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Datasheet for the decision of 14 March 2023

Case Number: T 1700/19 - 3.3.07

Application Number: 12753867.6

Publication Number: 2744810

IPC: C07D473/34, A61K31/52, A61P31/18, A61P31/20

Language of the proceedings: EN

Title of invention:
TENOFOVIR ALAFENAMIDE HEMIFUMARATE

Patent Proprietor:
Gilead Sciences, Inc.

Opponents:
Teva Pharmaceutical Industries Ltd
Sandoz GmbH
FRKelly

Headword:
Tenofovir alafenamide hemifumarate / GILEAD

Relevant legal provisions:
EPC Art. 54(3), 54(2), 56, 83
EPC R. 103(1)(a), 111(2)

Keyword:

Novelty - main request (yes)
Sufficiency of disclosure - main request (yes)
Inventive step - main request (yes)
Substantial procedural violation - (no)

Decisions cited:

G 0001/15

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Case Number: T 1700/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 March 2023

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Appellant: (Opponent 2)	Sandoz GmbH Biochemiestrasse 10 6250 Kundl (AT)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Appellant: (Opponent 3)	FRKelly 27 Clyde Road Ballsbridge D04 F838 Dublin (IE)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Respondent: (Patent Proprietor)	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 April 2019 concerning maintenance of the European Patent No. 2744810 in amended form.**

Composition of the Board:

Chairman M. Steendijk
Members: E. Duval
A. Jimenez

Summary of Facts and Submissions

I. The appeals were filed by all three opponents (appellants 1, 2 and 3) against the interlocutory decision of the opposition division finding that, on the basis of the main request filed on 19 February 2018, the European patent 2 744 810 (the patent) met the requirements of the EPC.

II. Claim 1 of this main request pertained to:

"Tenofovir alafenamide hemifumarate".

III. In the following, the abbreviations below are used:
- TAF denotes tenofovir alafenamide, i.e. GS-7340 or 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl] amino]phenoxyphosphinyl]methoxy]propyl]adenine;
- HF stands for hemifumarate;
- MF stands for monofumarate;
- GS-7339 is a diastereoisomer of TAF, namely 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl] amino]phenoxyphosphinyl]methoxy]propyl]adenine.

IV. The following documents are cited in the present decision:

D1: WO 2002/008241
D2: Rompp Lexikon, Chemie 10. Auflage, 1997, Georg Thieme Verlag, page 1896, "Impfen"
D3: WO 2008/143500
D11: US 61/524,224
D12: WO 2013/116720
D13: US 61/594,894
D15: Yadav et al., Indian Journal of Pharmaceutical Science, 2009, pages 359-370

D27: Childs et al, "The salt-cocrystal continuum", Molecular Pharmaceutics, 2007, 4(3), pages 323-338
D28: Aakeroy et al., "Cocrystal or salt: does it really matter?', Molecular Pharmaceutics, 2007, 4(3), pages 317-322
D32: Crystallisation 4th edition, 2001, chapter 5
D44: Bing Shi Lab Notebook 4433-178, 4 April 2011
D45: WO2017/134089
D46: WO2015/040640
D47: WO2015/107451
D48: Bing Shi Lab Notebook 4433-112, 16 December 2010
D49: Peter Fung lab Notebook 4805-44, 20 April 2011
D50: English translation of D51
D51: CN105237571
D53: Bing Shi Lab Notebook 4433-55, 13 July 2010 and XRPD results
D54: Stahl, Wermuth, "Handbook of pharmaceutical Salts: Properties, Selection and Use", 2002, chapter 11, pages 249-263
D55: Experimental Report of Hannes Lengauer
D56: Experimental Report of Arthur Pichler
D66: Declaration of Hannes Lengauer
D67: Declaration of Dr. Arthur Pichler

V. The opposition division decided that:

(a) Example 4 of D1 did not directly and unambiguously disclose TAF-HF. D12 was not prejudicial to novelty either, because its priority D13 did not contain an enabling disclosure of TAF-HF. Hence the claimed subject-matter was novel.

(b) Regarding inventive step, the closest prior art D1 related to TAF-MF. The problem to be solved was the provision of a further salt of TAF. Considering that TAF-HF had improved properties (lower

diastereomeric impurity, better chemical stability, increased thermal stability) compared with TAF-MF and was prepared in a non obvious way, the patent fulfilled the requirements of Article 56 EPC.

(c) Lastly, regarding sufficiency of disclosure, the patent disclosed the formation of a solid containing TAF-HF along with impurities, as well as methods enabling its purification. The requirements of sufficiency of disclosure were thus met.

VI. In the reply to the appeals dated 7 January 2020, the patent proprietor (respondent) defended its case on the basis of the same main request as upheld by the opposition division (see II. above), and on the basis of auxiliary requests 1-8 filed on 18 December 2018.

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VIII. Oral proceedings were held before the Board in the presence of appellant 1 and the respondent.

IX. The requests of the parties were the following:

(a) Appellants 1, 2 and 3 each request that the decision under appeal be set aside and that the patent be revoked in its entirety.

Appellant 2 further requests that the appeal fee be reimbursed under Rule 103(1)(a) EPC.

(b) The respondent requests that the appeals be dismissed and the patent be maintained in the form upheld by the opposition division, or, alternatively, that the patent be maintained on the

basis of one of auxiliary requests 1-8 filed on 18 December 2018.

X. The arguments of the appellants may be summarised as follows:

(a) The appealed decision was insufficiently reasoned as regards novelty over D12/D13 (Rule 111(2) EPC). Appellant 2's appeal fee was to be reimbursed under Rule 103(1)(a) EPC on account of this substantial procedural violation.

(b) The preparation of TAF-MF described in example 4 of D1 necessarily involved the formation of some TAF-HF. Accordingly, the subject-matter of claim 1 of the main request lacked novelty over D1.

(c) Claim 1 of the main request related to TAF-HF irrespective of whether it was a salt or a co-crystal, and was thus not entitled to priority from D11, which exclusively referred to co-crystals of TAF-HF. In contrast, D12, and its priority D13, disclosed TAF-HF by name. This disclosure was enabling in view of the skilled person's common general knowledge. Consequently, D12/D13 anticipated the subject-matter of the main request.

(d) Regarding inventive step for the main request, D1 disclosed TAF-MF. No improvement in view of purging of diastereomeric impurity or chemical stability had been demonstrated for the claimed TAF-HF in comparison with TAF-MF. The problem was the provision of a further fumarate of TAF. The claimed solution was obvious considering the similar development of tenofovir disoproxil as a hemifumarate, see D3 or D15.

Alternatively, starting from D3, the problem to be solved was the provision of another hemifumarate salt of tenofovir. The claimed solution was obvious in light of D1.

(e) The patent did not give all the necessary information to the skilled person as to how to separate TAF-HF from the solids obtained in example 1. The subject-matter of the main request was therefore insufficiently disclosed

XI. The respondent's arguments may be summarised as follows:

(a) Example 4 of D1 did not inevitably result in the formation of TAF-HF and did not anticipate the claimed subject-matter.

(b) The claimed subject-matter was also novel over D12. None of the priority documents (D11 for the patent, D13 for document D12) enabled the synthesis of TAF-HF, such that D12 was not prior art. However, if D13 was considered to enable TAF-HF, then D11 must also be considered enabling to at least the same extent. In this situation, D12 was not prior art either.

(c) Starting from the TAF-MF known from D1, the objective technical problem was to provide an improved form of TAF, in particular having improved chemical, thermal and thermodynamic stability, and an improved ability to purge TAF of its diastereomeric impurity GS-7339. The claimed solution, i.e. TAF-HF, was not obvious in light of

the prior art. The same conclusion applied when starting from D3.

(d) A degree of purity was not stipulated in claim 1 and was not required for compliance with Article 83 EPC. The skilled person could prepare solids containing TAF-HF (example 1 of the patent), could separate TAF-HF from this product without undue burden, and could also produce TAF-HF following examples 2 and 3. Hence the criteria of sufficiency of disclosure were met.

Reasons for the Decision

1. Procedural violation

1.1 During the proceedings before the opposition division, the parties debated the issue of novelty over D12, which claims priority from D13, and the question of whether TAF-HF is sufficiently disclosed in D12/D13, taking common general knowledge into account.

According to appellant 2, the appealed decision fails to contain a reasoning on crucial points of dispute regarding novelty over D12/D13, specifically on the common general knowledge reflected in D54 and its application in D55 and D56, and on appellant 2's evidence D66 and D67 and arguments regarding the issue of unintentional seeding. The decision would thus be insufficiently reasoned in the sense of Rule 111(2) EPC, and the reimbursement of the appeal fee would be equitable within the meaning of Rule 103(1)(a) EPC.

1.2 The Board does not agree with appellant 2 that the appealed decision is insufficiently reasoned in the sense of Rule 111(2) EPC.

In paragraph 7.3 of the appealed decision, after summarising the arguments of the parties, including those of appellant 2 based on the textbook D54 and the experimental evidence D55 and D56, the opposition division firstly addresses the content of D12 and D13, and concludes that D13 does not contain an enabling disclosure of TAF-HF. The opposition division then indicates (see page 10) that the "experimental data filed by opponent 2" (which implicitly refers to D55 and D56) "cannot be considered to form part of the common general knowledge. Having to resort to an experiment from a text book" (which is understood to refer to D54) "and to follow the experimental data of an active pharmaceutical ingredient (API) completely different from the one as presently claimed cannot lead the person skilled in the art to expect that tenofovir alafenamide hemifumarate would be obtained". Having found that the experiments D55 and D56 could not reflect common general knowledge, it was not essential for the decision to take position on the respondent's additional argument against D55-D56 regarding unintentional seeding, and thus on the appellant's counter-arguments based on D66 and D67.

The Board concludes that the opposition division did not merely repeat appellant 2's submissions in this regard, but duly considered them and gave a reasoning on this point of dispute. A deficiency in the above reasoning would at most constitute an error of judgement on substantive issues, but not a substantial procedural violation.

1.2.1 A further condition for the appeal fee to be reimbursed under Rule 103(1)(a) EPC is that the Board deems the appeal to be allowable. This condition is not met

either in the present case, because the Board can uphold the appealed decision, as explained below (see 2.).

1.3 Accordingly, a reimbursement of appellant 2's appeal fee is not justified under Rule 103(1)(a) EPC.

2. Main request

2.1 Novelty over D1

Example 4 of D1 describes the preparation of the fumarate salt of GS-7340, i.e. TAF-MF, by dissolving TAF and fumaric acid in refluxing acetonitrile (ACN) followed by cooling to 5°C. D1 does not explicitly mention any hemifumarate.

According to appellants 1 and 3, the hemifumarate is implicitly disclosed in D1, because example 4 inevitably results in the production of TAF-MF containing detectable quantities of TAF-HF, in light of paragraph [0066] of the patent.

The Board does not share this view. Paragraph [0066] of the patent indicates that, when "suspended in these solvents, the monofumarate form of tenofovir alafenamide [...] partially converts to the hemifumarate form in ACN, ethyl acetate, MTBE, and acetone, as well as at ambient temperatures". Apart from this statement, which does not specifically relate to the conditions used in example 4 of D1, the appellants did not provide evidence showing that TAF-HF is inevitably obtained in D1. In contrast, the evidence cited by the respondent (see the respondent's reply dated 7 January 2020, paragraphs 6.3-6.8, especially D53, and D44-D47) indicates that suspending TAF-MF in

ACN, even for extended periods of time, does not necessarily lead to the formation of TAF-HF.

Accordingly, D1 does not anticipate the subject-matter of the main request.

2.2 Novelty over D12

2.2.1 The patent has a date of filing of 15 August 2012, and claims priority from D11, filed on 16 August 2011.

The appellants raised an objection of lack of novelty over D12, filed and published in 2013, but claiming an earliest priority date of 3 February 2012 (from D13).

D12 would be part of the prior art under Article 54(3) EPC, and prejudicial to novelty, only if a subject-matter is:
- disclosed in D12, and entitled to priority from e.g. D13, and
- covered by the claims of the main request, but not entitled to priority from D11.

Following decision G 1/15, for any such subject-matter of claim 1 or D12 to be entitled to priority from D11 or D13, it is necessary and sufficient that it is disclosed for the first time, directly, or at least implicitly, unambiguously and in an enabling manner in the priority document.

2.2.2 Claim 1 of the main request relates to TAF-HF, without any explicit further limitation as to its form. All parties agree that claim 1 covers TAF-HF both as a salt, i.e. with proton transfer between TAF and fumaric acid, and in co-crystal form, which involves no proton transfer (see appellant 1's grounds of appeal,

paragraphs 5.7-5.9; appellant 2's grounds of appeal, paragraph 2.4; appellant 3's grounds of appeal, page 6; respondent's reply, paragraph 5.16). Considering that a continuum exists between co-crystals and salts depending on the extent of proton transfer in the solid state (see D27, abstract), the Board accepts this non-limiting interpretation of the wording "hemifumarate" in claim 1.

Document D11, from which the patent claims priority, does not contain the expression "hemifumarate". However, D11 mentions a composition comprising a pharmaceutically acceptable coformer and TAF in a ratio of about 0.5 (see page 2; lines 4-7; claims 1-3 of D11). The pharmaceutically acceptable coformer may in particular be fumaric acid (see page 4, lines 10-11, and claim 8 of D11). Thus these passages of D11 disclose the combination of TAF with fumaric acid at a ratio of about 0.5, in other words TAF-HF, without any limitation as to its form. The invention defined in claim 1 of the main request is not broader than the disclosure of D11 in this respect, but corresponds to it exactly. The Board cannot share the opinion of appellant 1 than the word "coformer" in D11 should be understood as referring exclusively to the formation of co-crystals. Document D15 (see page 360, penultimate paragraph on the left) does not define coformers in such terms. On the contrary, D11 explicitly indicates that the coformer may be any pharmaceutically acceptable compound that is capable of forming a complex, "e.g. a co-crystal complex or a salt", with TAF (see page 4 lines 3-6). The presence of further passages in D11 specifically disclosing TAF-HF in co-crystal form (see e.g. page 1, lines 23-28) does not change the fact that D11 contains a general disclosure of TAF-HF without limitation as to its form.

2.2.3 D12 discloses TAF-HF (see paragraphs [0057] and [0059]) and its preparation (see examples 6-8).

Its earliest priority D13 also mentions TAF-HF (as GS-7340 hemifumarate, see pages 2 and 19) but contains no example of its preparation.

2.2.4 The parties present opposing views as to whether the mere mention of TAF-HF in D13 is an enabling disclosure of this compound, considering the relevant common general knowledge. It is also debatable whether D11 provides an enabling disclosure for the preparation of TAF-HF, as a salt and/or as a co-crystal.

However, in the Board's opinion, if it is accepted that the mention of TAF-HF in D13 is an enabling disclosure of this compound, then it must follow that the equivalent mention in D11 of the combination of fumaric acid and TAF at a ratio of about 0.5, as co-crystal or salt, is an enabling disclosure of TAF-HF. Thus it is not possible for D12 to enjoy priority from D13 for TAF-HF without claim 1 enjoying priority from D11 for the same subject-matter.

In other words, it is not necessary to take position on the validity of the priority claims with regard to enablement. Either D12 enjoys a valid right to priority from D13 in respect of TAF-HF, in which case, for analogous reasons, present claim 1 of the main request also validly claims priority from D11 in respect of the same subject-matter. Or D12 does not enjoy a valid right to priority from D13 in respect of TAF-HF. In both cases, D12 is not prior art under Article 54(3) EPC.

2.2.5 Accordingly, D12 does not prejudice the novelty of the claimed subject-matter.

2.3 Sufficiency of disclosure

2.3.1 The appellants do not contest that example 1 of the patent describes the preparation of a mixture of TAF-HF along with GS-7339-MF and TAF-MF. However, they contend that the patent does not give the necessary information to the skilled person as to how to separate TAF-HF from the obtained solids, so that the claimed subject-matter is insufficiently disclosed.

2.3.2 The Board does not share this opinion. Claim 1 of the main request pertains to TAF-HF as such and does not mandate any degree of purity. Consequently, the Board shares the respondent's opinion that the criteria of sufficiency of disclosure are met already for the reason that example 1 discloses the preparation of TAF-HF.

Contrary to the appellant's view, the fact that TAF-HF is destined to be used as a pharmaceutical does not change this conclusion. Claim 1 does not mandate that TAF-HF be in a form suitable for pharmaceutical use. And in any case, the appellants have not established that the solid mixture of example 1 comprising TAF-MF, TAF-HF and GS-7339-MF would be unsuitable for such a use.

2.3.3 In addition, example 2 of the patent also enables the preparation of TAF-HF, in a form the purity of which the appellants have not contested, by seeding "with tenofovir alafenamide hemifumarate formed in Example 1" (see paragraph [0056]). This further example of the patent would thus enable the skilled person to obtain

isolated TAF-HF, supposing *arguendo* that such a degree of purity would be required.

The appellants countered that the wording of this seeding step in example 2 was ambiguous and possibly referred to purified TAF-HF of example 1, and that the skilled person would understand that the use of pure seed crystals is required.

The Board is not convinced by these arguments. Firstly, there is no reason to consider the reference, in example 2 of the patent, to the TAF-HF formed in example 1 as implying a further isolation or purification step, considering that no such additional step is mentioned in the patent. The Board thus considers that the solid directly resulting from example 1 is meant. Furthermore, there is no debate that the solid formed in example 1 contains some amount of the TAF-HF form which is to be obtained in example 2, and there is no indication in the textbooks D32 (see page 197, §5.2.2) or D2 (see page 1896) that any level of purity is mandatory in the seed crystals for them to effectively promote crystallisation. Thus, the common general knowledge does not teach that a pure seed crystal must be used, and the appellants have not raised serious doubts as to the effective use of the solid of example 1 as seed crystal in example 2.

2.3.4 Accordingly, the criteria of sufficiency of disclosure are met.

2.4 Inventive step

2.4.1 The parties agree on the choice of D1 as closest prior art. D1 discloses TAF-MF (which comprises a 1:1 stoichiometric ratio of TAF to fumaric acid).

The subject-matter of claim 1 of the main request differs in that TAF is in the form of a hemifumarate instead of a monofumarate (i.e. it comprises a 2:1 stoichiometric ratio of TAF to fumaric acid).

2.4.2 According to the respondent, TAF-HF exhibits the following improvements over TAF-MF:

(a) Purging of diastereomeric impurity

Paragraph [0064] and table 2 of the patent, as well as D48 and D49, show the respective preparations and isolations of TAF-HF and TAF-MF under similar conditions, involving dissolving fumaric acid (respectively 0.9 and 0.5 equivalents) and a mixture of TAF (GS-7340) with about 10% of its diastereoisomer (GS-7339) at 70°C in acetonitrile, then cooling down, seeding respectively with TAF-HF (GS-7340-03) and TAF-MF (GS-7340-02), cooling further and isolating the solid product. As summarised in the respondent's reply (see paragraphs 7.7-7.11), the amount of isomer left in the final product is lower in the case of TAF-HF (TAF:GS-7339 ratio 99.35:0.65) than in the case of TAF-MF (92.4:7.6).

Appellants 1 and 2 object that this property is not an intrinsic property of TAF-HF, but results from differences in the process parameters, in particular the amounts of fumaric acid employed resulting in different acidities. However, in the Board's opinion, these amounts of fumaric acid used in the process mirror the differentiating feature, namely the stoichiometric ratio of TAF to fumaric acid in the claimed complex of 2:1 instead of 1:1. It can thus be concluded that, starting from the same starting

material (TAF with 10% diastereomer), the formation of TAF-HF by combining TAF with the corresponding 0.5 equivalent fumaric acid and seeding with TAF-HF leads to higher TAF purities than the formation, under comparable conditions, of TAF-MF by combining TAF correspondingly with about 1 equivalent fumaric acid and seeding with TAF-MF. This effect thus credibly arises from the differentiating feature over the prior art.

(b) Increased chemical stability

The patent (see paragraph [0065] and table 3) and the post-published document D51 (see the translation D50, table 1 page 14) credibly show that TAF-HF is chemically more stable than TAF-MF, as measured by the lower rate of decrease of the active ingredient TAF when subjecting TAF-HF to several stress conditions. The effect observed in table 3 of the patent is not caused by the higher initial purity of TAF-HF (0.05% degradation products in TAF-HF vs 0.69% in TAF-MF at t=0), considering that in D50 the effect is also observed in the opposite situation (i.e. starting from TAF-HF with 97.40% purity vs TAF-MF with 97.74% purity). Accordingly, the difference in chemical stability can be attributed to the distinguishing feature of the invention compared with the closest state of the art.

The appellants submit that TAF-HF exhibits a higher relative increase in degradation products under certain storage conditions (namely 40°C/75% RH, cap closed or open) than TAF-MF. However, the relevant technical effect here is the stability of TAF-HF, i.e. the amount of the active ingredient TAF-HF remaining in the product over time, and not the relative increase in

degradation products. The appellants' argument does not call into question the fact that TAF-HF has improved stability.

2.4.3 Considering that an inventive step can be acknowledged taking into account the technical effects discussed above, it is not necessary to assess whether the claimed hemifumarate additionally achieves higher thermodynamic or thermal stability.

2.4.4 The objective technical problem to be solved can accordingly be formulated as the provision of an improved form of TAF, having improved chemical stability and an improved ability to purge TAF of its diastereomeric impurity GS-7339.

2.4.5 Obviousness

It was known at the priority date that, in the case of tenofovir disoproxil, the co-crystal with fumaric acid in a 2:1 molar ratio is more stable and less hygroscopic than the 1:1 fumarate salt (see D15, passage bridging pages 368-369; D3, page 3, lines 10-15). The appellants contend that this historical development would have provided the skilled person with a reasonable expectation that, in analogy to tenofovir disoproxil, TAF-HF would exhibit improved stability over TAF-MF.

The Board does not share this opinion. The properties of the hemifumarate in the case of TAF could not be extrapolated from those of tenofovir disoproxil. The prior art does not point to any such predictability. On the contrary, in light of the statements regarding the unique physicochemical properties of API solid forms, including salts and co-crystals in D15 (see page 359,

right column) and D28 (see page 317, left column), no such generalisation is possible. In the present case, the prior art gives no reason to assume that the modification involved, namely the use of a 2:1 molar ratio with fumaric acid instead of 1:1, would lead to the same effect in the structurally different compounds TAF and tenofovir disoproxil. Accordingly, the claimed subject-matter is not obvious starting from D1.

2.4.6 For the same reason, the objection of lack of inventive step starting alternatively from D3 is unconvincing. This objection supposes that the skilled person, starting from the tenofovir disoproxil hemifumarate of D3, would change the API to TAF and expect that similar advantageous physicochemical properties be still obtained. The claimed subject-matter is therefore not obvious starting from D3 either.

2.4.7 In conclusion, the main request satisfies the requirements of inventive step.

Order

For these reasons it is decided that:

1. The appeals are dismissed.

2. The request for reimbursement of the appeal fee is rejected.

The Registrar: The Chairman:

S. Sánchez Chiquero M. Steendijk

Decision electronically authenticated