed composition, even under high-humidity conditions. In addition, D2 and D7 proved that the claimed composition disintegrated faster than the formulation of the closest prior art. Therefore, the objective technical problem was that of providing an orally administrable pharmaceutical composition containing FTD and TPI which provided high stability of the active ingredients even under high-humidity conditions as well as excellent disintegrability.

The solution proposed in claim 1 was not obvious. D1 was concerned with improving the therapeutic effect of TAS-102. It was silent on the properties of Formulation Example 1 and dealt neither with the stability of TAS-102 in oral formulations nor with the disintegrability of such formulations. Therefore, the skilled person had no incentive to modify Formulation Example 1 to arrive at the composition of claim 1.

As regards D3, this disclosed pregelatinised starch as one among several disintegrants but contained no pointer to select partly pregelatinised starch, let alone for formulating TAS-102. There was also no teaching in the prior art that a concentration of partly pregelatinised starch of 3 to 7% by mass was advantageous for the stability of TAS-102, as shown in Table 6 of the patent.

VIII. The respondent's arguments relevant to the present decision can be summarised as follows.

Remittal and procedural violation

The opposition division did not commit any procedural violation. The added-matter objection on which the decision under appeal was based had been raised in the written proceedings and it was discussed at the oral proceedings before the opposition division. The case should not be remitted.

Admittance of auxiliary request 4

The new definition of component (d) in claim 1 of auxiliary request 4 changed the appellant's case. Even if the amendment addressed an added-matter objection,

it raised new issues. The amendment made the term "excipient" broader and unclear, and this had consequences for the discussion regarding inventive step.

Clarity - claim 1 of auxiliary request 4

Claim 1 was unclear for three reasons. First, it was uncertain to what extent the expression "consisting essentially of" limited the scope of the claim. According to established case law, the composition could contain non-recited compounds that did not materially affect the technical effect of the composition. The patent, however, did not indicate what compounds could be included without impairing the stability of the composition.

Secondly, the functional terms excipient, binder, lubricant, flavouring agent, colourant and taste-masking agent were ambiguous. There were compounds cited in claim 1 that could have more than one of those functions and, depending on their function, the amount allowed in the composition could be different. For instance, polyvinyl alcohol could be a binder or a lubricant. In the first case it could be present in an amount of 0.001 to 5% by mass, in the second case it could not be present because it was not listed among the lubricants in component (d). Also, a sugar acting as an excipient in component (b) could function as a flavouring agent or taste-masking agent according to component (d). Therefore, the presence and amount of a compound was subject to intellectual considerations. The intention of the formulator should not determine what was encompassed by the claim.

Thirdly, component (d) was not limited in relation to the excipients that could be present in the composition. It covered any additive that could normally be understood as an excipient.

Amendments - claim 1 of auxiliary request 4

Claim 1 resulted from an undisclosed combination of selections within the application as filed:

- partly pregelatinised starch was selected from the list of suitable disintegrants on page 8, lines 18 to 24 or in claim 6 as filed,
- the amount of binder and lubricant corresponded to the broadest ranges on page 11, lines 1 to 6,
- the amount of sugar excipient relative to the total excipient was selected from the options on page 10, lines 2 to 5,
- "consisting essentially of" was a selection among three options including "comprising" and "consisting of".

In addition, paragraph [0017] of the application as filed did not support the expression "consisting essentially of" because the paragraph referred to additives generally used, without particular limitation.

Inventive step - claim 1 of auxiliary request 4

D1 dealt with the therapeutic use of TAS-102. In the clinical trials, TAS-102 was administered as tablets. Tablets were illustrated only in Formulation Examples 1 and 2 of D1. Formulation Example 1 was the closest prior art because it contained more technical features in common with the composition of claim 1. The only

relevant distinguishing features in claim 1 were the presence of partly pregelatinised starch and the limitation of the amount of binder (hydroxypropylmethylcellulose) to a maximum of 5% by mass. The slight difference in the sugar/FTD ratio had no technical significance. The amount of disintegrant was not a difference. Formulation Example 1 contained two well-known disintegrating agents: 2.6% by mass of cornstarch and 2.6% by mass of crystalline cellulose. Their combination added up to 5.2% by mass, which fell within the range required by claim 1. If cornstarch was regarded as the only disintegrating agent, its content could be rounded to 3% by mass, which also fell within the range in claim 1.

The comparative examples on file did not demonstrate any technical effect linked to partly pregelatinised starch or to a low amount of the binder hydroxypropylmethylcellulose. On the one hand, Table 6 of the patent did not show that partly pregelatinised starch improved the stability of TAS-102, compared to cornstarch. On the other hand, the effect of partly pregelatinised starch or lower amounts of binder on tablet disintegrability, supposedly shown in D2 and D7, was irrelevant because claim 1 encompassed formulations that did not require disintegration. Disintegration applied only to tablets and capsules. Therefore, the objective technical problem was that of providing an alternative formulation of TAS-102.

Replacing cornstarch with partly pregelatinised starch was obvious in light of D3 (page 174, third paragraph, and page 175, last lines of the first paragraph), which taught that partly pregelatinised starch was the improved version of cornstarch. Reducing the amount of binder was associated with disintegration time, which

was not relevant for all compositions in claim 1. Therefore, it constituted an arbitrary modification of the closest prior art.

IX. The parties' final requests were as follows.

- The appellant requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of auxiliary request 4 filed with the statement of grounds of appeal. The appellant also requested that the appeal fee be reimbursed because the opposition division allegedly committed a substantial procedural violation.

  As an auxiliary measure, the appellant requested that the patent be maintained in amended form on the basis of auxiliary request 4.

- The respondent requested that the appeal be dismissed and the patent be revoked in its entirety. It also requested that the appellant's request that the case be remitted to the opposition division be refused and that auxiliary request 4 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Procedural violation and remittal (Article 113(1) EPC and Article 11 RPBA)

According to the appellant, the opposition division committed a procedural violation which justified remitting the case and reimbursing the appeal fee. The appellant put forward two reasons for the procedural violation:

(i) the opposition division had taken the appellant by surprise by agreeing with the respondent on an objection that had been discussed for the first time at the oral proceedings, and

(ii) the decision under appeal cited decision T 472/88, which had never been mentioned in the opposition proceedings.

1.1 With regard to reason (i), the decision under appeal concluded in point 7.3 that auxiliary request 1 added subject-matter because the nature and the amount of the disintegrating agent in claim 1 (partly pregelatinised starch and 3 to 10% by mass) involved a selection from two lists in the application as filed.

This combination of features had been introduced for the first time in auxiliary requests 3 and 4 filed on 15 April 2020. Subsequently, the opposition division issued two communications, neither of which raised

added-matter objections. The added-matter objection was raised for the first time in the respondent's letter of 24 August 2021 (point 3.21), i.e. less than one month before the oral proceedings held on 14 September 2021.

At the oral proceedings, the opposition division agreed with the respondent that the combination of features relating to the nature and amount of the disintegrating agent added subject-matter, and that this conclusion applied to all the auxiliary requests then on file. The appellant was given the opportunity to overcome the objection on two occasions and each time it filed a new auxiliary request. One of the new auxiliary requests was rejected and the other was not admitted.

1.1.1 According to the appellant, the respondent had raised multiple objections in writing and the appellant was not obliged to respond to each of them. This was particularly the case for the added-matter objection relating to the nature and amount of the disintegrating agent. The objection was late filed and contrary to the established case law, in particular to decision T 1621/16. Therefore, the appellant could not have expected the opposition division to agree with the objection at the oral proceedings and could not properly respond. Its right to be heard was violated.

1.1.2 The appellant's argument is not convincing. The respondent had raised the added-matter objection relating to the nature and amount of the disintegrating agent in its letter in preparation for the oral proceedings before the opposition division. There was no reason for the appellant to assume that the objection would not be discussed at the oral proceedings. It was evident that the patent could not be maintained without first discussing the question of

added subject-matter. Nor did the appellant request that the added-matter objection not be admitted into the proceedings. In addition, the appellant had no reason to assume that the opposition division would necessarily conclude that the objection had no merit: even if T 1621/16 constituted established case law, which in the Board's view appears debatable, it had to be assessed whether the rationale in that decision was applicable to the case at hand. Therefore, the appellant should have been prepared for the eventuality that the opposition division agreed with the respondent regarding added subject-matter. Furthermore, the opposition division interrupted the oral proceedings on two occasions after its conclusion on added subject-matter to let the appellant reflect on how to proceed further. On both occasions, the appellant took the opportunity to file additional auxiliary requests.

1.2 With regard to reason (ii), point 11.3.2 of the decision relates to auxiliary request 5 filed by the appellant during the oral proceedings before the opposition division. This claim request limited the expression "comprising" to "consisting essentially of". This limitation was first introduced in claim 1 of auxiliary requests 5 to 8 filed on 14 July 2021. In the submissions of the same date (pages 2 and 3), the appellant argued that the limitation derived implicitly from the application as filed, and relied on decision T 472/88 to support its view. The issues of added subject-matter and clarity related to this limitation were then discussed at the oral proceedings (minutes, page 3, third to sixth paragraphs). In point 11.3.2 of the decision, the opposition division merely applied the usual interpretation by the EPO of the expression "consisting essentially of", which is also the one outlined in the Guidelines F-IV, 4.20, and added a

reference to T 472/88 which had already been cited by the appellant in the written proceedings beforehand. That the opposition division did not follow the appellant's argument on this issue does not mean that the right to be heard was violated. In view of the above, citing T 472/88 and applying it to the facts of the case did not introduce any ground or evidence within the meaning of Article 113(1) EPC on which the appellant had not had an opportunity to present its comments at the oral proceedings.

1.3 Consequently, the Board holds that the opposition division did not commit any substantial procedural violation within the meaning of Article 113(1) EPC, and that remittal of the case in accordance with Article 11 RPBA, second sentence, and reimbursement of the appeal fee under Rule 103(1)(a) EPC, are not justified.

2. Admittance of auxiliary request 4 (Article 12(4) RPBA)

Auxiliary request 4 was filed by the appellant with the statement of grounds of appeal. It derives from auxiliary request 5 filed at the oral proceedings before the opposition and amends the definition of component (d) in claim 1 as follows:

"~~*further containing*~~ *additives selected from excipients other than the sugar having a critical relative humidity of 85% or more at 25°C,* ~~*which are selected from*~~
0.001 to 5% by mass in the total composition of a binder selected from hydroxypropyl cellulose, hypromellose, and polyvinyl alcohol,
0.001 to 3% by mass in the total composition of a lubricant selected from hydrogenated oils, sucrose fatty acid esters, and stearic acid,

flavoring agents,
colorants, and
taste-masking agents"

This amendment clarifies that binder, lubricant, flavouring agents, colourants and taste-masking agents according to component (d) are not excipients within the meaning of claim 1. Therefore they are not to be considered for the calculation of the total excipient, which is constituted of at least 90% by mass of the sugar in component (b). It is apparent that the amendment addresses the inconsistency between the definition of (d) in claim 1 and its basis in paragraphs [0003] and [0017] of the application as filed: the latter distinguishes between excipients other than the sugar of component (b) and the other ingredients recited in component (d), namely binders, lubricants, flavouring agents, colourants and taste-masking agents. Therefore, auxiliary request 4 removes clarity and added-matter issues raised in the decision under appeal, to the benefit of procedural economy. Contrary to the respondent's view, the Board does not consider that the amendment raises new issues in relation to inventive step.

For those reasons, the Board exercised its discretion to admit auxiliary request 4 into the appeal proceedings in accordance with Article 12(4) RPBA.

3. Interpretation of claim 1 of auxiliary request 4

At the oral proceedings before the Board, the parties construed the expression "consisting essentially of" in claim 1 in line with several decisions of the Boards of Appeal such as T472/88 (see point 3). In other words, they agreed that the orally administrable

pharmaceutical composition in claim 1 is to be understood as consisting of components (a) to (d), but allowing the presence of further non-active ingredients which do not materially affect the essential characteristics of the composition.

This interpretation raises the question of what are those essential characteristics that should not be materially affected. In this context, the appellant explained (see also patent, paragraphs [0008] to [0010] and [0013]) that FTD is a very potent active agent administered at very low doses. Therefore, it is paramount for the efficacy and safety of a treatment with FTD to administer the active compound at a very precise dose. FTD presents the problem that it hydrolyses easily, which means that humidity may produce undesirable variations in the FTD content in the dosage form to be administered. These variations may impair the efficacy and safety of the treatment. This explanation was not contested by the respondent.

Considering those circumstances, the Board agrees with the appellant that the skilled person would understand that the essential characteristic of the pharmaceutical composition in claim 1 that should not be materially affected is the chemical stability of FTD or its combination with TPI, TAS-102. This view is consistent with the general teaching of the patent, which focuses on the chemical stability of TAS-102 in formulations, especially under high-humidity conditions.

4. *Clarity (Article 84 EPC) - auxiliary request 4*

The main clarity objections raised by the respondent were directed to the expression "consisting essentially

of" and to the fact that the ingredients cited in claim 1 were associated with a function.

4.1 On the first aspect, the expression "consisting essentially of" limits the ingredients in the composition of claim 1 to those defined in components (a) to (d), although further non-active ingredients may be present provided they do not materially affect the chemical stability of TAS-102 (see point 3 above).

The respondent argued that this expression renders claim 1 unclear because the skilled person would not know which are the compounds that do not impair the stability of TAS-102 in the composition, and the patent does not contain any information in that respect.

The Board notes that, even if the composition of claim 1 may contain ingredients in addition to those of components (a) to (d), the nature and amount of those ingredients is strongly limited by the condition that they must not impair TAS-102 stability. Furthermore, the skilled person confronted with a composition containing components (a) to (d) and additional ingredients could easily determine whether or not the additional ingredients impair TAS-102 stability. Testing the chemical stability of active compounds in a composition is standard practice in the field of pharmaceutical formulations. Such tests were illustrated in Test Examples 1 to 5 of the patent for the particular case of TAS-102: the formulations were stored at 40°C and 75% relative humidity for a week or a month, and the amount of substances related to TAS-102 was determined. Therefore, the skilled person could easily determine by standard comparative tests whether or not a given composition consisted essentially of components (a) to (d).

4.2 With regard to the functional definition of the ingredients in claim 1, the Board agrees with the appellant that the criterion for assessing whether a compound has the function assigned to it is the function (or functions) that the skilled person would assign to that compound in the context of a given formulation. Contrary to the respondent's view, the formulator's intention is irrelevant in that respect.

It was undisputed that the functional features "excipient", "disintegrating agent", "binder", "lubricant", "flavouring agent", "colourant" and "taste-masking agent" are standard in the technical field of pharmaceutical formulations. The skilled person would have no difficulty in determining whether a given formulation ingredient fulfils one or more of these functions on the basis of common general knowledge. These are functional features which are generally allowed if the invention cannot be defined more precisely without unduly restricting the scope of the invention, as in the case at hand. Furthermore, in the present case, the main ingredients are not solely defined by functional features. They are further limited by structural features: the excipient according to component (b) is selected from lactose, sucrose, mannitol and erythritol; the disintegrating agent is partly pregelatinised starch; the binder is present in an amount of 0.001 to 5% by mass and is selected from hydroxypropyl cellulose, hypromellose and polyvinyl alcohol; and the lubricant is present in an amount of 0.001 to 3% by mass and is selected from hydrogenated oils, sucrose fatty acid esters and stearic acid. In view of common general knowledge and the structural limitations of the functional features, the Board

considers that the definition of the ingredients in claim 1 is not unclear.

The respondent's objection on this point was based on the possibility that an ingredient fulfils more than one function and, depending on its function, the amount of the compound in the composition could vary. For instance, polyvinyl alcohol is generally known to be a binder and a lubricant. If it was considered a binder, it could be present in an amount of 0.001 to 5% by mass while it could not be present if it was considered a lubricant. Similarly, a sugar according to component (b) could also be a taste-masking agent.

This argument is not convincing. The fact that polyvinyl alcohol is known to be a binder and a lubricant does not render the claim unclear. If polyvinyl alcohol is present in the composition, it necessarily plays the role of a binder, even if it also fulfils the function of a lubricant. Therefore, it should be counted as a binder that may be present in an amount of 0.001 to 5% by mass in the composition. Considering arbitrarily that polyvinyl alcohol could function exclusively as a lubricant and that therefore its presence would render the composition different from the one in claim 1 would be unrealistic. Certainly this is not how the skilled person would read the claim. Similarly, lactose will always be considered an excipient according to component (b), even if it could also be regarded as a taste-masking agent. Therefore, lactose is to be counted as a sugar constituting at least 90% by mass of the total excipient.

4.3 At the oral proceedings before the Board, the respondent also argued that claim 1 was unclear because component (d) was not limited in relation to the

excipients that could be present in the composition. It covered any additive that could be normally understood as an excipient.

This argument fails. The fact that "excipient" is a very broad term does not mean that it is unclear. "Excipient" is a standard term in pharmaceutical formulations (see also point 4.2 above).

4.4 The respondent also stated in its reply to the statement of grounds of appeal (point 4.6) that "*the term 'hydrogenated oils' as used in claim 1 is inherently unclear*". The reasons as to why this would be the case were not explained. Therefore, the statement is merely an unsubstantiated objection and has no merit.

4.5 In view of the above, claim 1 of auxiliary request 4 meets the requirements of Article 84 EPC.

5. Amendments (Article 123(2) EPC) - auxiliary request 4

5.1 Claim 1 in the application as filed is primarily based on claims 1 to 8.

Claims 1 to 5 directly and unambiguously disclose an orally administrable pharmaceutical composition comprising FTD and TPI at a molar ratio of 1:0.5 and a sugar having a critical relative humidity of 85% or more at 25°C as an excipient. The sugar is selected from lactose, sucrose, mannitol and erythritol, and it is present in 3.6 parts by mass or more based on 1 part by mass of FTP.

Claim 6, which is directed to a composition according to any of claims 1 to 5, discloses partly gelatinised

starch as one of five disintegrating agents. Claim 7, which refers back to claim 6, discloses that the amount of disintegrating agent in the pharmaceutical composition is 2 to 16% by mass.

Claim 8 specifies that the composition according to any of claims 1 to 7 is in a formulation form of a granule, a compression-moulded product or a mixture.

5.2 The features in claim 1 that are not disclosed in the claims as filed are the following:

- the amount of disintegrating agent is 3 to 7% by mass of the total composition,
- component (d),
- the amount of sugar having a critical relative humidity of 85% or more at 25°C is 90% by mass or more in the total excipient, and
- the composition consists essentially of components (a) to (d).

The basis for these features needs to be found in the description of the application as filed.

5.2.1 The amount of disintegrating agent is disclosed on page 9, lines 2 to 5. The most preferred range is 3 to 7% by mass of the total composition. Therefore, this limitation does not constitute a selection.

5.2.2 The additives in component (d) can be found on page 10, lines 12 to 21. The passage on page 10, lines 12 to 16 recites the ingredients in component (d) as examples of additives that can be contained in the composition. It mentions explicitly: excipients other than the sugar having a critical relative humidity of 85% or more at 25°C, binders, lubricants, flavouring agents,

colourants and taste-masking agents. Subsequently, the passage on page 10, lines 18 to 21 discloses hydroxypropyl cellulose, hypromellose and polyvinyl alcohol as examples of binders, and hydrogenated oils, sucrose fatty acid esters and stearic acid as examples of lubricants.

Subsequently, page 11, lines 1 to 6 discloses the concentration ranges for binder and lubricant. The broadest ranges, generally applicable, are those now in claim 1: the amount of binder is 0.001 to 5% by mass and the amount of lubricant 0.001 to 3% by mass.

5.2.3 The proportion of the sugar component (b) in the total excipient is disclosed on page 10, lines 2 to 4 as being: "*preferably 50% by mass or more, more preferably 70% by mass or more, more preferably 90% by mass or more, and particularly preferably 100% by mass*". Thus, 90% by mass or more is the most preferred range, and the most preferred option allowing the presence of excipients other than the sugar component (b). The range includes 100% by mass, which is the most preferred value and the upper limit of all the ranges disclosed. Therefore, "90% by mass or more", rather than a selection, constitutes the most preferred range consistent with the definition of component (d), which generally allows the presence of excipients other than component (b).

5.2.4 Contrary to the respondent's view, the limitation "consisting essentially of" does not constitute a selection from a list, either. As noted above (point 3), the expression limits the composition to components (a) to (d) but allows the presence of additional non-active ingredients which do not materially affect the technical effect of the

invention. Even if the expression "consisting essentially of" was not explicitly disclosed in the application as filed, a basis for it can be found on page 10, lines 7 to 16. This passage firstly states that the composition of the invention may further contain various generally used additives provided that the effects of the invention are not prevented. It then notes that such ingredients are not particularly limited to the ingredients recited in component (d), i.e. excipients other than the sugar having a critical relative humidity of 85% or more at 25°C, binders, lubricants, flavouring agents, colourants and taste-masking agents.

5.2.5 Therefore, the Board does not agree with the respondent that claim 1 results from multiple undisclosed selections. The only selection among equivalent options is that of the nature of the disintegrating agent. The other features are either defined in their broadest way and are applicable to all the embodiments of the invention, or are limited to the most preferred embodiments. Consequently, the Board holds that the combination of features in claim 1 is directly and unambiguously derivable from the application as filed.

5.3 It was not disputed that claim 2 is supported by claim 9 as filed.

5.4 Therefore, auxiliary request 4 meets the requirements of Article 123(2) EPC.

6. Inventive step (Article 56 EPC) - auxiliary request 4

6.1 As outlined above (point 3), FTD is a very potent active agent administered at very low doses. For this reason, it is essential that it be dosed with high

precision. The problem that arises with FTD-containing formulations is that FTD hydrolyses easily. Therefore, humidity may produce undesirable variations in the amount of FTD in a formulation, with a corresponding impact on the efficacy and safety of the therapeutic treatment. The patent is intended to solve this problem by providing an orally administrable formulation of TAS-102 which does not experience significant variations in its amount of active ingredients, even when stored under high-humidity conditions (patent, paragraphs [0008] and [0009]).

6.2 The closest prior art

It was common ground between the parties that D1, in particular Formulation Example 1, was the closest prior art.

D1 (abstract and paragraphs [0007] to [0010]) is a patent application intended to provide a suitable dosage regime of TAS-102 for treating cancer by oral administration. D1 proposes administering TAS-102 two to four times daily at a dose of 20 to 80 mg/m^2/day. On page 6, D1 discloses Formulation Example 1, which is a tablet suitable for the proposed administration of TAS-102. The tablet contains the following ingredients (percentages by mass have been added by the Board to facilitate subsequent discussion):

Ingredient	Amount (mg)	Mass%
FTD	20.00	15.0
TPI	9.42	7.1
Lactose	70.00	52.5
Crystalline cellulose	3.50	2.6
Magnesium stearate	1.00	0.75
Talc	1.00	0.75

Cornstarch	3.50	2.6
Hydroxypropylmethylcellulose	25.00	18.7
Total weight (per tablet)	133.42	100.0

D1 is silent on the stability problems of TAS-102 formulations during storage due to the sensitivity of FDT to hydrolysis. D1 does not disclose any information on Formulation Example 1 beyond its preparation using the indicated ingredients and corresponding amounts.

With regard to the function of each ingredient in Formulation Example 1, the parties did not call into question that formulation ingredients may have multiple functions. This is apparent from paragraph [0015] of D1, which assigns more than one function to ingredients generally used in formulations. For instance, lactose can be an excipient, a disintegrating agent or an absorbent, and starch can be an excipient, a binder, a disintegrating agent, a humectant or an absorbent. This was also common general knowledge. For instance, D8 (page 129, point 6) teaches that microcrystalline cellulose is generally known as an absorbent, suspending agent, tablet and capsule diluent, and tablet disintegrant.

It was undisputed that magnesium stearate is a lubricant and hydroxypropylmethylcellulose a binder.

6.3 The distinguishing features

6.3.1 The active compounds FTD and TPI in Formulation Example 1 are present at a molar ratio of 1:0.5, as required by claim 1. Therefore, component (a) does not constitute a difference.

6.3.2 With regard to component (b), the composition of claim 1 differs from Formulation Example 1 in that the lactose content is 3.6 parts by mass or more based on 1 part by mass of FTD. In Formulation Example 1, this ratio is slightly lower, namely 3.5.

6.3.3 As regards component (c), claim 1 differs in that the disintegrant is partly gelatinised starch. As noted by the respondent, the disintegrating agent in Formulation Example 1 is either the combination of cornstarch with crystalline cellulose, or cornstarch alone. This is confirmed by the common general knowledge in D3 (Table 7 and page 175, last lines of first paragraph and first lines of second paragraph), which discloses Starch 1500 and Avicel as customary disintegrants. Starch 1500 is pregelatinised starch (D3, page 110, third paragraph) and Avicel is microcrystalline cellulose (D3, page 175, second paragraph). In this connection, the parties made no distinction between pregelatinised starch and partly pregelatinised starch or between microcrystalline cellulose and crystalline cellulose.

The parties disputed whether the disintegrating agent in Formulation Example 1 was present at the concentration required in claim 1, i.e. of 3 to 7% by mass. The respondent considered that, if the disintegrating agent was the combination of cornstarch with crystalline cellulose, their combination in Formulation Example 1 amounted to 5.2% by mass, which fell within the range required by claim 1. Otherwise, if the disintegrating agent was cornstarch alone, it was present in an amount of 3% by mass because that was the result of applying common rounding rules to 2.6% by mass.

The Board agrees with the respondent that the skilled person would consider that the disintegrating agent is the combination of cornstarch and crystalline cellulose. This view is consistent with the common general knowledge disclosed in D3 (page 175, second paragraph) that: "*Avicel (microcrystalline cellulose) is a highly effective disintegrant. It has a fast wicking rate for water, hence, it and starch make an excellent combination for effective and rapid disintegration in tablet formulations*". Therefore, the amount of disintegrating agent does not constitute a difference over the closest prior art. Nevertheless, the Board will also consider the option that cornstarch is the only disintegrating agent.

6.3.4 With regard to component (d), it was undisputed that hydroxypropylmethylcellulose was a binder in Formulation Example 1, and that it was present at a concentration of 18.7% by mass. In contrast, claim 1 requires that the amount of binder does not exceed 5% by mass.

In addition, it was undisputed that magnesium stearate, and maybe also talc, had the function of lubricants in Formulation Example 1. In contrast, the lubricant according to claim 1 is to be selected from hydrogenated oils, sucrose fatty acid esters and stearic acid.

6.3.5 In summary, the Board identifies the following distinguishing features in claim 1:

- the lactose content is 3.6 parts by mass or more based on 1 part by mass of FTD,
- the disintegrant is partly pregelatinised cornstarch,

- the amount of binder does not exceed 5% by mass in the total composition, and
- the lubricant is selected from hydrogenated oils, sucrose fatty acid esters and stearic acid.

6.4 The technical effect

6.4.1 The parties discussed two technical effects associated with the distinguishing features. First, the chemical stability of TAS-102 in the formulation, especially under high humidity conditions. This effect is essential to prevent undesirable variations in the amount of TAS-102 during storage. Second, the disintegration time of the formulation. A short disintegration time reflects the ability of the formulation to quickly disintegrate in the patient's oral cavity, even without adding water, thus facilitating ingestion.

With respect to the second technical effect, the Board agrees with the respondent that claim 1 is not limited to formulations that require disintegration, such as tablets and capsules. Claim 1 (last two lines) is directed to a granule, a compression-moulded product or a mixture. It is well known that granules in the field of pharmaceutical formulations generally disintegrate immediately, thanks to their size and composition, and do not even require disintegrating agents. Therefore, disintegration time is an irrelevant parameter for part of the formulations encompassed by claim 1, which means that the parameter cannot be considered for the assessment of inventive step.

Consequently, the evidence on file relating to disintegration times has not been taken into consideration by the Board. The assessment of inventive

step below is based on the stability of TAS-102 as the only technical effect. The evidence relating to this effect can be found in the comparative tests disclosed in Tables 1, 2 and 6 of the patent and in the table in D7. In those comparative tests, stability was assessed by determining the amount of substances related to TAS-102 that could be found in the formulation after a certain period of storage at 40°C and 75% relative humidity. The lower the amount of related substances, the higher the stability of TAS-102.

6.4.2 The data in Table 6 of the patent.

Table 6 is reproduced below. It shows the stability results for several TAS-102 formulations after a storage time of two weeks.

[Table 6]

	Unit: parts by mass						
	Example						
	15	16			17		
FTD	1	1	1	1	1	1	1
TPI	0.471	0.471	0.471	0.471	0.471	0.471	0.471
Lactose hydrate	4.529	4.229	4.229	4.229	3.929	3.929	3.929
Corn starch	-	0.3	-	-	0.6	-	-
Partly pregelatinized starch	-	-	0.3	-	-	0.6	-
Low-substituted hydroxypropyl cellulose	-	-	-	0.3	-	-	0.6
Stearic acid	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Total	6.06	6.06	6.06	6.06	6.06	6.06	6.06
Total mass of the related substances (%)	0.188	0.2	0.266	0.332	0.282	0.334	0.391

The table discloses compositions comprising components (a), (b) and (d) as defined in claim 1. The compositions of Examples 16 and 17 further contain a disintegrating agent (component (c) of claim 1), namely cornstarch, partly pregelatinised starch or low-substituted hydroxypropyl cellulose. In Example 16, the disintegrating agent is present in an amount of 0.3 parts by mass, which corresponds to 5% by mass. In

Example 17, the disintegrating agent is present in an amount of 0.6 parts by mass, which corresponds to 10% by mass.

The parties did not dispute that the observed total mass of related substances was low in all cases. This means that the tested formulations can be considered storage stable. The issue under dispute was whether the presence of 3 to 7% by mass partly pregelatinised starch in the composition of claim 1 provides improved stability compared to the disintegrating agent in Formulation Example 1, i.e. a mixture of 2.6% by mass cornstarch and 2.6% by mass crystalline cellulose, or 2.6% by mass corstarch alone. In this respect, the Board notes that the compositions in Table 6 which contain cornstarch are slightly more stable than those containing the same amount of partly pregelatinised starch: when cornstarch is present in an amount of 0.3 parts by mass (i.e. 5% by mass), the total mass of TAS-102-related substances is 0.2%. This value goes up to 0.266% when the composition contains partly pregelatinised starch instead of cornstarch. Similar results are observed when cornstarch and partly pregelatinised starch are present in an amount of 0.6 parts by mass (i.e. 10% by mass), namely 0.282% and 0.334%, respectively. The Board also notes that the composition of Example 15, which does not contain a disintegrating agent, exhibits the highest stability with a total mass of related substances of only 0.188%.

These results firstly show that the addition of a disintegrating agent to the formulation produces a slight destabilisation of TAS-102. Nevertheless, the formulations containing 5% or 10% by mass of disintegrating agents still exhibit acceptable stability levels for storage. The degree of

destabilisation is slightly lower in formulations containing cornstarch than in formulations containing partly pregelatinised starch.

6.4.3 The data in Tables 1 and 2 of the patent.

Tables 1 and 2, reproduced below, disclose the results of stability tests obtained after a storage time of one month.

[Table 1]

	Unit: parts by mass			
	Example		Comparative Example	Reference Example
	1	2	1	1
FTD	10	10	10	10
TPI	4.71	4.71	4.71	4.71
Lactose hydrate	73.55	-	-	-
Sucrose	-	73.55	-	-
Crystalline cellulose	-	-	73.55	-
Critical relative humidity (%, at 25°C)	95 or more	85 or more	Not applicable	-
Total mass of the related substances (%)	0.19	0.36	1.64	0.15

[Table 2]

	Unit: parts by mass			
	Example		Comparative Example	
	3	4	2	3
FTD	10	10	10	10
TPI	4.71	4.71	4.71	4.71
Lactose hydrate	58.84	-	-	-
D-mannitol	-	58.84	-	-
D-sorbitol	-	-	58.84	-
Xylitol	-	-	-	58.84
Critical relative humidity (%, at 25°C)	95 or more	95 or more	50-60	75-85
Total mass of the related substances (%)	0.08	0.00	0.81	0.63

These tables show that lactose, sucrose and D-mannitol are suitable excipients for the formulation of TAS-102. The test designated "Comparative Example" in Table 1 also shows that a high amount of crystalline cellulose (73.55 parts by mass, which correspond to 82% by mass) has a destabilising effect on TAS-102 and produces a

total mass of related substances of 1.64%. This result, however, does not provide any valid information as to the effect of crystalline cellulose when present at a concentration of 2.6% by mass, as in Formulation Example 1.

6.4.4 The data in the table in D7

The table in D7, reproduced below, shows results obtained after a storage time of two weeks. These conditions are the same as in Table 6 of the patent.

Test Sample at 40°C/75%RH after 2 weeks (mg)	Base Formulation (D1)	Additional Comparative Example 1	Additional Example
FTD	20,00	20,00	20,00
TPI	9,42	9,42	9,42
Lactose	70,00 (3.5parts / 1 part of FTD)	70,00 (3.5parts / 1 part of FTD)	70,00 (3.5parts / 1 part of FTD)
Crystalline Cellulose	3,50	3,50	3,50
Magnesium Stearate	1,00	1,00	1,00
Talc	1,00	1,00	1,00
Cornstarch	3,50	3,50	
Partly Pregelatinized Cornstarch			3,50
Hydroxypropylmethyle cellulose	25,00		
Total weight	133,42	108,42	108,42
Total mass of related substances (%)	0,59	0,71	0,63
Initial Disintegration time (min)	19:13～20:57	06:32～08:16	02:18～03:06

The composition "Base Formulation (D1)" corresponds to Formulation Example 1 in D1. Comparing the total mass of related substances produced in "Base Formulation (D1)" with that of "Additional Comparative Example 1", it appears that hydroxypropylmethylcellulose has no negative impact on the stability of TAS-102, indeed rather the opposite. When the binder is eliminated from

the composition, the total mass of related substances increases from 0.59% to 0.71%.

A comparison of "Additional Comparative Example 1" with "Additional Example" also reveals that, contrary to the results in Table 6 of the patent, replacing cornstarch by partly pregelatinised starch may have a slight positive effect on TAS-102 stability: the total mass of related substances drops from 0.71% to 0.63%.

6.4.5 Conclusions on the technical effect

The data in Tables 1, 2 and 6 of the patent and the table in D7 do not allow the conclusion to be drawn that the presence of 3 to 5% by mass of partly pregelatinised starch results in an advantageous effect over the disintegrating agent in Formulation Example 1 of D1, irrespective of whether this is a mixture of cornstarch and crystalline cellulose or cornstarch alone. In the Board's view, it is highly likely that the effect on TAS-102 stability of the disintegrating agent in the composition of claim 1 and in Formulation Example 1 is comparable. Accordingly, the presence of 3 to 5% by mass partly pregelatinised starch in the composition of claim 1 does not significantly destabilise TAS-102.

It can also be derived from the table in D7 that the difference in the amount of binder in the formulations does not significantly affect the stability of TAS-102.

Furthermore, the Board notes that the composition according to claim 1 in Example 16 of Table 6 and the comparative composition in the same example containing cornstarch produce a total mass of related substances of below 0.3%. This comparative composition is closer

to the composition of claim 1 than Formulation Example 1 in D1. However, the table in D7 shows that Formulation Example 1 produces a considerably higher total mass of related substances, namely 0.59%.

Therefore, taking all the relevant data into consideration, the Board is of the view that a composition consisting essentially of components (a) to (d) as defined in claim 1 provides at least the same TAS-102 stability as Formulation Example 1.

6.5 In view of the demonstrated technical effect, the objective technical problem can be defined as that of finding a formulation containing TAS-102 which provides high stability of the active ingredients even under high-humidity conditions.

The Board is satisfied that this problem is solved by the composition of claim 1. Tables 1 and 2 of the patent show that the sugar excipients in component (b) of claim 1 at sugar/FTD mass ratios higher than 3.6 provide formulations in which TAS-102 is stable. Table 6 of the patent and the table in D7 show that the presence of 3% to 7% by mass partly pregelatinised starch in those formulations does not cause significant TAS-102 instability. Similarly, the table in D7 shows that the binder hypromellose does not contribute to TAS-102 instability, and Table 6 of the patent shows that 1% by mass of the lubricant stearic acid is not detrimental either. Contrary to the respondent, the Board sees no reason to realistically conclude that the presence of small amounts of unspecified excipients in component (d) can cancel out the effect shown on the stability of TAS-102. Furthermore, as the composition of claim 1 is essentially limited to components (a) to (d), and additional components must not affect TAS-102

stability, the Board considers that the evidence on file sufficiently proves that the claimed subject-matter is a suitable solution to the problem posed.

6.6 With respect to the obviousness of the solution proposed in claim 1, D1 does not mention the stability problems arising with TAS-102 formulations due to the sensitivity of TAS-102 to hydrolysis. Accordingly, D1 does not contain any information as to the stability of TAS-102 in Formulation Example 1. It appears from the tests carried out by the appellant in D7 that Formulation Example 1 exhibits acceptable levels of stability, but this information is missing from D1. Even if the skilled person measured the stability of TAS-102 in Formulation Example 1 and became aware that it was sufficiently storage stable, the Board fails to see how the skilled person would arrive at a composition as defined in claim 1 when seeking a further formulation providing TAS-102 stability. The skilled person could not expect that, after drastically reducing the amount of binder from 18.7% to no more than 5% by mass and exchanging cornstarch or cornstarch and crystalline cellulose with partly pregelatinised starch, TAS-102 would remain stable. Therefore, the subject-matter of claim 1 is not obvious from D1 alone.

The respondent combined D1 with the common general knowledge in D3 (page 174, third paragraph and Table 7; page 175, last lines of first paragraph) that partly pregelatinised starch is an alternative disintegrating agent to cornstarch. However, D3 does not contain any information relating to the equivalence of these disintegrating agents with respect to their impact on the stability of water-sensitive active ingredients. This would equally apply to the combination of

cornstarch and crystalline cellulose as the disintegrating agent.

There is also no pointer in any of the cited prior-art documents suggesting that the amount of binder in a formulation can be drastically reduced without significantly affecting the stability of water-sensitive active ingredients.

Therefore, the Board agrees with the appellant that the skilled person had no motivation to modify Formulation Example 1 in D1 so as to arrive at the composition of claim 1.

6.7 Therefore, auxiliary request 4 meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of the main request, filed as auxiliary request 4 with the statement setting out the grounds of appeal, and, if necessary, a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated