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Datasheet for the decision of 13 January 2022

Case Number: T 2077/18 - 3.3.07

Application Number: 11167101.2

Publication Number: 2386294

IPC: A61K9/24, A61K9/26, A61K31/675, A61K31/513, A61K31/535, A61P31/18

Language of the proceedings: EN

Title of invention:
Unitary pharmaceutical dosage form comprising Tenofovir DF

Patent Proprietor:
Gilead Sciences, LLC

Opponents:
KELTIE LLP
Sandoz AG
Accord Healthcare Ltd
Hetero Drugs Ltd.

Headword:
Unitary pharmaceutical dosage form/GILEAD

Relevant legal provisions:
EPC R. 111(2), 103(1)(a)
RPBA Art. 12(4)
EPC Art. 56, 123(2), 76(1)

Keyword:
Reimbursement of the appeal fees - No
Admission of documents
Main request - Inventive step (No)
Auxiliary requests 1-3, 3A - Inventive step (No)
Auxiliary requests 4A, 4, 4B - Extension of the subject-matter (Yes)
Auxiliary request 5 - Inventive step (No)
Auxiliary request 6 - Extension of the subject-matter (Yes)

Decisions cited:
T 1742/12

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Case Number: T 2077/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 13 January 2022

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Decision under appeal:

Interlocutory decision of the Opposition Division of the European Patent Office posted on 8 June 2018 concerning maintenance of the European Patent No. 2386294 in amended form.

Composition of the Board:

Chairman A. Usuelli
Members: D. Boulois
Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 386 294 was granted on the basis of a set of 24 claims.

Claim 1 as granted read:

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and a surfactant whereby the tenofovir DF is in a first component and the efavirenz and the surfactant are in a second component, wherein the first and second components are physically discrete, and wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition."

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

III. The appeal lies from the decision of the opposition division finding that the patent in amended form meets the requirements of the EPC. The decision was based on the main request filed with letter of 4 August 2016.

Claim 1 of the main request read:

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and a surfactant whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the surfactant are in a second

layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition."

IV. The documents cited during the opposition proceedings included the following:

D4: European Medicines Agency, "Scientific Discussion (Truvada)", EMEA, February 2005, pages 1-28, XP2417805

D5: WO 2004/064845 A1

D7: WO 03/045327 A2

D8: EP 1 332 757 A1

D9: Bristol Myers Squibb, "Sustiva", www.FDA.gouv, February 2005, pages 3-40, XP2417851

D10: GILEAD: "Truvada", www.FDA.gov, May 2005(2005-05), pages 1-29, XP002417852

D12: "Atripla Fact Sheet", www.FDA.gov, 12 July 2006 (2006-07-12), pages 1-2, XP002417854

D13: FDA: "Guidance for Industry Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV", www.FDA.org, May 2004(2004-05), pages 1-17, XP002417855

D14: Yuan et al., Vol 18, No 2, 2001, 234-237

D15: CA 2512475

D19: Rowe, Raymond et al, Handbook of pharmaceutical excipients, 2003, Ed4

D20: Lachman Leon et al., The Theory and Practice of Industrial Pharmacy, Philadelphia, USA, Lea and Febiger, 1986, pp 330-331.

D27: Press Release, Bristol-Myers Squibb and Gilead Sciences Establish Joint-Venture, 20 December 2004

D28: Chiarello, Kaylynn, Big Pharma Companies Team Up to Develop Once-Daily Triple-Combination HIV Drug, April 2005

D29: WO 99/61026

D32: Preformulation report

D35: WO 2006/135932 A2
D36: Priority document US 60 771, 353
D39: Lachman, Leon et al., The Theory and Practice of Industrial Pharmacy, Philadelphia, USA, Lea and Febiger, 1986, pp 190-194
D42: Declaration of inventor Munir Hussain
D43: Gao et al., Journal of Pharmaceutical Sciences, 2007, 96(11), 2970
D46A: Remington, 20th Edition, 2000, pages 872-878
D48: Aulton, Pharmaceutics, 2nd Edition, 2002, pages 250-251
D49: Press Release Gilead, 9 August 2005.

