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Datasheet for the decision of 6 May 2014

Case Number: T 2424/12 - 3.3.10

Application Number: 09178846.3

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Language of the proceedings: EN

Title of invention:
Crystallization of iodixanol in isopropanol and methanol

Applicant:
GE Healthcare AS

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step: all requests (no) - arbitrary modifications

Decisions cited:

Catchword:

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Case Number: T 2424/12 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 6 May 2014

Appellant: (Applicant)	GE Healthcare AS Nycoveien 1-2 P.O. Box 4220 Nydalen 0401 Oslo (NO)
Representative:	Bannan, Sally GE Healthcare AS P.O. Box 4220 Nydalen Nycoveien 1-2 0401 Oslo (NO)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 27 June 2012 refusing European patent application No. 09178846.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: P. Gryczka
Members: J. Mercey
D. Rogers

Summary of Facts and Submissions

I. The present appeal lies from the decision of the Examining Division refusing European patent application No. 09 178 846.3.

II. The Examining Division held that the subject-matter of the then pending main request and auxiliary request I lacked inventive step, *inter alia* documents (2), (3) and (4) being cited:

(2) WO-A-99/18054,
(3) WO-A-2007/064220 and
(4) WO-A-2006/016815.

Document (2), which was considered to represent the closest prior art, already described the crystallization of iodixanol from a solvent system consisting of methanol, isopropanol and water. The selection of particular ratios of these solvents characterising the claimed process was the result of routine experimentation, such that the claimed process was merely an obvious alternative to the process of document (2).

III. With a letter dated 4 April 2014, the Appellant (Applicant) submitted a main request and auxiliary requests 1 to 5, and at the oral proceedings before the Board held on 6 May 2014, the Appellant submitted auxiliary request 6.

Claim 1 of the main request reads as follows:

"Process for the crystallization of iodixanol from a crude product containing about 75-90 weight% iodixanol, 3-10 weight% iohexol, 0-7 weight% 5-acetamido-N,N'-

bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide (Compound A) and minor amounts of other impurities in an aqueous solution comprising the steps of:
a) adjusting the crude product comprising iodixanol in aqueous solution to the maximum concentration;
b) adding about 1 to 3 L methanol per kg iodixanol;
c) gradually adding a total of about 1.5 to 4 L isopropanol per kg iodixanol in one or several portions."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request exclusively in that the crystallization of iodixanol is "from a kg amount of a crude product".

Claim 1 of auxiliary request 2 differs from claim 1 of the main request exclusively in that step c) is restricted to the addition of isopropanol "in several portions".

Claim 1 of auxiliary request 3 is a combination of all the features of claim 1 of each of auxiliary requests 1 and 2.

Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 3 exclusively in that in step a), the adjusting is carried out "by water removal".

Claim 1 of auxiliary request 5 differs from claim 1 of auxiliary request 4 exclusively in that in step a), said water removal "is performed by evaporation and/or membrane separation".

Claim 1 of auxiliary request 6 differs from claim 1 of the main request exclusively in that in step b) about 2

L methanol, and in step c) about 2 L of isopropanol per kg iodixanol are added.

IV. The Appellant argued that the claimed process was inventive over document (2) as closest prior art, the objective technical problem being to provide a crystallization method for purifying iodixanol from kilogram quantities of crude iodixanol. The solutions proposed by claim 1 of all requests were characterised by the physical nature and quantity of the crude iodixanol starting material, namely an aqueous solution and a kilogram amount, and by the particular ratio of methanol to isopropanol, the processes of auxiliary requests 2 to 5 being additionally characterised by the fact that isopropanol was added in several portions. Document (2) did not suggest any of these features, let alone in order to scale up the crystallisation of iodixanol to an industrial-scale. Indeed documents (3) and (4) taught away from crystallizing from an aqueous solution of iodixanol.

V. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Inventive Step

Main request

2. The application is directed to a process for the crystallization of iodixanol from a crude product in an aqueous solution by adjusting the crude product to the maximum concentration, adding methanol and isopropanol.

2.1 Document (2) (cf. claims 1 and 8 and paragraph bridging pages 2 and 3) discloses a process for the crystallization of iodixanol from a (super)saturated solution, said solution having been produced from a non-saturated solution by e.g. evaporation of a solvent, the solvent being preferably a mixture of methanol (0-100%), isopropanol (0-80%) and water (0-10%). In Example 1, 80g of solid iodixanol containing 3 weight% water is crystallized by dissolving in 374 mL methanol, followed by addition of 48 mL of isopropanol, said amounts corresponding to 4.675 L and 0.6 L, respectively, per kg iodixanol.

2.1.1 The Board considers, in agreement with the Examining Division and the Appellant, that the closest prior art is the disclosure of document (2).

2.2 In view of this state of the art, the Appellant submitted that the problem underlying the present application was the provision of a crystallization method for purifying iodixanol from kilogram quantities of crude iodixanol.

2.3 As the solution to this problem, claim 1 of the main request proposes a crystallization process which is characterised by starting from an aqueous solution of iodixanol, reducing the amount of water therein to produce a concentrated solution, and then adding a specific ratio of methanol and isopropanol to iodixanol, namely 1 to 3 L methanol and 1.5 to 4 L isopropanol per kg iodixanol.

2.3.1 The Appellant submitted that the feature that litre quantities of methanol and isopropanol were added "per kg" of iodixanol further characterised the subject-

matter of claim 1 of the application *vis-à-vis* the process of document (2).

However, the specification that x litres of solvent are added to y kilograms of iodixanol does not mean that the process is restricted to the crystallization of kilogram amounts of iodixanol, but merely defines the ratio of the amount of solvent to iodixanol that should be used in the process. Hence, this "feature" does not further differentiate the subject-matter of claim 1 of the application from the process of document (2).

2.4 Since according to Example 1 of the present application, iodixanol crystals are obtained in a purity of 98.0-98.5% and a crystallization yield of 85-90%, the Board is satisfied that the technical problem as defined in point 2.2 above has been successfully solved by the claimed process.

2.5 Finally, it remains to be decided whether or not the proposed solution to the problem underlying the application is obvious in view of the state of the art.

2.5.1 Since document (2) itself (cf. claim 8) teaches that iodixanol may be crystallized from a mixture of methanol (0-100%), isopropanol (0-80%) and water (0-10%), the skilled person knows that water may be present in the crystallization medium. Thus, the skilled person would expect that crude iodixanol may also be crystallized from a supersaturated solution of iodixanol in water by adding methanol and isopropanol. Since no effect has been shown to be associated with the feature of crystallizing from such a concentrated solution of iodixanol in water, said feature is considered to be merely an arbitrary modification of the process already described in document (2).

2.5.2 Furthermore, the particular ranges of methanol and isopropanol to iodixanol defined in the claim, which, as conceded by the Appellant fell within the broad ratios for these solvents taught in claim 8 of document (2), have not been shown to be associated with any effect *vis-à-vis* the particular ratios used in Example 1 of document (2). Thus, the particular solvent ratios are neither critical nor purposive choices for solving the objective problem underlying the application. The act of picking out at random a range for the amount of solvent is within the routine practice of the skilled person faced with the mere problem of providing a crystallization method for purifying iodixanol from kilogram quantities of crude iodixanol. Therefore, the arbitrary choice of solvent ranges already taught in the state of the art for the crystallization of iodixanol cannot provide the claimed process with any inventive ingenuity.

2.6 For the following reasons, the Board is not convinced by the Appellant's submissions in support of the presence of an inventive step.

2.6.1 The Appellant argued that Example 1 of document (2) taught the skilled person to start the crystallization from solid iodixanol and not from a concentrated aqueous solution, even the maximum amount of water disclosed in the general teaching of document (2), namely 10%, not corresponding to an aqueous solution. Furthermore, documents (3) and (4) (see page 6 of each document, last and penultimate paragraph, respectively) taught that iodixanol at high concentrations in water was difficult to handle and that by using solvents other than methanol and isopropanol, higher initial water content was possible, such that handling problems

could be avoided, and in addition, time could be saved and energy consumption reduced. Thus these documents also taught away from crystallizing iodixanol from an aqueous solution.

However, document (2) teaches crystallization of iodixanol from a (super)saturated solution thereof comprising a mixture of methanol, isopropanol and up to 10% **water**, such that document (2) cannot be interpreted as teaching away from using water in the crystallization, let alone from starting from a concentrated solution in water and then adding methanol and isopropanol. With regard to documents (3) and (4), although these documents may indeed suggest that handling problems are associated with the use of iodixanol at high concentrations in water, it has not been shown that the present process overcomes these handling problems, no comparative examples in this respect having been furnished. Merely carrying out a teaching described in the prior art as undesirable cannot render a process inventive, unless it has been shown that the resulting process unexpectedly does not experience the difficulties foreseen. Therefore the Appellant's arguments do not convince the Board.

2.6.2 The Appellant submitted that the claimed process made it possible to scale up the crystallization process described in document (2), which was performed in Example 1 thereof on merely 80g of iodixanol, to a kilogram scale, as shown by Example 1 of the application in suit, wherein 700kg of iodixanol is crystallized.

However, there is no evidence available that the process described in document (2) could not also be performed on a larger scale, nor has the Appellant

provided any argumentation as to why this should not be the case. Hence, this argument of the Appellant lacks experimental support and thus does not convince the Board.

2.7 As a result, the Appellant's main request is not allowable as the subject-matter of claim 1 thereof lacks inventive step pursuant to Article 56 EPC.

Auxiliary request 1

3. Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the crystallization of iodixanol is specified as being from a kilogram amount of a crude product.

3.1 Thus in contrast to the main request (see point 2.3.1 above), the subject-matter of auxiliary request 1 does indeed also differ from the disclosure of document (2) by virtue of the crystallization being carried out on a kilogram amount of iodixanol.

3.2 However, scaling up of a process is a routine activity for the skilled person, and since the prior art does not teach away from so doing (see point 2.6.2 above), performing the process on kilogram quantities cannot confer inventiveness upon the already obvious crystallization process.

3.3 Thus, auxiliary request 1 is also not allowable for lack of inventive step pursuant to Article 56 EPC.

Auxiliary request 2

4. Claim 1 of auxiliary request 2 differs from claim 1 of auxiliary request 1 in that step c) is restricted to the addition of isopropanol in several portions.

4.1 However, in the absence of a surprising effect, such a manner of addition is merely an arbitrary technical modification well within the normal practice of the skilled person.

4.2 The Appellant argued that when in step (c) the isopropanol was added in two portions, the first portion being larger than the second, the crystallization required much longer than when the second portion was larger than the first.

However, since the two methods compared by the Appellant both fall within the scope of the claim, the claim not specifying how the several portions should be divided, the comparison is meaningless and cannot provide a basis for inventive step.

4.3 Thus, auxiliary request 2 is also not allowable for lack of inventive step pursuant to Article 56 EPC.

Auxiliary request 3

5. Claim 1 of auxiliary request 3 is a combination of all the features of claim 1 of each of auxiliary requests 1 and 2.

5.1 Since there is no inventiveness in the process being carried out on a kilogram amount (see point 3.2 above), nor in the isopropanol being added in several portions (see point 4.1 above), nor has the Appellant argued that the combination of these two features leads to any

unexpected effect, this request also does not involve an inventive step.

Auxiliary requests 4 and 5

6. Claim 1 of auxiliary request 4 differs from claim 1 of auxiliary request 3 in that in step a), the adjusting is carried out by water removal, Claim 1 of auxiliary request 5 further differing from claim 1 of auxiliary request 3 in that said water removal is performed by evaporation and/or membrane separation.

6.1 That a concentrated aqueous solution may be formed by removal of water from an aqueous solution, for example by evaporation, belongs to the common general knowledge of the skilled person, the Appellant not arguing otherwise. In addition, document (2) (see page 2, last three lines) teaches that the supersaturated solution from which *inter alia* iodixanol is crystallized may be produced from a non-saturated solution by evaporation.

6.2 The Appellant submitted that by specifying in step a) that the maximum concentration of crude product was obtained by removal of water, it was clearer that the crystallization process started from a concentrated aqueous solution and not from a solid, as in document (2).

However, the Board has already acknowledged (see point 2.3 above) for the subject-matter of the main request that the process starts from an aqueous solution, and has found this feature to not be associated with any inventiveness (see points 2.5.1 and 2.6.1 above).

6.3 Thus, auxiliary requests 4 and 5 are also not allowable for lack of inventive step pursuant to Article 56 EPC.

Auxiliary request 6

7. Claim 1 of auxiliary request 6 differs from claim 1 of the main request in that in step b) about 2 L methanol, and in step c) about 2 L of isopropanol per kg iodixanol are added.

7.1 Since no effect has been shown to be associated with the particular ratios of methanol and isopropanol to iodixanol specified *vis-à-vis* the particular amounts used in Example 1 of document (2), the subject-matter of this request is obvious for the same reasons as given in point 2.5.2 above.

7.2 The Appellant argued that since the particular amounts of methanol and isopropanol to iodixanol claimed, namely about 2 L per kg iodixanol, respectively, were even more specific than those of the other requests, they were further removed from the disclosure of document (2).

However, similarly to in point 2.5.2 above, the particular ratios of methanol and isopropanol to iodixanol used have not been shown to be associated with any effect *vis-à-vis* the particular amounts used in Example 1 of document (2), such that these ratios also represent merely an arbitrary choice and cannot contribute to inventive step.

7.3 Thus, auxiliary request 6 is also not allowable for lack of inventive step pursuant to Article 56 EPC.

8. Finally, the Appellant argued that since the application was filed under the Patent Prosecution Highway program and the invention was found patentable

by the USPTO, the Appellant expected that a patent would also be granted by the EPO.

However, as conceded by the Appellant at the oral proceedings, the Patent Prosecution Highway program does not discharge the EPO from reaching its own decision as to whether or not an invention fulfils the requirements of the EPC.

Other issues

In view of the negative conclusion in respect of inventive step for the subject-matter of the main and auxiliary requests 1 to 6 as set out in points 2 to 7 above, a decision of the Board on the issues under Articles 84 and 123(2) EPC raised in the communication of the Board dated 11 December 2013 is unnecessary.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated