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Datasheet for the decision of 13 November 2020

Case Number: T 0605/19 - 3.3.04

Application Number: 12803297.6

Publication Number: 2723369

IPC: A61K38/46, A61K38/17, A61P31/12, C12N9/16

Language of the proceedings: EN

Title of invention:
Composition and formulation comprising recombinant human iduronate-2-sulfatase and preparation method thereof

Patent Proprietors:
Green Cross Corporation
Medigenebio Corporation

Opponent:
James Poole Limited

Headword:
Method for producing iduronate-2-sulfatase/GREEN CROSS

Relevant legal provisions:
EPC Art. 56, 123(2)
RPBA Art. 12(2), 13(2)

Keyword:

Late-filed request - justification for late filing (yes)
Amendments - allowable (yes)
Inventive step - (yes)
Remittal - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0605/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 November 2020

Appellants: (Patent Proprietors)	Green Cross Corporation 107 Ihyeon-ro 30beon-gil Giheung-gu Yongin-si Gyeonggi-do 446-855 (KR)
(Patent Proprietor)	Medigenebio Corporation 107 Ihyeon-ro 30beon-gil Giheung-gu Yongin-si Gyeonggi-do 446-855 (KR)
Representative:	HGF 1 City Walk Leeds LS11 9DX (GB)
Respondent: (Opponent)	James Poole Limited One Southampton Row London WC1B 5HA (GB)
Representative:	Goodfellow, Hugh Robin Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 December 2018 revoking European patent No. 2723369 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	B. Claes
Members:	O. Lechner
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the patent proprietors ("appellants") lies from the opposition division's decision to revoke European patent No. 2 723 369 ("patent"), entitled "*Composition and formulation comprising recombinant human iduronate-2-sulfatase and preparation method thereof*".

II. The patent is based on European patent application No. 12 803 297.6, which was filed as an international application and was published as WO 2012/177020.

Claims 7 and 8 read:

"7. A method for preparing a composition for treating Hunter syndrome, comprising:
(1) transforming a host cell with an expression vector carrying an IDS gene to obtain a recombinant cell strain;
(2) culturing the recombinant cell strain in the presence of a hydrolysate in a serum-free medium and obtaining the culture;
(3) purifying IDS from the culture through anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography and affinity chromatography; and
(4) combining the purified IDS with a pharmaceutically acceptable carrier.

8. A method for preparing a composition for treating Hunter syndrome, comprising:
(1) transforming a host cell with an expression vector carrying an IDS gene to obtain a recombinant cell strain;

(2) culturing the recombinant cell strain in the presence of a hydrolysate in a serum-free medium and obtaining the culture;
(3) purifying IDS from the culture through anion exchange chromatography hydrophobic chromatography, cation exchange chromatography and affinity chromatography; and
(4) combining the purified IDS with a pharmaceutically acceptable carrier."

III. The patent was opposed under Article 100(a) EPC, on the ground of lack of inventive step, and under Article 100(b) and (c) EPC. The opponent is the respondent in these appeal proceedings.

IV. The opposition division held that the subject-matter of the claims of the main request and auxiliary request 1 did not involve an inventive step (Article 56 EPC). The claims of the main request were however found to comply with Articles 54, 83 and 123(2) EPC.

V. With their statement of grounds of appeal, the appellants re-submitted the main request and submitted auxiliary requests 1 to 7. They argued in favour of inventive step and submitted seven further documents.

VI. With their reply to the appeal, the respondent submitted arguments to the effect that the claimed subject-matter lacked inventive step (Article 56 EPC) and submitted five documents.

VII. In a further letter the appellants submitted arguments addressing the respondent's reply and filed a new document.

VIII. In a communication pursuant to Article 15(1) RPBA accompanying the summons to oral proceedings, the board expressed, *inter alia*, the preliminary opinion that the methods of claims 1 to 5 of auxiliary request 1 involved an inventive step.

IX. In reply to the board's communication, the respondent submitted, *inter alia*, further arguments.

X. The appellants submitted a new main request (corresponding to the previously pending auxiliary request 1, as filed with the statement of grounds of appeal, with deleted product-by-process claims 6 and 7) limited to the five method claims which the board considered to involve an inventive step (see section IV.). Former auxiliary requests 2 to 8, as filed with the statement of grounds of appeal, were renumbered as auxiliary requests 1 to 7.

XI. Oral proceedings were held by videoconference with the agreement of both parties. During the oral proceedings, the appellants filed a new main request (claims 1 to 5) and withdrew all other pending claim requests.

Compared to claim 1 of the previously filed main request (see section X.), claim 1 has been amended by the insertion of the wording "for treating Hunter syndrome". Claim 1 of the main request thus reads:

"1. A method for preparing an iduronate-2-sulfatase (IDS) composition <u>for treating Hunter syndrome</u> having an amino acid sequence of SEQ ID NO: 1, wherein a cysteine residue at position 59 in the IDS amino acid sequence is converted into formylglycine (FGly) at a molar ratio of 75% or higher, comprising:

culturing a recombinant cell strain transformed with a gene encoding IDS represented by SEQ ID NO: 1 and obtaining the culture; and

purifying the culture through anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography, and affinity chromatography, wherein the cation exchange chromatography is performed using an eluting buffer with a pH of 4.0 to 6.0;

wherein said method comprises:

(1) transforming a host cell with an expression vector carrying an IDS gene to obtain a recombinant cell strain;

(2) culturing the recombinant cell strain in the presence of a hydrolysate in a serum-free medium and obtaining the culture;

(3) purifying IDS from the culture through anion exchange chromatography, hydrophobic chromatography, cation exchange chromatography and affinity chromatography;

(4) combining the purified IDS with a pharmaceutically acceptable carrier; and

wherein the host cell is a Chinese hamster ovary cell." (emphasis added by the board)

Claims 2 to 5 are dependent on claim 1.

At the end of the oral proceedings, the chair announced the decision of the board.

XII. The following documents are referred to in this decision:

D1 Bielicki *et al.*, Biochemical Journal (1993), Vol. 289, pages 241-246

D5 Muezner *et al.*, Genetics in Medicine (2006), Vol. 8(8), pages 465-473

D7 US 6,153,188

D8 Burrow *et al.*, Biologics: Targets & Therapy (2008), Vol. 2(2), pages 311-320

D11 Clarke, Expert Opin. Pharmacother. (2008), Vol. 9(2), pages 311-317

XIII. The appellants' arguments, in so far as relevant for the decision, can be summarised as follows.

Admittance of the main request into the appeal proceedings

The request was filed in reaction to an added subject-matter objection raised by the respondent against the previous main request for the first time during the oral proceedings in appeal. The amendment was straightforward, addressed the objection and did not add any new issues.

Main request - claim 1

Amendments (Article 123(2) EPC)

The amendment to claim 1 found a basis in claims 7 and 8 of the application as filed.

Inventive step (Article 56 EPC)

The disclosure in document D1 represented the closest prior art. The claimed process differed from the

process disclosed in document D1 in the use of a hydrolysate-supplemented serum-free medium in the upstream process, and, in the downstream process, a four-step chromatographic purification method including anion exchange chromatography (AEX), hydrophobic chromatography (HIC), cation exchange chromatography (AEX) and affinity chromatography (AFC).

The claimed method resulted in an iduronate-2-sulfatase (IDS) preparation characterised by having been prepared in a serum-free process and having

(i) a higher FGly content of ≥ 75%,

(ii) a higher sialic acid content resulting in a reduced isoelectric point (pI), and

(iii) a high purity of > 99.9%

compared to the enzyme prepared as described in document D1.

It was known in the art that the enzyme activity of iduronate-2-sulfatase was dependent upon the post-translational modification of cysteine to FGly within the enzyme's catalytic site (i.e. position 59 - see documents D5, page 466, right-hand column, first paragraph; D8, page 315, right-hand column, first paragraph and page 317, left-hand column, first full paragraph; and D11, page 312, right-hand column, first paragraph). Moreover, sialylation of the enzyme prolonged its circulating half-life (see document D5, page 466, right-hand column, first paragraph).

Example 2 of the patent demonstrated that iduronate-2-sulfatase compositions having a higher level of FGly conversion provided improved therapeutic effects compared to the commercially available iduronate-2-sulfatase agent Elaprase (which was the iduronate-2-sulfatase described in documents D8 and D11).

The objective technical problem could be formulated as the provision of a method for preparing a therapeutically suitable iduronate-2-sulfatase with improved efficacy.

None of the known methods described in the cited art resulted in an iduronate-2-sulfatase preparation with such a high FGly content and such a high content of sialic acid. In fact, the method disclosed in document D1 resulted in an iduronate-2-sulfatase preparation with about 50% FGly content.

As explained in paragraphs [0042] and [0094] of the patent, the presence of hydrolysate as serum-free cell culture medium supplement in the upstream process had an important influence on the final FGly content. This was not suggested in the state of the art. Furthermore, there was no suggestion in the art to use a four-step chromatographic purification protocol involving a cation exchange chromatographic step in order to obtain the claimed enzyme.

Although various chromatographic techniques were known in the art, the specific combination of chromatographic techniques for the purification of iduronate-2-sulfatase had neither been disclosed nor suggested.

XIV. The respondent's arguments, in so far as they are relevant to the decision, can be summarised as follows.

Admittance of the main request into the proceedings

The objection under Article 123(2) EPC to the omission of the feature "for treating Hunter syndrome" (see e.g.

claim 1 of the previous main request) had already been raised against granted claim 1 in the notice of opposition. Furthermore, the opposition division had expressed the view that such omission conflicted with the requirements of Article 123(2) EPC, in its annex to the summons to oral proceedings. The request was thus not filed in response to a new objection. Since this request could have been presented in the proceedings before the opposition division, it should not be admitted into these oral proceedings.

Amendments (Article 123(2) EPC)

No objections under Article 123(2) EPC were formulated.

Inventive step (Article 56 EPC)

The appellants had correctly identified the closest prior art and the technical differences with the claimed invention.

There was no evidence on file which of the method steps described in the patent was (or were) the cause of the increased FGly conversion. This applied even more to the claimed method, since it did not include every process step and detail of Example 1.

No technical effect could be attributed to the routine purification steps of the claimed method. There were no data showing whether FGly conversion was increased when using the claimed purification method as compared to an alternative purification protocol. Also, no particular technical or therapeutic effect had been shown for an iduronate-2-sulfatase having an FGly content value of "75% or higher" compared to values below 75%.

In view of the above, the objective technical problem could be formulated as the provision of an alternative method for preparing a therapeutically suitable iduronate-2-sulfatase.

Hydrolysate supplementation had been a routine feature of cell culture for decades. Each of the four chromatographic steps of the claim was a standard purification protocol for proteins known to the skilled person.

Document D1 disclosed the use of serum-free media for culturing the iduronate-2-sulfatase producing cells. Consequently, this feature could not provide an inventive step for the claimed invention.

The skilled person would have arrived at the claimed subject-matter in an obvious way using common general knowledge and perhaps some routine trials and experiments, but without inventive effort.

XV. The appellants requested that the decision under appeal be set aside and that the patent be maintained based on the claims of the new main request filed during the oral proceedings.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

Admissibility of the appeal

1. The appeal complies with the requirements of Article 108 and Rule 99 EPC and is admissible.

Admittance of the main request filed during oral proceedings into the appeal proceedings (Article 13 RPBA)

2. The parties were notified of the summons to oral proceedings after 1 January 2020. Thus, Article 13 RPBA 2020 applies.

3. The new main request, filed during the oral proceedings, constitutes an amendment to the respondent's case governed by Article 13(2) RPBA 2020.

4. The appellants justified the timing of the filing as a response to an objection under Article 123(2) EPC against the previous main request, which the respondent had raised for the first time at the oral proceedings in appeal.

5. The respondent held that the new main request could have already been filed during the opposition proceedings, since the objection had already been raised in the notice of opposition and the opposition division had indicated in its preliminary opinion that this omission violated Article 123(2) EPC.

6. The new main request consists of claims 1 to 5 of auxiliary request 1 filed with the appellants' statement of grounds of appeal (see sections V. and X.). In its preliminary opinion the board had expressed no concerns under Article 123(2) EPC in relation to this request. In their replies to the statement of grounds of appeal and to the board's preliminary opinion, the respondent argued for the lack of inventive step (Article 56 EPC); however, they did not raise any objection regarding added subject-matter (Article 123(2) EPC).

7. The appellants filed this new main request in response to an objection under Article 123(2) EPC against the omission of the phrase "for treating Hunter syndrome" in claim 1 of the earlier main request. In appeal, this objection was raised for the first time at the oral proceedings. This is contrary to the requirements of Article 12(2) RPBA, according to which the "*statement of grounds of appeal and the reply shall contain a party's complete case. They shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should specify expressly all the facts, arguments and evidence relied on ...*".

8. The amendment is simple and not to the surprise of the respondent. Consequently, also in this context the board decided to take this new main request into account in the appeal proceedings (Article 13(1) and (3) RPBA 2020).

Main request

Amendments (Article 123(2) EPC)

9. The board is satisfied that the sole amendment over claim 1 of the previous main request, i.e. the addition of "for treating Hunter disease" in claim 1, finds a basis in claims 7 and 8 of the application as filed (see section II.). The respondent did not express any objections of added subject-matter. The board thus considers that the claims comply with the requirements of Article 123(2) EPC.

Inventive step (Article 56 EPC)

Closest prior art

10. The board agrees with the parties that the method for producing and purifying recombinant iduronate-2-sulfatase for treating Hunter syndrome disclosed in document D1 represents the closest prior art. The enzyme was expressed in Chinese hamster ovary (CHO)-K1 cells which were alternately grown in medium containing fetal calf serum (FCS) and serum-free medium (see page 242, right-hand column, last two paragraphs). The last culture step before harvesting was performed in medium without FCS. The recombinant enzyme was purified from the collected medium by a three-step chromatography column procedure comprising

(a) anion exchange chromatography (PBE94 column run in an anion exchange mode, iduronate-2-sulfatase with pI < 4, elution buffer Polybuffer 74 with pH 4 (see page 242, right-hand column, last paragraph; page 243, right-hand column, chapter "*Large-scale production of rI2S*", paragraph 2)), followed by

(b) affinity chromatography (Blue-A agarose column; see page 243, left-hand column, line 6 and right-hand column, last paragraph, lines 7 to 12), and

(c) size exclusion chromatography (LKB Ultrachrom GTi fast protein liquid chromatography system with a TSK G3000SW Ultrapac column; see page 243, left-hand column, lines 7 to 11).

Document D1 reports an overall recovery rate of > 15% iduronate-2-sulfatase activity (see page 243, right-hand column, last paragraph, lines 12 to 14).

Objective technical problem

11. The claimed method differs from the method disclosed in document D1 at least in that

(i) the cells are cultured in a hydrolysate-supplemented serum-free medium, and

(ii) the expressed enzyme is purified from the medium by a four-step chromatographic process comprising cation exchange chromatography as an additional (third) purification step.

12. It was disputed between the parties whether or not the use of hydrolysate and/or the additional cation exchange chromatography step could be linked to particular technical effects of the final iduronate-2-sulfatase preparation going beyond those of the enzyme preparation disclosed in document D1, such as a higher FGly conversion, a higher content of sialic acid or a better therapeutic effect. However, this question can be left undecided if the board were to conclude that the solution to a more general objective technical problem was not obvious.

13. The board therefore considers that, in favour of the respondent, the objective technical problem may be formulated as the provision of an alternative method for the preparation of an iduronate-2-sulfatase suitable for the treatment of Hunter syndrome.

14. The claimed method results in an iduronate-2-sulfatase composition that has an FGly content of 75% or higher at amino acid position 59 and that is suitable for the treatment of Hunter syndrome. Example 1 of the patent provides an iduronate-2-sulfatase preparation with a conversion of cysteine at position 59 to FGly at a molar ratio of 75% or higher. The board is thus satisfied that the claimed invention solves the problem.

Obviousness

15. The question to be answered when assessing the obviousness of the claimed subject-matter is whether or not, having regard to the state of the art, the skilled person, when faced with this objective technical problem, would have modified the process disclosed in document D1 and arrived at the claimed method.

16. The respondent argued that the method steps recited in the claims, including both the use of hydrolysate in serum-free cell culture as well as four-step chromatographic protein purification methods, were employed routinely in purification protocols and that their combination did not go beyond the normal progress of technology.

17. The board is not persuaded by the respondent's arguments. While the serum-free cell culture, including the addition of hydrolysate (see document D33, page 36, last paragraph), and four-step chromatographic protein purification protocols (see documents D1 and D31) may have been known as routine steps in protein production and purification methods, the board has not found convincing arguments as to why the skilled person would have been motivated to develop an alternative to the

existing successful process for the large-scale preparation and purification of iduronate-2-sulfatase for medical use described in document D1. In fact, neither document D1 itself nor any other cited document suggests modifying the method of document D1 so as to arrive at the claimed method according to claim 1. There is no pointer to combine the various steps according to the claimed alternative method or, in particular, to use a serum-free, hydrolysate-supplemented cell culture and an additional chromatographic purification step in a method for producing and purifying iduronate-2-sulfatase.

18. Even when assuming that the skilled person always tries to further develop existing methods and that the known basic purification techniques to be used in a method as claimed were limited in number, the board considers that a large number of possibilities to combine these techniques and optimise their parameters were at the disposal of the skilled person even when starting from the method of document D1. In view of the many options at hand, the skilled person was not in a situation involving merely conventional trial-and-error experimentation as suggested by the respondent. Indeed, the respondent did not present any technical considerations specific to the production of iduronate-2-sulfatase that would have led the skilled person to select, from the set of possibilities of conventional techniques by routine trials, the additional elements of the claimed purification method compared to the method of D1. Moreover, the respondent did not demonstrate how the skilled person would have arrived at the claimed method relying on common general knowledge and routine experimentation only.

19. The board furthermore considers that a person skilled in the art would rather have been motivated to streamline the purification process disclosed in document D1 than to add an additional chromatographic step to arrive at the claimed alternative method for producing iduronate-2-sulfatase.

20. The board thus concludes that, when starting from the method disclosed in document D1, representing the closest prior art, it was not obvious to a person skilled in the art to arrive at the claimed alternative method which additionally results in an iduronate-2-sulfatase composition having at amino acid position 59 an FGly content of 75% or higher and being suitable for the treatment of Hunter syndrome.

21. Thus, the claimed subject-matter involves an inventive step (Article 56 EPC).

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 with the order to maintain the patent on the basis of the claims of the main request filed during the oral proceedings and a description to be adapted accordingly.

The Registrar: The Chair:

A. Chavinier Tomsic B. Claes

Decision electronically authenticated