V. According to the decision under appeal:
a) The main request met the requirements of Articles 123(2) and 76(1) EPC.
b) The claimed subject-matter was sufficiently disclosed.
c) The parent application could not be considered relevant for novelty, in view of the decision G 1/15. D35 could also not be considered as a prior art under Article 54(3) EPC, as D35 could at best claim the same priority date.
d) The claimed subject-matter was novel over D15, D27 and D28.
e) As regards inventive step, the opposition division was of the opinion that the skilled person would start from a specific formulation of one or more of the drugs described in claim 1 of the main request, which led to the choice of D5/D15. The subject-matter of claim 1 of the main request differed from the teaching of D5/D15 in the bi-layer tablet form, and the total amount of the active substances which was greater than about 60% by weight of the composition. The problem was defined as the provision of a stable, high drug load dosage form comprising tenofovir DF, efavirenz, and

emtricitabine, wherein the active substances, particularly efavirenz, retained the required bioavailability and led to a better patient compliance. The solution was not obvious, since formulating a combination of these drugs was not trivial and the prior art did not disclose any guidance how to provide an effective fixed dose combination of these drugs.

VI. Opponent 04 and opponent 03 (hereinafter appellants 04 and 03) filed an appeal against said decision.

VII. With the statement setting out the grounds of appeal, appellant 03 submitted the following items of evidence:
A50: WO 96/22082
A51: J. Wechsler, "Combination Product Raise Manufacturing Challenges", Pharmaceutical Technology, March 2005
A52: Press Release, Jan. 9 2006, Bristol-Myers Squibb and Gilead Announce Data Supporting Bioequivalence for Single -Pill Fixed Dose Regimen of Sustiva and Truvada.

Appellant 03 requested furthermore a reimbursement of the appeal fee arguing that a substantial procedural violation had occurred in the first instance proceedings.

VIII. With its reply dated 4 March 2019, the patent proprietor (hereinafter the respondent) filed a main request corresponding to the main request filed in the opposition proceedings and auxiliary requests 1-3, 3A, 4, 4A, 4B, 5, and 6.

IX. The subject-matter of claim 1 of the auxiliary requests read as follows:

Auxiliary request 1

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and a surfactant whereby the surfactant is in a stabilizing configuration with the tenofovir DF and whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the surfactant are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition."

Auxiliary request 2

Claim 1 of auxiliary request 2 is identical to claim 1 of the main request, this request consisting in the submission of amended pages of the description.

Auxiliary request 3

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and sodium lauryl sulfate whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the sodium lauryl sulfate are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition."

Auxiliary request 3A

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and sodium lauryl sulfate whereby the sodium lauryl sulfate is in a stabilising

configuration with the tenofovir DF and whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the sodium lauryl sulfate are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition."

Auxiliary request 4

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and sodium lauryl sulfate whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the surfactant are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another , and wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, and hvdroxvpropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2."

Auxiliary request 4A

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and sodium lauryl sulfate whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the sodium lauryl sulfate are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl

sulfate, and hydroxypropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2."

Auxiliary request 4B

"1. A unitary composition comprising tenofovir DF, efavirenz and emtricitabine and sodium lauryl sulfate whereby the sodium lauryl sulfate is in a stabilising configuration with the tenofovir DF and whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the sodium lauryl sulfate are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, and hydroxypropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2."

Auxiliary request 5

"1. A method of preparing a unitary composition comprising tenofovir DF, efavirenz and emtricitabine and a surfactant whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the surfactant are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition, said method comprising preparing the first layer comprising tenofovir DF and emtricitabine, preparing the second layer comprising efavirenz and a surfactant,

and placing both layers into stabilizing configuration with one another; wherein the first layer is made by dry granulation and the second layer is made by wet granulation"

Auxiliary request 6

"1. A method of preparing a unitary composition comprising tenofovir DF, efavirenz and emtricitabine and a surfactant whereby the tenofovir DF and emtricitabine are in a first layer and the efavirenz and the surfactant are in a second layer, wherein the first and second layers are physically discrete and are in contact with one another, and wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrvstalline cellulose, sodium lauryl sulfate, and hvdroxvpropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2, comprising preparing the first layer comprising tenofovir DF, preparing the second layer comprising efavirenz and a surfactant, and placing both layers into stabilizing configuration with one another "

X. A communication from the Board, dated 2 June 2020, was sent to the parties. In this, it was considered in particular that the main request appeared to lack inventive step over D49.

XI. Oral proceedings took place on 13 January 2022. During the oral proceedings the respondent changed the order of the requests and moved auxiliary request 4A ahead of auxiliary request 4.

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

Reimbursement of the appeal fees

According to appellant 03, the decision under appeal fails to set out the factual and legal considerations supporting the decision taken by the opposition division. For this reason, the decision of the opposition division was insufficiently reasoned in the sense of Rule 111(2) EPC with regard to Articles 83 and 56 EPC. This failure amounted to a substantial procedural violation and gave rise to the appellant's need to file an appeal in order to preserve its rights. Hence, the reimbursement of the appeal fee is equitable within the meaning of Rule 103(1)(a) EPC.

Admission of A50-A52, D46A and D48

According to appellant 03, A50 was used to rebut the position of the opposition division in section 3.7 of its decision. A51 and A52 supplemented the disclosure content of D49 and rebutted the position of the opposition division in sections 6.6.9 and 6.3.13, respectively.

Main request - Inventive step

According to appellant 03, D5, D29 and D49 could be seen as closest prior art. When starting from D49, the distinguishing feature between D49 and claim 1 was the "drug load of greater than 60%". The resulting technical effect was a relatively small tablet. Hence, the objective technical problem was to provide a bi-layered tablet, containing TDF (tenofovir DF) and FTC (emtricitabine) in the first layer and EFV (efavirenz)

and SDS (sodium lauryl sulfate) in the second layer, wherein the tablet size should be relatively small. The solution was obvious in view of D29, D5 and D28.

According to appellant 04, D49 was the closest prior art. The claimed solution, namely a "drug load of greater than 60%" was obvious in view of D28.

Auxiliary requests 1-3, 3A - Inventive step

The same arguments as for the main request applied to these auxiliary requests.

Auxiliary request 4A, 4, 4B - Amendments

The subject-matter of claim 1 of these requests was not derivable from the application as filed or from the parent application, neither in view of claim 13, nor in view of page 5 of the description.

Auxiliary request 5 - Inventive step

According to appellant 03, the selection of wet and dry granulation was an arbitrary selection without any effect. It was common general knowledge that basically three different methods existed for producing tablets: 1) wet granulation; 2) dry granulation; 3) direct-compression. In absence of any unexpected technical effect the choice of any one of those methods was an obvious alternative. Paragraphs [0004] and [0007] referred to a simple formulation, not a bi-layer tablet. D4 disclosed that Truvada® was prepared by wet granulation, and D20 showed that Sustiva® was also prepared by wet granulation. There was however no effect shown for the use of dry granulation, which

remained an arbitrary choice and an obvious alternative.

According to appellant 04, all the method steps of claim 1 were usual and mandatory steps for preparing a bi-layer tablet. The use of a dry granulation was a straightforward measure without any effect and the use of the wet granulation was known from D29.

Auxiliary request 6 - Amendments

The situation was similar to auxiliary requests 4-4B.

XIII. The arguments of the respondent may be summarised as follows:

Admission of A50-A52, D46A and D48

No decision was taken during opposition proceedings in relation to the admission of the documents D46A and D48 which should not be admitted. A50-A52 were late-filed, *prima facie* not relevant and could have been filed earlier.

Main request - Inventive step

D5 and D10 were the appropriate choice for the closest prior art. D28 and D49 were business updates regarding the respondent's development of the coformulation of tenofovir DF, emtricitabine and efavirenz which contained no technical details. D49 provided nothing more than a general disclosure that bi-layer technology was considered to be an option for co-formulating tenofovir DF, emtricitabine and efavirenz. Its disclosure could not be enabled.

The disclosure of D49 differed from the claims of the main request in that one layer contained tenofovir DF and emtricitabine and the other layer contained efavirenz and a surfactant, that the first and second layers were in contact with one another, and that the drug loading was greater than about 60% by weight. The effects of these differences were that the chemical stabilities of the three active ingredients were maintained and all three were bioavailable, that no barrier was required between the two layers, and that a combined daily dosage of all three active ingredients could be included in a single tablet which a human could swallow, thereby enhancing patient convenience. The objective technical problem addressed and solved in view of D49, therefore, was to construct a bilayer composition which provided the combined daily dosage of the three active ingredients so that they are stable and bioavailable. There was no pointer or teaching towards the solution provided in the patent. D28 in particular was a press release about the respondent's intention to reformulate the active ingredients from SUSTIVA® and TRUVADA® into a single dosage form, which included a statement that "You cannot make a pill more than 1.8 g". This merely stated a problem without pointing to any practical solution. It provided no guidance as to how to fit 1100mg of the active ingredients into a 1.8g tablet (TRUVADA® contains a total of 500mg of API (tenofovir DF and emtricitabine) and weighs 1000mg, and SUSTIVA® contains 600mg efavirenz and weighs 1200mg). The solution was not obvious.

Auxiliary requests 1-3, 3A - Inventive step

The arguments submitted in relation to the main request applied also to these requests.

Auxiliary request 4A, 4, 4B - Amendments

A basis for the amendments could be found in original claim 13. It was obvious from the application as filed or from page 5 of the parent application, that the specific disclosure of claim 13 could apply to bi-layer tablets.

Auxiliary request 5 - Inventive step

The claims described a particularly advantageous method of preparing the unitary composition, by dry granulation of the first layer and wet granulation of the second layer. The skilled person would not have known how to provide a high drug load dosage form of the three active ingredients, they would not have considered dry granulation to be a viable option because they would have expected that tenofovir DF would clog up the formulation machinery when dry granulated because of its extreme stickiness. Mixture of tenofovir DF and emtricitabine overcame these difficulties as shown by the example in the patent. None of the cited documents disclosed the method of preparation of the forms disclosed therein. The description of the patent mentioned that wet granulation had an incidence on the stability of the composition, in particular on tenofovir DF, which was difficult to formulate, as shown in D42 (see paragraphs [0004] and [0007]).

Auxiliary request 6 - Amendments

The subject-matter of the original method claims 18-20 had to be read in relationship with the teaching of the

description, and their subject-matter could be associated with original claim 13.

XIV. Requests

Appellant 03 requested that the decision under appeal be set aside and the patent be revoked. Additionally, appellant 03 requested reimbursement of the appeal fee because of a substantial procedural violation in the proceedings before the opposition division.

Appellant 04 requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and the patent be maintained according to the sets of claims filed as auxiliary requests 1-3, 3A, 4A, 4, 4B, 5, and 6 with letter of 4 March 2019. The respondent also requested that documents A50-A52 filed in the appeal proceedings and documents D46A and D48 filed during the opposition proceedings not be admitted into the proceedings.

The other parties did not submit any requests.

Reasons for the Decision

1. Reimbursement of the appeal fee

1.1 According to appellant 03, the decision under appeal failed to set out the factual and legal considerations supporting the decision taken by the opposition division and was insufficiently reasoned in the sense of Rule 111(2) EPC. This failure amounted to a substantial procedural violation and gave rise to the

appellant's need to file an appeal. Reimbursement of the appeal fee was thus equitable.

Appellant 03 raised two main points with regard to the reasoning of the opposition division on the subject of sufficiency of disclosure.

The first is that the opposition division failed to explain why it concluded that the skilled person would know how to prepare compositions with a drug amount of more than 60%, when it had considered in its assessment of inventive step that the skilled person was not aware how the drug amount could be increased.

The second is that the opposition division failed to explain why it considered the proprietor's explanations sufficiently credible that the skilled person could generalise the single example disclosed in the patent. In this context the opposition division had allegedly failed to give reasoning on two key arguments of opponent 3, namely that the patent did not disclose a concept fit for generalisation as required by the case law and that the proprietor carried the burden of proof in this particular case.

1.2 The Board is of the view that the first objection, which is principally based on an alleged contradiction in the decision, is a criticism of the judgment of the opposition division. Even on the assumption that there had been an error of judgment, this is not a matter which the Board can take into account when assessing whether or not a substantial procedural violation occurred. The Board would nevertheless like to point out that the tests for sufficiency of disclosure and inventive step are not the same.

As to the second point, the Board refers to paragraphs 3.7 and 3.8 of the decision which addresses the issue of sufficiency over the whole range claimed. The Board is of the view that these paragraphs together with paragraph 3.6 provide a logical chain of reasoning (albeit a short one) which explains why the division reached its conclusion. It thus appears that the reasoning on sufficiency of disclosure complies with the minimum requirements for a decision being sufficiently reasoned within the meaning of Rule 111(2) EPC.

1.3 Appellant 03 also considers that in the reasoning of the opposition division as regards Article 56 EPC, several crucial points were missing:
a) Opponent 03 argued that D29 could be the closest prior art and the decision was silent why D29 could not be regarded as a suitable starting point.
b) In the present case, it was necessary to apply the problem-solution approach to more than one starting point (see the Guidelines and T 1742/12). The decision of the opposition division did not explain why it did not follow this established case law.
c) The opposition division did not explain why it agreed with proprietor's definition of the problem.
d) The opposition division did not give any reasoning why document D5 did not disclose formulations having a drug load greater than 60%.
e) The opposition division did not explain why the disclosure of D29 was not convincing as regards the drug amounts.
d)+ e) There was no reasoning in the decision why the mathematical calculations presented during oral proceedings as regards the drug amounts were not followed.

f) Opponent 03 emphasized that the closest prior art D5 disclosed references which pointed to the claimed solution; the opposition division failed to give any reasoning why these pointers had been disregarded.

1.4 The Board is not convinced by these arguments. The Board notes the following points in response to this objection.

The choice of the closest prior art is explained in paragraph 6.3 of the decision of the opposition division.

The opposition division did not mention explicitly D29 in its discussion as to the choice of the closest prior art, but stated clearly which criteria it applied in its choice. Reference is made in particular to point 6.3.12 of the decision. Given that D5/D15 discloses a formulation of more than one antiviral substance in a single composition, it appears clear that prior art documents which disclose formulations comprising only one antiviral such as in D7/D8 and D29 cannot be chosen as closest prior art or as a suitable starting point for the assessment of inventive step. The omission of an explicit reference to D29 in the discussion concerning the selection of the closest prior art does therefore not constitute a procedural violation. The Board considers that the reasoning concerning the choice of the closest prior art provides sufficient explanation why no other prior art was chosen as a suitable starting point.

The opposition division applied furthermore the problem-solution approach on the basis of the documents chosen, which follows the established jurisprudence as regards the assessment of inventive step. Each step is

clearly referred to and explained, including the determination and the establishment of the technical effect derivable from the distinguishing feature. That effect is also explained and based on the example of the patent and on document D12.

The opposition division also explained in its decision why the drug loading in the formulation specified in claim 1 was not obvious (see points as regards the amounts of drug present in the formulations in paragraph 6.6.3-6.6.6 of the decision). Said arguments appear to be therefore explicitly present in the decision.

Moreover, the Board notes that the reasoning on inventive step appears clear and takes the main points of argument submitted by the parties into account. There is no requirement that each and every argument presented is considered in a decision.

1.5 Consequently, there is no substantial procedural violation and a reimbursement of the appeal fees is not justified.

2. Admission of A50-A52, D46A and D48 into the appeal proceedings

2.1 Documents A50-A52 have been filed by appellant 03 with its statement of grounds of appeal, at the earliest stage of the appeal proceedings.

2.1.1 A50 has been mentioned by appellant 03 in its statement setting out the grounds of appeal in relation to the requirement of sufficiency of disclosure, and is regarded as a response to the decision of the opposition division. The Board sees thus no reason to

hold A50 inadmissible. It therefore forms part of the appeal proceedings (Article 12(4) RPBA 2007).

2.1.2 A51 is a document of common general knowledge and has been filed in particular to supplement the disclosure content of D49, which is a document used in the assessment of inventive step, and also as a response to several points of the decision of the opposition division relating to the choice of D49 as the closest prior art (point 6.3.13 of the decision) and obviousness (point 6.6.9 of the decision); for these reasons, it is clear that this document could not have been filed earlier. The Board sees thus no reason to hold A51 inadmissible. It therefore forms part of the appeal proceedings (Article 12(4) RPBA 2007).

2.1.3 A52 has been cited as a new closest prior art in the statement of grounds of appeal of appellant 03, and constitutes therefore a new fact. Moreover, this document does not appear to provide more information than D49 which is already in the proceedings. This document could and should have been filed earlier in the opposition proceedings and its filing in the appeal proceedings is contrary to the principle of procedural economy. This document is therefore not admitted into the appeal proceedings (Article 12(4) RPBA 2007).

2.2 Documents D46A and D48 were filed by appellant 03 during the opposition proceedings in response to the opinion of the opposition division. Their admissibility was not objected by the respondent during the opposition proceedings. The opposition division did not take a decision on the admittance of these documents.

2.2.1 D46A is a document of common general knowledge relating to bi-layer tablets. Appellant 03 referred to this

document in its statement of grounds of appeal in support of the choice of D49 as closest prior art and in response to the decision of the opposition division to consider that this document was not a suitable starting point for the assessment of inventive step.

In view of the nature and importance of the document on an essential point of the assessment of inventive step, and considering that it was filed during the opposition proceedings, the Board sees no reason to hold D46A inadmissible. It therefore forms part of the appeal proceedings (Article 12(4) RPBA 2007).

2.2.2 D48 is a also a document of common general knowledge relating to the excipients used in pharmaceutical dosage forms, in particular surfactants. As for document D46A, in view of the nature of the document D48 and its early filing in the opposition proceedings, the Board sees no reason to hold D48 inadmissible. It therefore forms part of the appeal proceedings (Article 12(4) RPBA 2007).

3. Main request - Inventive step

3.1 The invention relates to an combination of efavirenz (EFV), emtricitabine (FTC) and tenofovir DF (TDF) which provides an unitary form with acceptable stability and bioequivalence. The invention aims in particular to overcome the unexpected incompatibility of tenofovir DF and the surfactant used in the formulation Sustiva® of efavirenz (see par. [0009] of the specification).

3.2 Appellant 03 mentioned documents D5, D29 and D49 as possible closest prior art while appellant 04 considered D49 and the respondent's choice was D5 or

D10. In its decision the opposition division selected document D5 as the closest prior art.

3.2.1 D5 discloses in its formulation G a tablet comprising tenofovir DF combined with emtricitabine, the active agents being present in an amount greater than 60% by weight. This document does not disclose a bilayer tablet and does not disclose the presence of efavirenz and a surfactant.

D10 discloses film-coated tablets comprising 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. This document does not disclose the weight amounts of the active substances, a bilayer tablet and the presence of efavirenz and a surfactant.

D29 discloses in example 8 a tablet comprising more than 60% by weight of efavirenz and sodium lauryl sulfate. This document does not disclose a bilayer tablet and does not disclose the presence of emtricitabine and tenofovir.

D49 is a press release relating to the evaluation of three new formulations, as bilayer tablets involving the co-formulation of Truvada® (emtricitabine and tenofovir disoproxil fumarate) and Sustiva® (efavirenz and sodium lauryl sulfate) as individually formulated layers combined together in one tablet (see the first paragraph). This document does not disclose the weight amount of the active substances.

3.2.2 Document D49 addresses therefore the problem of providing a formulation for the same three active ingredients included in the composition defined in present claim 1 and shows the largest number of

similarities with the claimed subject-matter; D49 represents therefore the closest state of the art.

3.2.3 In its reply to the statement of grounds of appeal the respondent argued that there was no concrete technical disclosure in D49, i.e. that this document was not a technical document and that its disclosure was not enabling. In its view D49 was completely silent as to the exact formulation of each layer and the distinguishing features between the claimed subject-matter and the teaching of D49 were that one layer contains tenofovir DF and emtricitabine and the other layer contains efavirenz and a surfactant, that the first and second layers are in contact with one another, and that the drug loading is greater than about 60% by weight.

The Board notes that under Article 54(2) EPC, the state of the art comprises everything made available to the public by means of a written or oral description, by use, or in any other way, before the filing or priority date of the European patent application. This is obviously the case for D49, a press release from the respondent published on the date of 9 August 2005.

The Board is furthermore of the view that D49 provides concrete technical information that can be put in practice by a skilled person. D49 relates indeed to a bilayer tablet technology, which is technology well known and used at the publication date of D49 (see for instance D46A). D49 also mentions explicitly and concretely the co-formulation of Truvada® and Sustiva® which are known formulations, comprising respectively emtricitabine co-formulated with tenofovir DF fumarate and efavirenz co-formulated with sodium lauryl sulfate (see D9 and D10).

Finally, document D49 has a clear technical disclosure, namely a unitary composition where Truvada® and Sustiva® have been co-formulated as individual layers, that is to say, the 1st layer comprises tenofovir DF and emtricitabine, whereas the 2nd layer comprises efavirenz and the surfactant, whereby the 1st and 2nd layers are physically discrete and are in contact with another. Accordingly, the only distinguishing feature between the claimed subject-matter and the teaching of D49 is that the drug loading is greater than about 60% by weight.

3.3 According to the respondent, the technical problem addressed and solved in view of D49, is to construct a bilayer composition which provides the combined daily dosage of the three active ingredients so that they are stable and bioavailable.

According to appellant 03, the problem is the provision of a bi-layer tablet containing tenofovir DF and emtricitabine in the first layer and efavirenz and sodium lauryl sulfate in the second layer, wherein the tablet size should be relatively small.

According to appellant 04, the problem is the provision of a unitary fixed dose combination of tenofovir DF, emtricitabine and efavirenz with a reduced size of the tablet.

3.4 In view of the distinguishing features between the claimed subject-matter and D49, the problem to be solved can only be as defined by the appellants, in particular the provision of a tablet with reduced size or relatively small. The Board is convinced that this problem is solved in view of the example of bilayer

tablets of the contested patent (see for instance Table 3 of the specification).

3.5 The claimed solution to this problem is the unitary composition defined in claim 1 which is characterised by a drug loading greater than about 60% by weight.

3.6 It remains to determine whether the claimed solution is obvious.

3.6.1 As to obviousness, the documents D28, D29 and D5 were mentioned by the appellants.

D28 is a press release from the respondent relating to the combination of Sustiva® (efavirenz and sodium lauryl sulfate) and Truvada® (emtricitabine and tenofovir DF) for a once-daily treatment. The document discloses that the aim of the combination is to develop a tablet that is small enough to swallow. D28 mentions that "if formulators simply combined the three existing formulations into a trilayer tablet, the drug would be 2.2 g. You cannot make a pill more than 1.8 g" and "limiting the volume and how many excipients are used in the formulations to use could be one way to create a single tablet that is less than 1.8 g". In view of this teaching, the skilled person would consider reducing the size of the bi-layer tablet by providing an unitary dosage form with a high drug load, i.e. with a reduced amount of excipients.

As explained by appellant 04, Truvada® contains 300 mg of tenofovir DF and 200 mg of emtricitabine, whereas Sustiva® tablets contain 600 mg of efavirenz giving an overall amount of the active ingredients of 1,100 mg added to 1,100 mg of excipients (see D10 and D9). Simply combining Truvada® and Sustiva® would give an

overall weight of the composition of 2.2 g, while D28 requires that the maximum weight of a tablet for it to be swallowed is 1.8 g. Based on the combination of Truvada® and Sustiva® as on the market, the amount of the active ingredients in the triple combination formulation has to be kept as 1,100 mg. This amount is about 61.1% by weight of a tablet of 1.8 g.

Moreover, D29 discloses in example 8 a tablet comprising efavirenz and sodium lauryl sulfate in an amount greater than 60% by weight of the tablet. This document also indicates that by removing lactose from the formulation it is possible to prepare tablets having about 70% of drug load. D5 discloses in formulation G a tablet obtained by wet granulation and comprising tenofovir DF and emtricitabine in an amount of about 71% by weight. In view of the disclosure of D29 and D5, it appears therefore that distinct formulations comprising either efavirenz and sodium lauryl sulfate or tenofovir DF and emtricitabine in amounts higher than 60% by weight are known and that the skilled person would not have any difficulty in the preparation of an unitary dosage by combing the three active ingredients at the claimed amounts by putting in practice the teaching of D29 and D5.

In view of the disclosure of D28, D29 and D5, and since bi-layer tablet technology was well known at the priority date of the contested patent (see for instance D46A), there is a clear incentive to make bi-layer tablets as claimed with a drug load higher than 60% by weight.

3.7 Consequently, the claimed subject-matter is obvious and the main request does not involve an inventive step (Article 56 EPC).

4. Auxiliary requests 1-3, 3A - Inventive step

In comparison to claim 1 of the main request, the subject-matter of claim 1 of auxiliary request 1 has been amended by the feature **"whereby the surfactant is in a stabilizing configuration with the tenofovir DF"**..

The subject-matter of claim 1 of auxiliary request 2 is identical to claim 1 of the main request, this request differing through amendments of the description.

In comparison to claim 1 of the main request, the subject-matter of claim 1 of auxiliary request 3 has been been amended by the specification that the surfactant is **"sodium lauryl sulfate"**.

In comparison to claim 1 of auxiliary request 1, the subject-matter of claim 1 of auxiliary request 3A has been amended by the specification that the surfactant is **"sodium lauryl sulfate"**.

None of the amendments made to claim 1 of these requests has an incidence on the assessment of inventive step as done for the main request, since all these features are disclosed in the closest prior art D49. The conclusion reached for the main request applies *mutatis mutandis* to auxiliary requests, 1-3 and 3A, which lack an inventive step for the same reasons (Article 56 EPC).

5. Auxiliary request 4A, 4, 4B - Article 123(2) and 76(1) EPC

5.1 The subject-matter of claim 1 of auxiliary request 4A relates to a unitary composition with a "first layer"

and a "second layer", characterised *inter alia* by the feature "**wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, and hydroxypropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2.**"

This feature originates *expressis verbis* from dependent claim 13 of the patent application EP 11 167 101.2 and of the parent application EP 06 773 195.0 (published as WO2006/135933), which have an identical description and set of claims.

Original claim 13 read as follows:
"13. The composition of claim 12 **wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, and hydroxypropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2.**"

Claim 13 was dependent on claim 12, which read:
"12. The composition of claim 2 which further comprises magnesium stearate, croscarmellose sodium, microcrystalline cellulose and hydroxypropyl cellulose."

Claims 1 and 2 as originally filed or of the parent application read:
"1. A composition comprising tenofovir DF and a surfactant whereby the surfactant is in a stabilizing configuration with the tenofovir DF.
2. The composition of claim 1 additionally including efavirenz and emtricitabine."

Consequently, none of the relevant claims of the patent or parent application related to an unitary bi-layer composition comprising tenofovir DF and emtricitabine in a first layer, and efavirenz and sodium lauryl sulfate in a second layer.

The presence of layers is disclosed in original dependent claim 5, itself dependent from claim 4, but the association of this feature with the feature of claim 13 is not derivable directly and unambiguously from the original application or from the parent application.

A pointer for this association can neither be found on page 5 (lines 27 to 30) of the description, which was cited by the respondent as possible basis. Said passage mentions indeed the presence of layers, but is not limited to bi-layers, and makes a reference to the examples: "Typically, the components of the dosage form of this invention conveniently are organized in multiple layers, ordinarily a bilayer as shown in the exemplified embodiment. However, if emtricitabine is present in its own component then the dosage form will constitute at least a trilayer structure."

The examples can furthermore not be seen as a possible basis since they are limited to specific tablets characterised by a specific repartition of the amounts of excipients among the two layers, said repartition not being included in claim 1 of auxiliary request 4A.

Accordingly, auxiliary request 4A contravenes Article 76(1) EPC and Article 123(2) EPC.

5.2 Since the feature **"wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, and hydroxypropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2."** was also present in claim 1 of auxiliary request 4 and 4B in combination with the feature of a first and second layer,the same conclusions as regards Article 76(1) EPC and Article 123(2) EPC apply to these requests.

6. Auxiliary request 5 - Inventive step

6.1 Claim 1 of auxiliary request 5 relates to a method of preparing a bi-layer composition with a first layer comprising tenofovir DF and emtricitabine and a second layer comprising efavirenz and a surfactant, by preparing the first layer by dry granulation and the second layer by wet granulation, and placing both layers into stabilizing configuration.

6.2 D49 remains the closest prior art and discloses the co-formulation of Truvada® (emtricitabine and tenofovir disoproxil fumarate) and Sustiva® (efavirenz and sodium lauryl sulfate) as individually formulated layers combined together in one tablet. This document does not disclose in particular the weight amount of the active substances and the specific preparations of the first layer (tenofovir DF and emtricitabine) by dry granulation and of the second layer (efavirenz and surfactant) by wet granulation.

6.3 There does not appear to be any technical effect linked with the specific granulation methods of claim 1 of auxiliary request 5.

6.3.1 According to the respondent, the technical effect was that it was fundamentally surprising that it was possible to make a dry granulation since a priori a dry granulation would not work.

6.3.2 This argument is however not supported by any evidence. The description of the contested patent mentions only the problems linked with the manufacture of an unitary composition comprising all three drugs combined together, either by wet or dry granulation, which failed either to make a stable product, a product having the desired bioequivalence, or caused emtricitabine and tenofovir DF to dissolve in a eutectic mixture when all three drugs were wet granulated with sufficient water to granulate the low soluble efavirenz (see par. [0004]-[0007]). These problems are irrelevant in the case of a bi-layer tablet.

D42, which was also cited by the respondent in support of its arguments, does not give any further evidence as to an effect, but only mentions the difficulties to formulate tenofovir DF in view of its stickiness, or efavirenz in view of its tendency to agglomerate (see point 10); this document does however not mention or show any advantage linked with a specific way of granulation, such as dry granulation.

6.4 In absence of any unexpected or particular technical effect the choice of any one of those granulation methods is an obvious alternative.

The claimed method is indeed obvious based on D49 in combination with D28. Manufacturing a bi-layer tablet based on Sustiva® and Truvada® necessarily involves

preparing the 1st layer comprising tenofovir DF and emtricitabine, preparing the 2nd layer comprising efavirenz and a surfactant, and placing both layers into stabilizing configuration with one another.

Moreover, D29 shows the preparation of a composition comprising efavirenz and sodium lauryl sulfate by wet granulation (see claim 17) and D4 disclosed that Truvada® was also prepared by wet granulation. Since dry granulation is a well-known alternative pharmaceutical manufacturing process per se, the dry granulation of tenofovir DF and emtricitabine, (Truvada®) is a obvious alternative granulation method.

Since the high drug load was previously also found to be obvious for the main request (see point 3.6 above), it results that the claimed solution of auxiliary request 5 is obvious.

Therefore, claim 1 of auxiliary request 5 is not based on an inventive step and this request does not meet the requirements of Article 56 EPC.

7. Auxiliary request 6 - Article 123(2) EPC and Article 76(1) EPC

The subject-matter of claim 1 of auxiliary request 6 relates to a method of preparing a unitary composition with a "first layer" and a "second layer", which has been amended *inter alia* by the feature **"and wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrvstalline cellulose, sodium lauryl sulfate, and hydroxvpropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2".**

Auxiliary request 6 does not meet the requirements of Article 123(2) EPC and Article 76(1) EPC for the same reasons set out in relation to auxiliary requests 4A, 4 and 4B.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated