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Datasheet for the decision of 8 January 2019

Case Number: T 0293/16 - 3.3.07

Application Number: 06787716.7

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Language of the proceedings: EN

Title of invention:
Sustained release of antiinfective aminoglycosides

Patent Proprietor:
Insmed Incorporated

Opponent:
Generics [UK] Limited

Headword:
Aminoglycosides/ INSMED

Relevant legal provisions:
EPC Art. 56, 111(1)
RPBA Art. 13(1)

Keyword:

Inventive step - Main and auxiliary requests 1 to 3 (no)
Late-filed auxiliary request - admitted (yes)
Remittal to the department of first instance - (yes)

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Case Number: T 0293/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 January 2019

Appellant: (Opponent)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Elkington & Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Insmed Incorporated 10 Finderne Ave, Building 10 Bridgewater, NJ 08807-3365 (US)
Representative:	CMS Cameron McKenna Nabarro Olswang LLP Cannon Place 78 Cannon Street London EC4N 6AF (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 27 November 2015 concerning maintenance of the European Patent No. 1909759 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	Y. Podbielski

Summary of Facts and Submissions

I. European Patent 1 909 759 was opposed on the grounds that its subject-matter lacked novelty and inventive step and extended beyond the content of the application as filed. The following documents were among those cited during the first-instance proceedings:

D8: WO 03/075890
D10: Declaration of Mr Leserman dated 14 January 2015

II. The opposition division held that the patent and the invention to which it related according to auxiliary request 2 met the requirements of the Convention. The decision was based on a main request and two auxiliary requests filed on 18 September 2015.

This decision was appealed by the opponent (hereinafter "the appellant").

III. Claim 1 of the request considered by the opposition division to comply with the requirements of the EPC read as follows:

"1. A lipid antiinfective formulation comprising amikacin and a lipid formulation, wherein the weight ratio of lipid to amikacin is 0.75:1 or less, the lipid formulation comprises a phospholipid and a sterol and the lipid formulation is a liposome."

Independent claim 8 related to a method for preparing the formulation of claim 1.

IV. The opposition division held that the main request and auxiliary request 1 did not comply with the requirements of Article 123(2) EPC.

Claim 1 of auxiliary request 2 was considered to comply with Article 123(2) EPC and was novel over D8 in view of the requirement that the weight ratio of lipid to amikacin was 0.75:1 or less. As to inventive step, the opposition division held that the technical effect associated with the distinguishing feature was a reduction of the lipid burden, a faster nebulization and in increased drug concentration. The technical problem over document D8 was therefore the provision of an improved formulation comprising amikacin, a phospholipid and a sterol. D8 disclosed a weight ratio of lipid to amikacin of 1:1 and did not indicate that this ratio could be further lowered. The subject-matter of auxiliary request 2 was therefore inventive.

V. With the statement setting out the grounds of appeal filed on 7 April 2016 the appellant requested that the decision under appeal be set aside and the patent be revoked.

VI. The patent-proprietor (hereinafter: the respondent) replied to the appeal of the opponent by letter of 19 August 2016. It requested to dismiss the appeal (i.e. to maintain the patent on the basis of the set of claims held allowable by the opposition division) and filed three auxiliary requests. Claim 1 of auxiliary requests 1 to 3 read as follows:

Auxiliary request 1:

"1. A lipid antiinfective formulation comprising amikacin and a lipid formulation, wherein the weight ratio of lipid to amikacin is 0.75:1 or less, the lipid formulation comprises dipalmitoylphosphatidylcholine

(DPPC) and cholesterol and the lipid formulation is a liposome."

Auxiliary request 2:

"1. A lipid antiinfective formulation for use in administration by inhalation to treat a pulmonary infection in a patient, wherein the formulation comprises amikacin and a lipid formulation, wherein the weight ratio of lipid to amikacin is 0.75:1 or less, the lipid formulation comprises dipalmitoylphosphatidylcholine (DPPC) and cholesterol and the lipid formulation is a liposome."

Auxiliary request 3:

"1. A lipid antiinfective formulation for use in administration by inhalation to treat a pulmonary infection in a patient, wherein the formulation comprises amikacinand *(sic)* a lipid formulation, wherein the weight ratio of lipid to amikacin is 0.75:1 or less, and the lipid formulation comprises dipalmitoylphosphatidylcholine (DPPC) and cholesterol, the lipid formulation is a liposome and the dosing schedule is once a day or less."

VII. In a communication pursuant to Article 15(1) RPBA issued on 25 October 2018, the Board expressed the preliminary opinion that the main request complied with the requirements of Rule 80 EPC and Articles 123(2) and 54 EPC. It furthermore observed in relation to the assessment of inventive step that claim 1 covered also compositions comprising non-encapsulated amikacin. It was therefore not clear whether the respondent's arguments as to the absence of known methods for preparing the compositions of claim 1 applied also to

the preparation of compositions wherein a large portion of amikacin was not encapsulated in the liposomes.

VIII. By letter of 16 November 2018 the respondent submitted inter alia the following documents:

D19: Liposome technology - Entrapment of dugs and other materials (1992)
D21: Declaration of Mr Leserman dated 16 November 2018

IX. Oral proceedings were held on 8 January 2019. In the course of these proceedings the respondent submitted a new set of claims as auxiliary request 4.

Claim 1 of this request read as follows:

"1. A method of preparing a lipid antiinfective formulation comprising amikacin and a lipid formulation, wherein the weight ratio of lipid to amikacin is 0.75:1 or less, the lipid formulation comprises a phospholipid and a sterol, and the lipid formulation is a liposome, the method comprising: mixing a stream of a lipid solution or mixture, with a stream of an amikacin solution or mixture, wherein the two streams are mixed in line."

X. The appellant's arguments, as far as relevant to the present decision, can be summarised as follows:

(a) Inventive step

Claim 1 of the main request did not require the amikacin to be encapsulated in the liposomes. The weight ratio 0.75:1 simply defined the proportion between amikacin and lipid, no matter whether amikacin was encapsulated in the liposomes or not. This

interpretation was in line with the general teaching of the patent and technically made sense. Indeed, liposome formulations containing part of the active ingredients outside of the liposomes were disclosed for instance in D19. The composition of claim 1 differed from those disclosed in D8 only in a lower ratio of lipid to amikacin. Any advantage arising from this distinguishing feature, such as a lower lipid burden, was an obvious consequence of decreasing the lipid to amikacin ratio. D8 specifically suggested lowering the lipid portion. This did not imply any technical difficulty considering that a large amount of amikacin could remain outside of the liposomes. Thus, a skilled person could simply follow the encapsulation process of D8 and then add further free amikacin to obtain the desired lipid to amikacin ratio. Hence, claim 1 was obvious over D8. The same arguments and conclusions applied to the subject-matter of claim 1 of auxiliary requests 1 to 3.

(b) Admittance of auxiliary request 4

The appellant's arguments concerning the interpretation of the product claims were already included in the statement setting out the grounds of appeal. Hence, the respondent should have submitted a request limited to process claims at an earlier stage of the proceedings. Accordingly, auxiliary request 4 was not to be admitted into the proceedings.

XI. The respondent's arguments, as far as relevant to the present decision, can be summarised as follows:

(a) Inventive step

The gist of the patent-in-suit was to provide high loaded liposomes. It was therefore clear that the weight ratio recited in claim 1 was to be determined by considering only the amount of amikacin encapsulated in the liposomes. Free amikacin, if present, was not considered for determining the ratio. This interpretation was confirmed in various passages of the description. As explained by Mr Leserman in his declarations (D10 and D21), document D8 did not disclose any suitable method for preparing high-loaded liposomes satisfying the requirement of having a weight ratio of lipid to amikacin of 0.75:1 or less. Hence, the skilled person would not have been able to provide the formulation according to claim 1. The main request was therefore inventive. The same arguments applied to the subject-matter of auxiliary request 1.

Claim 1 of auxiliary request 2 related to formulations for use in administration by inhalation. Claim 1 of auxiliary request 3 further indicated that the dosing schedule was once a day or less. It was clear from the description that the formulations defined in these claims did not contain any free amikacin. Thus, in respect to these claims the weight ratio of claim 1 could only relate to the encapsulated amikacin.

(b) Auxiliary request 4

This request derived from the deletion of claims 1 to 7 from the main request. Hence, the filing of this request did not introduce any new issue and did not increase the complexity of the case. Auxiliary request 4 was therefore admissible.

XII. The appellant requested that the decision under appeal be set aside and the patent be revoked. The appellant further requested not to admit auxiliary request 4 into the appeal proceedings.

XIII. The respondent requested that the appeal be dismissed and the patent be maintained on the basis of the set of claims held allowable by the opposition division (main request), or, as an auxiliary measure, that the patent be maintained on the basis of one of auxiliary requests 1-3 filed on 19 August 2016 or auxiliary request 4 filed in the course of the oral proceedings before the Board.

Reasons for the Decision

Main request

1. Inventive step

The invention underlying the patent in suit concerns a liposomal formulation containing amikacin as active ingredient. As explained in paragraph [0004] of the description a common objective pursued in the field of liposomal drug delivery systems is to lower the lipid to drug ratio as much as possible.

1.1 Closest prior art

1.1.1 In agreement with the decision under appeal, the parties consider document D8 as the closest prior art. The Board sees no reason to differ.

1.1.2 D8 relates to a method of entrapment of a bioactive agent in a liposome or in a lipid complex (page 2,

lines 6 to 9). Specific methods for preparing liposomal formulations comprising amikacin as active ingredient are disclosed in examples 1 and 1a to 1d. Data concerning the weight ratio of lipid to amikacin are provided in Figure 3 (concerning example 1a) and Table 2 (concerning example 1c). In all these cases the ratio is greater than 0.75:1. The ratio for the composition of example 1d (calculated by the appellant) is also greater than 0.75:1, namely 1:1. Thus, the formulation of claim 1 of the main request differs from the formulations of D8 in the requirement that the ratio of lipid to amikacin is 0.75:1 or less.

1.2 Technical problem

1.2.1 The patent does not contain any experiment comparing the formulation of claim 1 with those of D8. It is nevertheless credible that reducing the ratio of lipid to active ingredient results in a reduction of the lipid burden, as claimed by the respondent. The technical problem is therefore defined as the provision of a liposome formulation comprising amikacin that results in a lower lipid burden.

1.3 Obviousness

1.3.1 It is self-evident that reducing the ratio of lipid to drug results in a reduction of the lipid burden. Moreover, providing compositions with a decreased lipid to active ingredient ratio is also the purpose of D8 (see page 8, lines 25 to 29). Hence, an inventive step cannot be based on the mere idea of providing a liposome composition with a reduced lipid to drug ratio.

1.3.2 However, the main argument of the respondent in support of an inventive step over D8, is that the skilled person would not be able to provide a liposome formulation wherein the weight ratio of lipid to encapsulated amikacin is 0.75:1 or less. In this regard it refers to the declaration of Mr Leserman (document D10) according to which it would not be possible to prepare such an amikacin formulation by the methods disclosed in D8. Only by the use of the "in-line" infusion method described in the patent (paragraph [0100]) was it possible to achieve the lipid to amikacin ratio set forth in claim 1.

1.3.3 In this regard the Board concurs with the appellant that neither claim 1 nor any other part of the patent indicates that the lipid to amikacin weight ratio is to be calculated by considering only the encapsulated amikacin, i.e. by disregarding the amount of amikacin outside of the liposomes, as argued by the respondent. Indeed, claim 1 defines a composition containing amikacin and a lipid formulation in the form of liposomes and indicates that "the weight ratio of lipid to amikacin is 0.75:1 or less". The weight ratio is therefore independent from the degree of amikacin encapsulation and the claim is not limited to formulations wherein a minimum amount of amikacin is encapsulated. Excluding from the calculation of the weight ratio the amount of amikacin which is outside of the liposomes would amount to attributing to said ratio a meaning which is not supported by the wording of claim 1.

1.3.4 In this context the Board observes that it follows from the description of the patent that the largest part of the amikacin included in the formulation can be outside of the liposomes. According to paragraph [0057] of the

description a lipid antiinfective formulation in the form of liposomes is a composition wherein at least 1% of the active ingredient is in the liposomes. According to the preferred embodiment at least 25% of the active ingredient is in the liposomes. The Board also notes that liposome formulations wherein the active ingredient is only partially encapsulated are known in the art (e.g. D19, page 312 last paragraph). As explained by the appellant such formulations may provide an immediate (non-encapsulated part) and delayed (encapsulated part) release of the drug.

1.3.5 Having regard to the fact that even 99% of amikacin may be outside of the liposomes (see point 1.3.4 above), it is not clear why only the small amount of encapsulated drug should be taken into account in determining the weight ratio of claim 1, as argued by the respondent. There is no indication in the patent that from the total amount of amikacin included in the formulation one has to subtract the amount outside of the liposomes before calculating the lipid to amikacin weight ratio.

In his second declaration (document D21) Mr Leserman refers to a note at the end of Table 10 of the patent which indicates that only the entrapped amount of amikacin was considered in calculating the lipid to drug weight ratio. In this regard it is observed that this ratio is reported also in other tables such as Tables 2 and 6. None of these tables however, contains the same note as Table 10. Thus, this note appears to indicate that, in contrast to the measurements performed and described in other part of the description, in Table 10 the lipid to drug weight ratio has been calculated only by considering the encapsulated drug.

1.3.6 To summarise, the Board considers that claim 1 covers formulations wherein (a relevant) part of amikacin is outside of the liposomes. Both the encapsulated and the non-encapsulated part of amikacin are to be considered in the calculation of the weight ratio recited in claim 1.

1.3.7 The Board sees no reason why the skilled person would not be able to prepare an amikacin formulation as defined in claim 1 of the main request. In this respect it agrees with the appellant that the skilled person could apply the process disclosed in the examples of D8 and then decrease the lipid to drug weight ratio by adding further free (i.e. non-encapsulated) amikacin.

In document D10, Mr Leserman explains that the liposomes in D8 are prepared by passive encapsulation, a method that would not allow to obtain a weight ratio of lipid to amikacin of 0.75:1 or less (paragraph 36). It is however clear from the further declaration of Dr Leserman (document D21) that the lipid to drug ratio referred to in D10 is calculated only by considering the encapsulated amikacin (paragraph 6). As explained above (see point 1.3.6), the weight ratio recited in claim 1 is determined by considering both the encapsulated and the non-encapsulated part of amikacin. Hence, the conclusions of Mr Leserman do not cast doubt on the possibility of preparing a formulation as defined in claim 1.

1.4 The subject-matter of claim 1 of the main request therefore does not comply with the requirements of Article 56 EPC.

Auxiliary request 1

2. Claim 1 of auxiliary request 1 specifies that the lipid formulation comprises dipalmitoylphosphatidylcholine (DPPC) and cholesterol.

2.1 DPPC and cholesterol are present also in the lipid formulations used in D8 (see examples 1a to 1d). Hence, the limitations introduced in claim 1 of auxiliary request 1 do not provide any inventive contribution over D8. Accordingly this request does not comply with Article 56 EPC either.

Auxiliary requests 2 and 3

3. Claim 1 of auxiliary request 2 relates to the lipid formulation of claim 1 of auxiliary request 1 "for use in administration by inhalation to treat a pulmonary infection in a patient" (see point VI above).

Claim 1 of auxiliary request 3 differs from claim 1 of of auxiliary request 2 in specifying that the dosing schedule is once a day or less (see point VI above).

3.1 In respect to both requests the respondent submitted the argument that it was clear, on the basis of the teaching of the description, that the formulations for use in administration by inhalation to treat pulmonary infections referred to in these requests did not contain any free (i.e. non-encapsulated) amikacin. In this regard it referred to page 21 of the description.

3.2 Page 21 of the description (lines 10 to 18) mentions some studies wherein an amikacin formulation has been tested in an animal model to mimic the pseudomonas infection seen in cystic fibrosis patients. Although

the expression "liposomal amikacin" is used in this passage, there is no clear indication that the formulations do not contain any free amikacin. Furthermore, there does not appear to be in any other part of the description a link between the subject-matter of auxiliary requests 2 and 3 and the requirement that the formulations do not contain any free amikacin. Finally and more importantly, claim 1 does not contain any limitation in this regard.

Hence, the respondent's argument is not convincing.

3.3 Thus, the arguments and conclusions put forward with respect to the main request and auxiliary request 1 also apply to claims 1 of the auxiliary requests 2 and 3. Therefore, these requests do not comply with Article 56 EPC.

Auxiliary request 4 - Admittance

4. Claim 1 of auxiliary request 4 relates to a method for preparing the lipid antiinfective formulation defined in claim 1 of the main request. In essence, it corresponds to claim 8 of the main request (the wording is not identical because claim 1 of auxiliary request 4 incorporates the definition of the formulation whereas claim 8 of the main request refers back to claim 1). Dependent claims 2 to 17 correspond to dependent claims 9 to 24 of the main request.

4.1 Thus, the subject-matter of auxiliary request 4 is entirely incorporated in the main request, i.e. a request that was filed during the proceedings before the opposition division and maintained throughout the appeal proceedings.

Accordingly, the filing of auxiliary request 4 does not increase the complexity of the case. In contrast, it limits the scope of the examination to the process claims. The fact that these claims had not been discussed before the filing of auxiliary request 4 is primarily due to the choice of the appellant to focus its objections on the product claims. However, this circumstance cannot penalize the respondent.

4.2 For these reasons, the Board, in the exercise of its discretion pursuant to Article 13(1) RPBA, decides to admit auxiliary request 4 into the appeal proceedings.

5. Remittal

5.1 The primary function of an appeal is to consider whether the decision issued by the first-instance department is correct. Hence, a case is normally remitted if essential questions regarding the patentability of the claimed subject-matter have not yet been examined and decided by the department of first instance.

5.2 These observations fully apply to the present case. The opposition division came to the conclusion that the subject-matter of claim 1 of auxiliary request 2 (current main request) was novel and inventive. This implied that claim 8 of the same request, concerning a process for preparing the formulations of claim 1, was also novel and inventive. As explained above, said claim 8 is essentially identical to claim 1 of current auxiliary request 4 (see point 4 above).

Contrary to the opposition division, the Board in the present decision came to the conclusion that the formulations defined in claim 1 of the current main

request do not involve an inventive activity (see point 1 above). This means that claim 1 of auxiliary request 4 relates to a process for preparing a non-inventive product.

The patentability of auxiliary request 4 depends therefore on the assessment of the process steps leading to the preparation of the amikacin formulation. However, this assessment has not been made during the first instance proceedings.

5.3 Under these circumstances the Board considers it appropriate to remit the case to the opposition division for further prosecution (Article 111(1) EPC). This conclusion was agreed upon by the parties during the oral proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated