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Datasheet for the decision of 22 July 2015

Case Number: T 0970/12 - 3.3.02

Application Number: 09166600.8

Publication Number: 2111855

IPC: A61K9/12, A61K31/496, A61K31/7036, A61P11/00

Language of the proceedings: EN

Title of invention:
Antibacterial compositions for the treatment of infections of the upper and lower airways

Applicant:
CHIESI FARMACEUTICI S.p.A.

Headword:
Inhalation formulations of hypertonic solution containing hyaluronic acid/CHIESI FARMACEUTICI

Relevant legal provisions:
EPC Art. 52(1), 54(2), 56, 76(1), 108, 110, 122(1)
EPC R. 101(1), 136(1)
RPBA Art. 15(1)

Keyword:
Re-establishment of rights (yes)
Admissibility of appeal (yes)
Main request filed at appeal: allowable (yes)

Decisions cited:
T 0387/11

Catchword:

Europäisches Patentamt
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Case Number: T 0970/12 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 22 July 2015

Appellant: (Applicant)	CHIESI FARMACEUTICI S.p.A. Via Palermo, 26/A 43100 Parma (IT)
Representative:	Minoja, Fabrizio Bianchetti Bracco Minoja S.r.l. Via Plinio, 63 20129 Milano (IT)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 14 December 2011 refusing European patent application No 09166600.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	U. Oswald
Members:	M. C. Ortega Plaza
	L. Bühler

Summary of Facts and Submissions

I. The present appeal lies from a decision of the examining division refusing European patent application No. 09166600.8, published as EP 2111855, under Article 97(2) EPC. The application was filed as a divisional application of European patent application No. 07007272.3, published as EP 1847256 (parent application).

II. The following documents *inter alia* have been cited during the examination and appeal proceedings:

D1 WO 95/26735
D2 G. Petrigni, L. Allegra, Pulmonary Pharmacology & Therapeutics 19, 166-171, available online January 2006
D6 M. R. Elkins et al., N Engl J Med, 354(3), 229-240, January 2006
D9 P. Buonpensiero et al., Adv Ther, 27(11), 1-9, 2010

III. The examining division's decision is based on a main request (which is the set of claims as filed) and an auxiliary request filed with the letter of 11 October 2011 together with an amended page 4 of the description.

Claim 1 of the main request before the examining division read as follows:

"1. Inhalation compositions in the form of sterile monodose ampoules of 5-7% hypertonic solution containing hyaluronic acid or a salt or ester thereof with a low molecular weight or an intermediate

molecular weight at a concentration of between 0.01% and 1%."

IV. The examining division considered that the main request and the auxiliary request did not meet the requirements of Article 76(1) EPC.

The examining division was of the opinion that the parent application as filed related to *"the combined use of antibiotics and hyaluronic acid in a hypertonic solution"* and that the presence of antibiotics in the formulations was *"an essential feature"* of the invention. Moreover, it considered that the examples illustrated the combined use with antibiotics, either simultaneously in a single formulation or as a kit-of-parts. Thus, in the examining division's opinion, the ampoules of hypertonic saline solutions with hyaluronic acid in examples 16 and 17 were to be understood in the context of example 18, which related to a kit-of-parts.

V. The appealed decision was sent to the applicant on 14 December 2011. On 6 April 2012 the applicant filed a request for re-establishment into the time limit for filing an appeal against the aforementioned decision. The fee for re-establishment of rights was paid and the omitted act completed on the same day by means of the filing of a notice of appeal and a statement of grounds of appeal and the payment of the appeal fee.

With its grounds of appeal the appellant requested that a patent be granted on the basis of the set of claims as initially filed (main request) or, alternatively, on the basis of the auxiliary request filed with letter of 11 October 2011 together with amended page 4 of the description (it also filed a copy of the auxiliary

request and the amended page of the description with its grounds of appeal).

VI. The board sent a communication to the applicant on 1 August 2013. The communication dealt with the issue of admissibility of the appeal, which hinged on the allowability of the request for re-establishment of rights. The board expressed a preliminary opinion in this respect and asked for clarification of the concrete circumstances.

VII. With a letter dated 18 September 2013 a response to said board's communication was filed. With its response the applicant's representative provided further arguments and evidence concerning the issue of re-establishment of rights.

VIII. The board sent a communication pursuant to Article 15(1) RPBA on 6 June 2014.

In said communication the board summarised the facts on file in relation to the request for re-establishment of rights and expressed its preliminary opinion on the substance of the appeal in case the appeal were to be considered admissible. It also referred *inter alia* to documents D1, D2 and D6.

The board made a detailed analysis in relation to added subject-matter for the main request and the first auxiliary request (including amended page 4 of the description). It also expressed a positive preliminary opinion in relation to novelty over documents D1 and D2.

IX. With a letter dated 24 October 2014 the appellant filed a reply to the board's communication. It filed as

annexes therewith two auxiliary requests (second and third), document D9 and a further document.

X. The oral proceedings scheduled for 25 November 2014 were cancelled. Summons to attend oral proceedings on 22 July 2015 were sent on 16 April 2015.

XI. Oral proceedings were held on 22 July 2015.

During the oral proceedings the appellant filed a new main request (containing three claims) and amended pages 4 and 5 of the description.

XII. Claim 1 of the main request reads as follows:

"1. Inhalation formulations in sterile monodose ampoules of 5-7% hypertonic solution containing hyaluronic acid or a salt or ester thereof with a low molecular weight or an intermediate molecular weight at a concentration of between 0.01% and 1%."

Claim 1 of the main request differs from claim 1 of the application as filed in that the expression "compositions" has been replaced by "formulations" and in that the expression "in the form of sterile monodose ampoules" has been replaced by "in sterile monodose ampoules".

XIII. The appellant's submissions, as far as relevant for the present decision, may be summarised as follows:

Re-establishment of rights

With respect to the request for re-establishment of rights, the appellant submitted that, on the day of notification of the decision under appeal, that is, on

27 December 2011, its representative had left the office unexpectedly since he had been informed that his mother's health had suddenly deteriorated. The experienced assistant previously in charge of monitoring dates and time limits was no longer at the office due to his early retirement on 16 December 2011, which had initially been planned for 31 December 2011. The new assistant was still in the period of training. She could not get any advice from any professional representative of the association because they were out of office in keeping with the turns of work (the appellant used the expression "*alternation*") planned for the Christmas and New Year holiday. The assistant, who was not familiar with the case, erroneously believed that the sub-authorised professional representative who had been present at the oral proceedings before the department of first instance was in charge of monitoring the time limits for the appeal. She therefore did not register any time limit for this decision.

Unexpectedly, on 28 December 2011, the representative's mother died. The appellant's representative returned to the office on Friday, 30 December 2011 and was subsequently out of the office from 2 January 2012 onwards. The bereavement caused him to suffer considerable psychological stress. He therefore did not take note of the contested decision which had led to the inadvertent omission of the recording of the time limits for filing an appeal. On 13 March 2012, the sub-authorised professional representative drew the representative's attention to the missing appeal, thereby removing the cause of non-compliance with the time limits for filing an appeal.

Main request

The parent application as originally filed described inhalation formulations with antibiotics as a first aspect of the invention (page 4, lines 18 to 23) and inhalation formulations without antibiotics as a further aspect of the invention (page 4, line 27 to page 5, line 6). Additionally, inhalation formulations without antibiotics were described in examples 17 and 18. Moreover, the wording of claim 1 of the main request found literal support in the text in the first paragraph on page 6 of the parent application as filed.

The description was amended in order to avoid discrepancies with the wording of claim 1 of the main request, especially in relation to the definition of hyaluronic acid and its molecular weight.

Document D6, disclosing 7% hypertonic saline solutions used for the treatment of cystic fibrosis, represented the closest prior art. The subject-matter claimed in the main request differed from the disclosure of document D6 in that hyaluronic acid was added to the inhalation solution in order to improve the tolerability of the treatment. The problem solved by the claimed invention addressed the patient compliance of inhalation formulations of hypertonic saline solutions, which were irritative. The post-published document D9 confirmed that the addition of hyaluronic acid to a hypertonic saline solution improved the pleasantness and tolerability of the treatment.
None of the other cited prior art documents provided a disclosure or suggestion for the addition of hyaluronic acid to a hypertonic saline solution. The subject-matter of the main request was thus inventive.

XIV. The following requests are on file:

The appellant requested that it be re-established in the time limit for filing the notice of appeal, that the decision under appeal be set aside, and that a patent be granted on the basis of the main request filed during the oral proceedings of 22 July 2015 and the description as amended during the oral proceedings of 22 July 2015.

Reasons for the Decision

1. Re-establishment of rights and admissibility of the appeal

1.1 The time limit for filing the notice of appeal under consideration expired on 27 February 2012. On 13 March 2012, that is 14 days after the expiry of the time limit for filing the notice of appeal, the representative's attention was drawn to the fact that no appeal had been filed. Thereby the cause of non-compliance with the time limits for filing an appeal was removed. The request for re-establishment was filed on 6 April 2012, that is less than two months after discovery of the omission and of the expiry of the time limit for filing the appeal. Therefore, the time limits pursuant to Rule 136(1) EPC have been observed. The board is also satisfied that the other conditions for admissibility of the request for re-establishment are fulfilled.

1.2 Pursuant to Article 122(1) EPC a request may be granted if the time limit has been missed in spite of all due care required by the circumstances having been taken.

1.3 In the board's judgement, the circumstances leading to the omission were exceptional and the appellant's representative found himself in an extraordinary situation that hindered him on his return to the office on 30 December 2011 and after his leave beginning on 2 January 2012 from paying attention to the notification of the contested decision on 27 December 2011. As a consequence, he was unaware of the time limits for the appeal and unable to make arrangements for meeting them (cf. decision T 387/11 of 6 July 2012).

1.4 In the light of the evidence provided it is credible that the appellant's representative suffered considerable psychological stress at the end of December 2011 and in January 2012, subsequent to the sudden death of his mother. Moreover, on the day of notification of the contested decision, that is on 27 December 2011, the representative left the office in the morning since he had been informed that his mother's health had suddenly deteriorated. The experienced assistant previously in charge of monitoring dates and time limits had retired early and was no longer at the office at that time. The new assistant was still in the training period. She could not seek advice from any of the four other professional representatives of the association because they were on leave in keeping with the turns of work planned for the Christmas and New Year holiday. The assistant erroneously believed that the sub-authorised professional representative, who had represented the appellant at the oral proceedings before the examining division, was in charge of monitoring the time limit for appeal. The circumstances were thus exceptional: No professional representative was present and the newly appointed assistant had no experience in handling

incoming notifications of decisions, even though she had worked for some time at the office in another function. Moreover, it was not apparent to her from the file who had the responsibility for the appeal, since the sub-authorisation that had been given to the professional representative in Munich was not expressly limited to the representation at the oral proceedings before the examining division and there was no information in the verbal arrangement between the two representatives involved that the sub-authorisation was not intended to change responsibility for the appeal. In view of the considerable psychological stress due to his sudden bereavement, the appellant's representative could not be reasonably expected to become aware of the notification of the contested decision during his short presence at the office on 30 December 2011 and immediately after his return from leave in January 2012. In the board's judgment, this extraordinary situation persisted, so the appellant's representative could not have been expected to note the omission before receipt of an email on 13 March 2012 from the sub-authorised professional representative drawing his attention to the missing notice of appeal.

1.5 For the above reasons, the board allowed the request for re-establishment of rights.

2. Main request

2.1 Added subject-matter

2.1.1 The present application is a divisional application and therefore the provisions expressed in Article 76(1) EPC in relation to the content of the earlier application (parent application as filed) have to be examined.

2.1.2 Claim 1 of the main request is a product claim, which relates to:

(i) inhalation formulations
(ii) in sterile monodose ampoules of 5-7% hypertonic solution containing
(iii) hyaluronic acid or a salt or ester thereof with low molecular weight or an intermediate molecular weight at a concentration of between 0.01% to 1%.

2.1.3 A *verbatim* basis for claim 1 of the main request can be found on page 6, first paragraph, of the parent application as filed, with the exception of the expression "inhalation" before the term "formulations".

Hence, it has to be investigated whether or not the above-mentioned passage on page 6 of the parent application as filed refers to inhalation formulations, i.e. to formulations suitable for inhalation.

The generic disclosure in the parent application as filed refers to the administration of several formulations containing *inter alia* hyaluronic acid as being "by inhalation (nasal administration or administration in the upper airways) or bronchial administration" (page 4, lines 19 to 21). Furthermore, the parent application as filed specifies that "The invention also allows treatment of patients who have to discontinue antibiotic treatment of the lower airways by inhalation due to bronchial intolerance" (page 4, lines 27-28 and page 5, line 1). This disclosure is immediately followed on page 5 by the following: "It has also been found that the administration of a hypertonic solution, associated with hyaluronic acid or its salts, leads to better tolerability, with a reduction in the inflammatory component affecting the

mucosa of the airways, a lower risk of discontinuance of the treatment, and better compliance by patients" (page 5, lines 2 to 6). Therefore, the administration mentioned in this passage is to be understood within the context of the description, so that the hypertonic solutions containing hyaluronic acid according to the "invention" have to be suitable for administration by inhalation. This teaching directly and unambiguously applies to the formulations explicitly disclosed in the first paragraph of page 6, which also mentions esters of hyaluronic acid in addition to salts thereof. Moreover, the second and fifth paragraphs on page 6, which explicitly mention that the formulations are rendered suitable for administration by aerosols, confirm that the formulations in the first paragraph on page 6 which are suitable for inhalation are disclosed in the parent application as filed.

That the whole parent application describes inhalation formulations (i.e. suitable for inhalation), irrespective of whether or not they also contain an antibiotic, is also supported by the examples of the parent application as filed. In fact, the parent application as filed does not disclose other kinds of formulations such as injection formulations or oral liquid formulations.

Examples 16 and 17 of the parent application as filed illustrate inhalation formulations in disposable ampoules of hypertonic solutions of hyaluronic acid without antibiotics as those generically disclosed in the first paragraph on page 6. The description of the specific products in examples 16 and 17 is not restricted to their use in a kit-of-parts mode as in example 18, but corresponds to the sterile monodose

ampoules of the first paragraph on page 6 of the parent application as filed and of claim 1 of the main request.

The parent application as filed describes two different aspects of the "invention", the first one relating to inhalation formulations comprising a hypertonic solution, hyaluronic acid and an antibiotic (page 4, lines 18 to 23) and the second to inhalation formulations comprising a hypertonic solution and hyaluronic acid (page 4, line 27 to page 5, line 6). The technical teaching on pages 5, 6 and examples 16 and 17 is not restricted to the use of the formulations with an antibiotic in the form of a kit-of-parts product, but it provides an allowable basis for a separate product claim such as claim 1 of the main request.

2.1.4 Therefore, claim 1 of the main request does not contain added subject-matter. Additionally, dependent claim 2 relates to the preferred mode defined on page 6, lines 4 and 5 of the parent application as filed, and the nasal route is also mentioned in the parent application as filed as the administration route for the upper airways.

2.1.5 Page 4 of the description has been amended in order to acknowledge the prior art which was generally cited as background (Rule 42(1(b)) EPC). Additionally, deletion of the redundant word "patient" has also been undertaken in line 23.

2.1.6 The amendments undertaken on page 5 of the description were introduced as a direct reply to an objection of lack of consistency between the claims and the description raised by the board under Article 84 EPC.

These amendments do not introduce added subject-matter, since they merely delete definitions concerning some "preferred" ranges for the molecular weight of hyaluronic acid. Additionally, the specification of the units as Da on page 5 derives directly and unambiguously from the content of page 6 of the parent application as filed. The board accepts the appellant's submission that the terms "low molecular weight" and "intermediate molecular weight" are employed in claim 1 in relation to the well-known hyaluronic acid (HA) and should thus be given their ordinary meaning in the art. The broad ranges for the molecular weight of HA defined in the description encompass both alternatives.

2.1.7 Consequently, the main request does not contain added subject-matter (Article 76(1) EPC).

2.2 Novelty

2.2.1 Document D1 discloses saline solutions containing hyaluronic acid (page 6, line 1 to page 7, line 22), which may be administered in the form of an aerosol. Document D1 does not explicitly disclose whether the saline solutions are isotonic, hypotonic or hypertonic. The skilled person would not have concluded without any mention of the saline concentration in document D1 that the saline solutions in said document are hypertonic, since he knew from his common general knowledge that hypertonic saline solutions caused local irritation.

Thus, document D1 does not disclose inhalation compositions according to claim 1 of the main request.

2.2.2 Document D2 discloses inhalation solutions containing hyaluronic acid with a molecular weight of 400 to 4000 kilodaltons suitable for aerolisation (page 167, right-

hand column, last paragraph to page 168, left-hand column, first paragraph). Document D2 discloses colloidal preparations of hyaluronic acid (HA) in saline (page 168, right-hand column, under heading "exercise test") which are administered by aerosol. However, document D2 does not disclose whether these preparations are isotonic, hypotonic or hypertonic. Therefore, document D2 fails to disclose 5-7% hypertonic saline solutions containing hyaluronic acid as defined in claim 1 of the main request.

2.2.3 Consequently, the subject-matter of claim 1 of the main request is novel vis-à-vis documents D1 and D2 (Articles 52(1) and 54(2) EPC).

2.3 Inventive step

2.3.1 Document D6, which discloses inhalation formulations in the form of monodose ampoules of 7% hypertonic saline solution further containing quinine sulfate as taste-masking agent (page 230, right-hand column, last paragraph), represents the closest prior art. Moreover, it further discloses that "inhaled hypertonic saline acutely increases mucociliary clearance and, in short-term trials, improves lung function in people with cystic fibrosis" and that "long-term safety and efficacy of inhaled hypertonic saline in a long-term trial was tested" (abstract). The treatment in document D6 with the hypertonic saline solutions improved lung function and reduced the frequency of exacerbations, whereas the most frequent treatment-related adverse reactions were cough, chest tightness and pharyngitis (Table 3 on page 239).

The technical problem to be solved lies in the provision of alternative inhalation formulations of

hypertonic saline solutions exhibiting good patient compliance.

The solution lies in the addition of hyaluronic acid or a salt or ester thereof with a low molecular weight or an intermediate molecular weight at a concentration of between 0.01% and 1%, instead of quinine sulfate.

The problem is plausibly solved in the light of the content of the patent application, which states that: "it has been found that the administration of a hypertonic solution, associated with hyaluronic acid or its salts, leads to better local tolerability, with a reduction in the inflammatory component affecting the mucosa of the airways, a lower risk of discontinuance of the treatment, and better compliance by patients affected by cystic fibrosis" (page 4 under the heading "Description of the invention").

Moreover, the appellant filed during appeal proceedings the post-published document D9 in order to show that the underlying problem has actually been solved by the claimed invention. Document D9 states that: "The inhaled solution of 0.1% hyaluronic acid and hypertonic saline significantly improved tolerability and pleasantness compared to hypertonic saline alone" (page 1, right-hand column, lines 5 to 8).

Hence, the remaining question is whether or not the proposed solution was obvious to the skilled person.

Since neither document D1 nor document D2 disclose inhalation formulations of hypertonic saline solutions, the problem of patient compliance caused by inhalation with the 5-7% hypertonic solution does not arise. Therefore, the skilled person has no hint in documents

D1 or D2 to add hyaluronic acid as a solution to the stated problem.

The fact that document D1 discloses inhalation compositions containing hyaluronic acid in saline solutions for the treatment of respiratory disorders, especially emphysema (page 3, lines 1 to 21), does not teach the skilled person what to do when looking for an alternative to the 7% hypertonic saline solutions disclosed in document D6. Documents D1 and D2 do not teach the skilled person that adding hyaluronic acid to inhalation hypertonic saline solutions would allow the achievement of good patient compliance.

None of the other documents available on file suggests the obviousness of the proposed solution to the technical problem defined above.

Consequently, the main request complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The appellant is re-established in his rights.

2. The decision under appeal is set aside.

3. The case is remitted to the department of first instance with the order to grant a patent in the following version:

claims:
Nos. 1 to 3 filed as main request during the oral proceedings

description: pages 1 to 3 and 6 as originally filed,
pages 4 and 5 as filed during the oral proceedings

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated