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Case Number: T 1590/15 - 3.3.07

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Language of the proceedings: EN

Title of invention:
Efavirenz compressed tablet formulation

Patent Proprietor:
Merck Sharp & Dohme Corp.

Opponents:
Sölch, Günter
Generics [UK] Limited (trading as Mylan)

Headword:
Efavirenz/ MSD

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Case Number: T 1590/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 25 October 2018

Appellant: (Patent Proprietor)	Merck Sharp & Dohme Corp. 126 East Lincoln Avenue Rahway, NJ 07065-0907 (US)
Representative:	Horgan, James Michael Frederic Merck & Co., Inc. European Patent Department Merck Sharpe & Dohme Limited Hertford Road Hoddesdon Hertfordshire EN11 9BU (GB)
Appellant: (Opponent 3)	Generics [UK] Limited (trading as Mylan) Building 4 Trident Place Mosquito Way Hatfield Hertfordshire AL10 9UL (GB)
Representative:	Gillard, Richard Edward Elkington and Fife LLP Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Party as of right: (Opponent 1)	Sölch, Günter Nordring 27 83624 Otterfing (DE)
Representative:	Basfeld, Rainer Fritz Patent- und Rechtsanwälte Partnerschaft mbB Postfach 1580 59705 Arnsberg (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 June 2015 concerning maintenance of the European Patent No. 1332757 in amended form.**

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
P. Schmitz

Summary of Facts and Submissions

I. Three oppositions had been filed against European Patent 1 332 757 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 and of the parent application. Opponent 2 withdrew its opposition during the opposition proceedings.

The following documents were among those cited by the parties:

D1: WO 99/51239
D2: WO 96/37457
D9: Pharmaceutical dosage forms: Tablets, Volume 1, 1980, 113-117
D10: Encyclopaedia of pharmaceutical technology, Volume 16, 1997, pages 363 and 382-390
D12: US 5,519,021.

II. The appeals of the patent proprietor (hereinafter: appellant-patent proprietor) and of opponent-3 (hereinafter: appellant-opponent) lie against the decision of the opposition division according to which the patent and the invention according to auxiliary request 4 met the requirements of the Convention. The decision was based on the patent as granted as main request, on auxiliary requests 1 and 2 filed on 25 October 2013 and on auxiliary requests 3 and 4 filed on 30 January 2015. On the latter date the appellant-patent proprietor also filed auxiliary requests 5 to 7.

Claim 1 of the patent as granted and of auxiliary request 1 read as follows:

"1. A compressed tablet comprising: efavirenz, filler/ disintegrant, superdisintegrant, binder, surfactant, a diluent/compression aid which comprises lactose, lubricant, and solvent, wherein the efavirenz is crystalline, which tablet is obtainable by a granulation process in which the superdisintegrant and disintegrant are added intragranularly and the lactose is added extragranularly and which tablet:

(i) comprises from 1 to 75% of efavirenz by weight of the total composition of the compressed tablet;

(a) providing the tablet comprises no more than 10% by weight of the total weight of superdisintegrant; or
(b) wherein the binder is a hydroxypropylcellulose; or

(ii) contains 600 mg of efavirenz in the total composition of the compressed tablet".

Claim 1 of auxiliary request 2 differed form claim 1 of the patent in that feature (ii) was amended as follows:

"...(ii) contains 600 mg of efavirenz in the total composition of the compressed tablet wherein the tablet is about 50% drug loaded."

Claim 1 of auxiliary request 3 differed form claim 1 of the auxiliary request 2 in that feature (i) was amended as follows:

"...(i) comprises from 1 to 75% of efavirenz by weight of the total composition of the compressed tablet and the process is wet granulation;"

Claim 1 of auxiliary request 4 differed form claim 1 of the auxiliary request 2 in the deletion of feature (i)(a)

Claim 1 of auxiliary request 5 differed form claim 1 of the auxiliary request 4 in that feature (i) was amended as follows:

"...(i) comprises from 1 to 75% of efavirenz by weight of the total composition of the compressed tablet and the process is wet granulation;"

Claim 1 of auxiliary request 6 read as follows:

"1. A compressed tablet comprising: efavirenz, filler/ disintegrant, superdisintegrant, binder, surfactant, a diluent/compression aid which comprises lactose, lubricant, and solvent, wherein the efavirenz is crystalline, which tablet is obtainable by a granulation process in which the superdisintegrant and disintegrant are added intragranularly and the lactose is added extragranularly and which tablet contains 600 mg of efavirenz in the total composition of the compressed tablet wherein the tablet is about 50% drug loaded."

Claim 1 of auxiliary request 7 differed from claim 1 of auxiliary request 6 in specifying that the weight of the tablet is 1200 mg and in the deletion of the feature "...wherein the tablet is about 50% drug loaded."

III. In the decision under appeal the opposition division came to the conclusion that the main request and auxiliary requests 1 to 3 did not comply with Articles 123(2) and 76(1) EPC.

The subject-matter of auxiliary request 4 was considered to comply with the requirements of the EPC. As to inventive step, the opposition division held that document D2 was the closest prior art. In its view there was no pointer for combining the teaching of this document with the teachings of documents disclosing the use of lactose extragranularly and documents disclosing the use of disintegrants and superdisintegrants intragranularly. Hence, the subject-matter of auxiliary request 4 could not be derived from the state of the art in an obvious manner.

IV. In the statement setting out the grounds of appeal sent on 2 November 2015 the appellant-patent proprietor defended its case on the basis of the same requests submitted during the oppositions proceedings.

V. Together with the statement setting out the grounds of appeal filed on 2 November 2015 the appellant-opponent submitted *inter alia* the following documents:

D24: Remington: The Science and Practice of Pharmacy, Volume II, 1995, pages 1615-1620
D27: Pharmaceutics: The Science of Dosage Form Design, 1988, pages 308-310.
D29: AIDS Clin Care, 1997, 9(10), 75-79

VI. In a communication pursuant to Article 15(1) RPBA issued on 16 August 2016 the Board commented *inter alia* on inventive step, observing that the features characterising the tablets of claim 1 of the

patent-in-suit appeared to be standard features well known in the field of tablets technology, as it was evident from the prior art documents on file. It concluded expressing the opinion that the patent did not comply with the requirements of Article 56 EPC.

VII. Opponent 1 did not make any submission during these appeal proceedings, and informed the Board with a letter dated 28 August 2017 that it would not attend the oral proceedings.

VIII. Oral proceedings were held on 25 October 2018. They were attended by both appellants.

IX. The appellant-opponent argued essentially as follows with regard to inventive step:

Document D2 provided on page 17 a generic disclosure of immediate release tablets. The tablets defined in the patent-in-suit and in the auxiliary requests differed from the tablets of D2 in that they were prepared by a granulation process. This implied a further distinguishing feature, namely the indication that the disintegrant and the superdisintegrant were within the granules whereas the lactose was outside. Example 8 of the patent described a method for preparing a compressed tablet of efavirenz according to claim 1 without providing any experimental data. The technical problem was therefore the provision of further efavirenz immediate release tablets. The use of the granulation technology for preparing tablets was disclosed for instance in documents D9 and D10. D24 to D26 described the use of disintegrants and superdisintegrants in immediate release tablets. Lactose was a commonly used excipient. The feature concerning the amount of efavirenz (600 mg) was

suggested in D29. Thus, the skilled person would have arrived at the subject-matter of all the requests in an obvious manner.

X. The appellant-patent proprietor argued essentially as follows with regard to inventive step:

The efavirenz formulation used in the clinical trials was a capsule containing the active ingredient in crystalline form. It was a challenge for the inventors to develop an efavirenz tablet bioequivalent to the capsule without affecting the stability of the crystalline form. In paragraphs [0005] and [0032] of the patent there were clear statements as to the achievement of these objectives. The appellant-opponent did not provide any counter evidence in this regard. Starting from the disclosure of document D2, the technical problem was therefore the provision of improved efavirenz tablets bioequivalent to capsules. The documents submitted by the appellant-opponent indicated that various technologies were available to produce tablets. It was also clear that there were many possibilities on how to use the various excipients. For instance, disintegrants, superdisintegrants and fillers could be added intragranularly or extragranularly. The skilled person was faced with several possibilities and there was no pointer towards the specific solution adopted in the present case. Thus, the patent met the requirements of inventive step. The same arguments and conclusion applied to the assessment of inventive step of the auxiliary requests.

XI. The appellant-patent proprietor requested that the decision under appeal be set aside and the opposition be rejected or, alternatively, that the patent be maintained according to one of auxiliary requests 1 to

7, wherein auxiliary requests 1 and 2 had been filed on 25 October 2013 and auxiliary requests 3 to 7 had been filed on 30 January 2015.

XII. The appellant-opponent requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request (patent as granted)

1. Inventive step

1.1 The invention underlying the patent-in-suit relates to efavirenz tablets obtainable by a granulation process. All the tablets included in claim 1 are characterised *inter alia* by the presence of a superdisintegrant and a disintegrant which are added intragranularly and by the presence of lactose which is added extragranularly.

The tablets covered by claim 1 (see point II above) are split in two groups as follows:

- group (i) relates to tablets comprising from 1 to 75% of efavirenz. This embodiment comprises the following two sub-groups:

  (i)(a) tablets comprising no more than 10% by weight of superdisintegrant;
  (i)(b) tablets wherein the binder is a hydroxypropylcellulose;

- group (ii) relates to tablets containing 600 mg of efavirenz.

1.2 Closest prior art

1.2.1 Both appellants consider document D2 as the closest prior art.

D2 relates to a process for the preparation of efavirenz. On page 17 (lines 4 to 8), D2 briefly describes immediate release tablets containing, in addition to the active ingredient and lactose, other excipients such as disintegrants, lubricants and binders.

The distinguishing features of the subject-matter of claim 1 over D2 are the use of granulation and the subsequent location of the disintegrant, superdisintegrant and lactose with respect to the granules. Moreover, D2 fails to indicate whether efavirenz is used in crystalline form.

1.3 Technical problem

1.3.1 Paragraph [0032] of the patent states that the tablet claimed in the patent-in-suit is bioequivalent to a capsule with a smaller dose and more bioavailable than other tablet compositions. It further states that the formulation of the invention overcomes the expected loss of crystallinity of efavirenz.

1.3.2 However, the patent does not disclose any experiment in which the tablets of claim 1 have been tested. Nor provides the description of the patent any experimental data characterising the pharmacological and chemical properties of the tablets. In particular, there are no pharmacokinetic data that could possibly be considered to assess the bioequivalence with a different

formulation or data showing the crystalline state of efavirenz.

The Board also notes that the main technical effect relied upon by the appellant-patent proprietor, namely the bioequivalence to the capsule formulation is rather vague and undefined since the description does not identify any specific capsule. This fact would also render impossible for the appellant-opponent to set up experiments to verify the assertion made in the patent. As to the effect of preventing the expected loss of crystallinity, it is noted that the description does not identify any specific crystalline form of efavirenz. There is also no indication in the description or in the prior art documents that crystallinity of efavirenz could easily be lost during the preparation of tablets.

1.3.3 According to the case law of the boards of appeal, some beneficial effects or advantageous properties to which the patent proprietor merely refers, without offering sufficient evidence, cannot be taken into consideration in determining the problem underlying the invention (Case Law of the Boards of appeal of EPO, 8th edition 2016, I.D.4.2). In other words the burden of proving that the claimed invention achieves the technical effects alleged in the description of the patent rests upon the patent proprietor. It follow from the above considerations that the technical effects alleged in paragraph [0032] of the patent cannot be taken in consideration for the formulation of the technical problem.

1.3.4 Nevertheless, having regard to the fact that the tablets contain a disintegrant and a superdisintegrant, it is reasonable to expect that they would provide a

rapid release of the active ingredient. The technical problem is therefore formulated as the provision of further efavirenz immediate release tablets.

1.4 Obviousness

1.4.1 The synthesis of efavirenz in crystalline form is disclosed in example 6 of D12. There is no indication in D12 that particular precautions need to be taken when handling crystalline efavirenz. Furthermore, the passage linking columns 17 and 18 of D12 discloses the possibility of preparing immediate release tablets. Thus, using efavirenz in crystalline form does not provide any inventive contribution to the subject-matter of claim 1.

1.4.2 The textbooks submitted by the appellant-opponent show that both the process for preparing the tablets defined in claim 1 and the excipients included in these tablets are commonly encountered in the field of tablets technology.

Indeed documents D9 (see section II, pages 113-114) and D10 (see introduction, page 363) indicate that granulation is a standard technology commonly used for the preparation of tablets. In particular, wet granulation "has been used for the longest time in the industrial production of tablets" (D10, page 363, 5th paragraph). Disintegrants and superdisintegrants are known substances used to facilitate the disintegration of tablets (see for instance D24, page 1619). When used in tablets prepared by granulation, they can be incorporated into the granules or they can be added to the granules prior to compression (D24, page 1619, paragraph bridging left and right columns). Finally, lactose is a very common excipient. In D27 (see page

309, Section "Diluents") it is explained that lactose deforms easily under pressure and as a result of this ductility, good tablets are normally produced.

1.4.3 Hence, the textbooks considered in the previous paragraph clearly indicate that the technical features characterising the tablets of claim 1, are standard features commonly adopted in the field of tablets technology. In the absence of any surprising properties linked to these features, these features do not provide any contribution to the subject-matter of claim 1.

1.4.4 The first alternative embodiment covered by claim 1 (group (i), see point 1.1 above) relates to tablets comprising from 1 to 75% of efavirenz.

D2 does not provide any restriction as to the amount of active ingredient. The Board considers that the selection of a broad range (1 to 75%), which is not linked to any particular effect, is deprived of any inventive merit. Furthermore, using less than 10% of superdisintegrant (sub-group (i)(a)) is suggested by document D24 which indicates that superdisintegrants are effective at a concentration of 2% to 4% (page 1619, left column). Document D24 on page 1618 (left column heading "Cellulosic solutions") also teaches the use of hydroxypropylcellulose as binder (sub-group (i)(b)). Thus, groups (i)(a) and (i)(b) are not inventive.

1.4.5 The second alternative embodiment of claim 1 (group (ii), see point 1.1 above) concerns tablets containing 600 mg of efavirenz. In this regard it is noted that table 1 of document D29 (page 2) reports that 600 mg is the daily dosage of efavirenz. In the Board's view, a person skilled in the art would in principle consider to include the entire daily dose of active ingredient

in a tablet, in the absence of any indication that this may involve some technical difficulties or it may result in some side effects. Thus, also group (ii) of claim 1 does not involve an inventive activity.

1.4.6 The Board agrees with the appellant-patent proprietor that the skilled person seeking to solve the problem of providing efavirenz tablets would be confronted with several possibilities in terms of suitable processes and excipients. It furthermore agrees that the information leading to the subject-matter of claim 1 is disclosed in different prior art documents.

However, these facts alone cannot justify the presence of an inventive activity in a case in which there is no evidence of particular effects or advantages deriving from the specific combination of features of claim 1, and there is no evidence of particular technical problems that it was necessary to overcome in order to prepare the tablets of claim 1. Indeed, the choice of specific processes or ingredients among those commonly known to the skilled person is an arbitrary one and is deprived of any inventive activity if, having regard to the absence of any particular technical effects, the objective technical problem is simply defined as the provision of further compositions or processes. This conclusion is in principle independent on how many alternatives (processes or ingredients) are disclosed in the prior art.

It follows that the subject-matter of claim 1 does not meet the requirements of Article 56 EPC.

Auxiliary requests 1 to 7

2. The appellant-patent proprietor did not submit any argument in relation to these requests. For the reasons explained below, the Board considers that the arguments and conclusion set out in respect to the main request apply also to the subject-matter of the auxiliary requests:

2.1 Claim 1 of auxiliary request 1 is identical to claim 1 of the main request.

2.2 In claim 1 of auxiliary request 2 group (i) is identical to group (i) of the main request and is therefore obvious.

In group (ii) it is specified that the tablet is about 50% drug loaded. There is however no evidence of particular effects or advantages linked to this specific value of drug loading. Nor is there any indication of particular difficulties to be overcome in order to prepare tablets with this specific drug loading. Since document D2 does not provide any restriction in this regard, in the Board's view the skilled person would consider preparing tablets containing 50% by weight of efavirenz. Thus, also group (ii) of claim 1 is obvious.

2.3 In claim 1 of auxiliary requests 3 to 5, group (ii) is identical to group (ii) of claim 1 of auxiliary request 2. Thus, these requests are obvious at least because they include this obvious embodiment.

2.4 Claim 1 of auxiliary request 6 is identical to group (ii) of auxiliary request 2 and is therefore obvious.

2.5 Claim 1 of auxiliary request 7 specifies that the tablet comprises 600 mg of efavirenz in a 1200 mg compressed tablet. Thus, the subject-matter of this request is equivalent to the subject-matter of group (ii) of auxiliary request 2, which indicates that the tablet comprises 600 mg of efavirenz and is about 50% drug loaded. Thus, auxiliary request 7 is not inventive for the same reasons as given above with regard to embodiment (ii) of auxiliary request 2.

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:

S. Fabiani J. Riolo

Decision electronically authenticated