Internal distribution code:
(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 13 March 2014

Case Number: T 0289/10 - 3.3.07

Application Number: 99107148.1

Publication Number: 955062

IPC: A61K47/10, A61K47/26, A61K38/27

Language of the proceedings: EN

Title of invention:
Human growth hormone aqueous formulation

Patent Proprietor:
Genentech, Inc.

Opponents:
Novo Nordisk A/S
PFIZER LIMITED
Sandoz GmbH

Headword:
Human growth hormone aqueous formulation/Genentech, Inc.

Relevant legal provisions:
EPC Art. 100(b)

Keyword:
Sufficiency of disclosure (no)

Decisions cited:
G 0001/03

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0289/10 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 13 March 2014

Appellant: (Opponent 1)	Novo Nordisk A/S Novo Allé 2880 Bagsvaerd (DK)
Representative:	Ford, Hazel J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Party as of right : (Opponent 2)	PFIZER LIMITED Ramsgate Road SANDWICH, KENT CT13 9NJ (GB)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Party as of right: (Opponent 3)	Sandoz GmbH Biochemiestrasse 10 6250 Kundl/Tirol (AT)
Representative:	Breuer, Markus Henkel, Breuer & Partner Patentanwälte Erika-Mann-Straße 23 80636 München (DE)
Respondent: (Patent Proprietor)	Genentech, Inc. 1 DNA Way South San Francisco CA 94080-4990 (US)
Representative:	Kiddle, Simon John Mewburn Ellis LLP 33 Gutter Lane London EC2V 8AS (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 17 December 2009 rejecting the opposition filed against European patent No. 955062 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman: J. Riolo
Members: D. Boulois
D. T. Keeling

Summary of Facts and Submissions

I. European patent No. 0 955 062 was granted on the basis of a set of eight claims. Independent claim 1 read as follows:

"1. A stable aqueous liquid pharmaceutical formulation for storage for 6-18 months at 2-8°C, comprising human growth hormone, a buffer providing a pH in the range of 5.5 to 7, 0.1 to 1% by weight of a non-ionic surfactant, mannitol, and phenol as preservative."

II. Three oppositions were filed against the granted patent. The patent was opposed under Article 100 (a), (b), and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, the patent was not sufficiently disclosed and its subject-matter extended beyond the content of the application as filed.

III. The present appeal lies from the decision of the Opposition Division to reject the oppositions (Article 101(2) EPC). The decision was based on the claims as granted.

According to the decision under appeal, the subject-matter of the claims of the patent did not violate Article 123(2) EPC.

As regards disclosure, the patent described the concrete and preferred amounts of the components contained in the claimed formulations and indicated how they should be prepared. Moreover, none of the documents presented by the opponents evidenced to show that the claimed formulations would not exhibit the alleged stability over the whole scope of claim 1. The invention was thus disclosed in a manner sufficient to be carried out by a

person skilled in the art over the whole scope of the claims without undue burden.

The subject-matter of claims 1-8 was considered to be novel over the prior art and involved an inventive step.

IV. Opponents 01, 02 and 03 filed an appeal against this decision.

V. By a letter dated 15 September 2010 the respondent (proprietor) filed a new main request.

The subject-matter of claim 1 of the main request read as follows, difference compared with the main request shown in bold:

"1. A stable aqueous liquid pharmaceutical formulation for storage for 6-18 months at 2-8°C, comprising human growth hormone, a buffer providing a pH in the range of 5.5 to 7, 0.1 to 1% **by weight by volume** of a non-ionic surfactant, mannitol, and phenol as preservative."

The first auxiliary request corresponded to the claims as granted.

VI. By a letter dated 8 November 2011, appellant 01 submitted arguments regarding sufficiency of disclosure and a new document named "*Declaration of Mats Reslow*" comprising experimental reports.

VII. By a letter dated 29 January 2014, the respondent announced that it would not be attending the oral proceedings before the Board of Appeal. It requested that the decision be based on the written submissions,

in particular to the proprietor's response dated 15 September 2010.

VIII. By a letter dated 28 January, appellant 02 withdrew its appeal and announced that it would not be attending the oral proceedings.

IX. By a letter dated 12 February 2014, appellant 03 withdrew its appeal and announced that it would not be represented at oral proceedings.

X. On 20 February 2014 the Board sent a communication pursuant to Article 15(1) RPBA.
The Board gave *inter alia* a preliminary opinion regarding the requirements of sufficiency of disclosure and concluded that the existence of formulations falling under the scope of the claims, as shown by the experimental reports of the "*Declaration of Mats Reslow*" , but not fulfilling the claimed requirements of stability might signify a lack of disclosure of the invention.

XI. Oral proceedings took place on 13 March 2014 in the presence of appellant 01.

XII. The arguments of the appellant, as far as relevant for the present decision, may be summarised as follows:

According to appellant 01, the experimental reports filed within the "*Declaration of Mats Reslow*" showed that the claims encompassed formulations which do not have the required stability. Formulations comprising the same components as Norditropin Simplex Xx, but having a different pH, also within the claimed range, are not stable. Such formulations showed a high degree of precipitation of the growth hormone product.

Figure 1 showed in particular the high degree of precipitation at the pH values of 5.5 and 5.7. Besides, the patent did not teach that such instability could exist at the claimed pH range and how to solve the said problem of instability.
Formulations falling within the scope of the claims therefore did not show the claimed technical effect of stability.

XIII. The respondent's written arguments, as far as relevant for the present decision, may be summarised as follows.

The claims of the patent were restricted to formulations comprising a specific combination of components for which the examples of the patent provided sufficient experimental support to show that the claimed formulations would be capable of long-term storage.
As regards the pH, the skilled person was told the pH that the buffer needs to provide.
The proper test to apply was whether the skilled person had adequate information to make and test the claimed formulations and to recognise those formulations that do or do not possess the requisite stability, thereby arriving at formulations having the claimed stability with a reasonable rate of success and without an burden of undue experimentation.

XIV. The appellant (opponent 01) requested that the decision under appeal be set aside and the patent be revoked.

The respondent (patent proprietor) requested in writing that the decision under appeal be set aside and that the patent be maintained according to the set of claims filed as main request with letter of 15 September 2010 or, in the alternative that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible

2. Main Request - Article 100(b) EPC

Claim 1 of the main request refers to "*a stable aqueous liquid pharmaceutical formulation for storage for 6-18 months at 2-8°C",* further comprising human growth hormone, a buffer providing a specific pH range, a non-ionic surfactant in a specific concentration, mannitol, and phenol as preservative.

2.1 The feature "*for storage for 6-18 months at 2-8°C"* is a functional feature defining a technical result achieved by the claimed aqueous liquid pharmaceutical formulation.
This feature and the technical result involved are key elements of the claimed invention, since the composition has been designed specifically to enhance the stability of an aqueous liquid formulation of hGH (see for instance paragraphs [0001], [0012]).
Thus, the skilled person must have been taught by the description how to prepare a composition providing a stability "*for storage for 6-18 months at 2-8°C, in particular* which compounds to choose and in which amounts, to achieve the claimed technical effect.

2.2 Appellant 01 filed letter dated 8 November 2011 an experimental report, wherein tests that have been carried out to investigate the stability of aqueous hGH formulations, in particular according to the pH of the formulations which varied from 5.5 to 7.0.
The tested formulations all contained
1) hGH 10 mg/ml,

2) Histidine buffer at 0.68 mg/ml,
3) Poloxamer 3.0 mg/ml,
4) mannitol 40 mg/ml,
5) phenol 3.0 mg/ml.
Immediately after their preparation, the formulations were visually examined. The formulations prepared at pH 5.5 and 5.7 showed a high and rapid degree of precipitation and were thus found highly unstable, since the remaining hGH concentration in these formulations was respectively 13% and 34%.
On the other hand the formulations prepared at pH of 5.9 to 7.0 showed an acceptable stability.

The results reported in this experimental report, namely the appearance of precipitates immediately after mixing the components, prove that the claimed technical effect, i.e. storage stability up to 18 months at 2-8°C, cannot be achieved by all formulations falling within the scope of claim 1. These experimental tests demonstrate thus the existence of non-working embodiments covered by the scope of the claims.

These experimental tests have neither been contested, nor be commented on by the respondent.

2.3 As the effect is part of the claim, insufficiency of disclosure may arise if formulations falling under the scope of the claims do not show the **technical effect** expressed in the claim.
Decision G1/03 indeed stipulates that "*if a claim comprises non-working embodiments, this may have different consequences, depending on the circumstances. ... . If an effect is expressed in a claim, there is lack of sufficient disclosure. Otherwise, i.e. if the effect is not expressed in a claim but is part of the problem to be solved, there is*

a problem of inventive step." (OJ, 2004, 413, point 2.5).

The question whether an invention has been disclosed sufficiently clearly and completely is however not to be decided solely on the basis of the content of the claims. If an invention involves the task of manufacturing a composition with certain properties, as in the present case a long-term storage stability, and this task is performed by means of several variables, then there might be sufficient disclosure if an occasional lack of success notwithstanding strict adherence to the prescribed limits of those variables is encountered and if clear information contained in the description, regarding the effects of individual variables on the properties of the product, enables the person skilled in the art to deduce the action to be taken to remedy this occasional lack of success and to achieve the desired property quickly and reliably.

In the present case, the description of the patent specification provides a working pH range of 5.5 to 7.0 and does not envisage any instability linked within the said range, especially at pH 5.5 or 5.7. The description does not provide any clear information or measure which would enable the person skilled in the art to bring about the desired storage stability quickly and reliably of formulations having a pH of 5.5 or 5.7.

Accordingly, the patent does not disclose the invention according to claim 1 of the main request in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The requirements of Article 100(b) EPC are not met.

3. Auxiliary Request (set of claims as granted on which the decision of the opposition division is based)- Article 100(b) EPC

The subject-matter of claim 1 of this request is similar to that of the main request, apart the concentration of the non-ionic surfactant which is expressed "by weight" instead of "by weight by volume". The features "*for storage for 6-18 months at 2-8°C"* and the pH range are thus also present.
The auxiliary request, for the same reasons as given above for the main request, does not meet the requirements of Article 100(b) EPC.

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:

L. Fernández Gómez J. Riolo

Decision electronically authenticated