Internal distribution code:

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

Datasheet for the decision of 12 December 2024

Case Number: T 1815/22 - 3.3.04

Application Number: 16760801.7

Publication Number: 3341409

IPC: C07K16/24, C07K1/16

Language of the proceedings: EN

Title of invention:
Biopharmaceutical compositions

Applicant:
GlaxoSmithKline Intellectual Property (No.2) Limited

Headword:
Antibody variants/GLAXOSMITHKLINE

Relevant legal provisions:
EPC Art. 84

Keyword:
Claims - clarity - main request (yes)

Decisions cited:
T 1156/01, T 1497/08

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 1815/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 December 2024

Appellant: (Applicant)	GlaxoSmithKline Intellectual Property (No.2) Limited GSK Medicines Research Centre Gunnels Wood Road Stevenage SG1 2NY (GB)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstraße 3 81675 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 4 March 2022 refusing European patent application No. 16 760 801.7 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman	B. Rutz
Members:	D. Luis Alves
	L. Bühler

Summary of Facts and Submissions

I. The applicant (appellant) filed an appeal against the decision of the examining division refusing European patent application No. 16 760 801.7, entitled "*Biopharmaceutical compositions*". The application was filed as an international application which was published as WO 2017/033121.

II. In the decision under appeal, the examining division dealt with a single (main) claim request. It held that claim 1 was not clear because it defined the claimed composition by means of unusual parameters. Further, the methods of measuring the parameters were neither stated in the claim nor belonged to the common general knowledge. Moreover, the definition by unusual parameters did not allow a reasonable comparison with the prior art, which included antibody compositions not defined by means of the same parameters.

III. With the statement of grounds of appeal, the appellant filed a main request and nine auxiliary requests. Claim 1 of the main request is identical to claim 1 of the request considered by the examining division. Furthermore, three documents were filed.

IV. Independent claim 1 of the main request reads as follows:

"1. A composition comprising:

(a) an anti-IL-5 antibody comprising a heavy chain sequence as shown in SEQ ID NO: 1 and a light chain sequence as shown in SEQ ID NO: 2; and

(b) a variant of the antibody wherein residue N31 of the light chain is deamidated to aspartic acid or iso-aspartic acid,

wherein the composition comprises 3% or less oxidised antibody variant at W52 of the heavy chain amino acid sequence, 50% or less oxidised antibody variant at M64 of the heavy chain amino acid sequence, and 20% or less deamidated antibody variants at N31 of the light chain amino sequence."

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

D3 Tyther and Jenkins, "Chapter 13: Quality Issues Arising from Post-Translational Modification of Recombinant Antibodies", in "Antibody Expression and Production", ed. Al-Rubeai, Cell Engineering 7, 2011, 293-303

D5 WO 2014/158231 A1

D6 Kang *et al.*, Journal of Chromatography A 1283, 2013, 89-97

D7 Goetze *et al.*, MAbs 2(5), 2010, 500-507

D8 Haberger *et al.*, MAbs 6(2), 2014, 327-339

D10 Wang *et al.*, Journal of Pharmaceutical Sciences 96(1), 2007, 1-26

VI. The appellant's arguments relevant to this decision may be summarised as follows.

The percentage of deamidated variants and the percentage of oxidised variants were not unusual parameters. Instead, they were structural features.

Documents D3, D6, D7 and D10 disclosed that post-translational modifications of antibodies impacted the structure and function of the antibodies and consequently the product quality.

Document D8 disclosed deamidated and oxidised variants of the antibody Herceptin (see "Introduction" and Tables 1 and 2). Further, documents D5, D7 and D10 all mentioned percentages of oxidised or deamidated variants. Therefore, the structural features in claim 1 were not unusual in the technical field.

Methods for determining the relative amount of variants in an antibody composition belonged to the common general knowledge. For identifying specific amino acid post-translational modifications, LC-MS/MS was the gold standard (see documents D3, D8 and D10).

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request or, alternatively, on the basis of one of the sets of claims of auxiliary requests 1 to 9 filed with the statement of grounds of appeal. Further, the appellant requested that the case be remitted to the examining division once the clarity objections raised in the decision under appeal were overcome.

Reasons for the Decision

Main request
Clarity (Article 84 EPC) - Claim 1

1. The application concerns compositions comprising the IL-5 antibody Mepolizumab. Because the production of antibodies results in heterogeneous compositions characterised by the presence of variants of the antibody of interest, the need arises to define which antibody variants affect antibody function and to define the compositions in terms of which variants may be present and at what level.

2. Claim 1 is directed to a composition comprising (i) an anti-IL-5 antibody comprising a heavy chain sequence as shown in SEQ ID NO: 1 and a light chain sequence as shown in SEQ ID NO: 2, and (ii) a variant of the antibody where residue N31 of the light chain is deamidated to aspartic acid or iso-aspartic acid. Further, the claim defines limitations on the presence of antibody variants as follows: oxidised antibody variants at W52 of the heavy chain amino acid sequence should be 3% or less; oxidised antibody variants at M64 of the heavy chain amino acid sequence should be 50% or less; and deamidated antibody variants at N31 of the light chain amino sequence should be 20% or less.

3. The examining division held that the claim was not clear because the percentage of oxidised variants and the percentage of deamidated variants amounted to unusual parameters for defining an antibody to IL-5. Moreover, although methods of measuring these parameters were known to the skilled person and disclosed in the application, they were not recited in the claim.

4. Claim 1 provides the complete amino acid sequences of the light and heavy chains of the antibody. The objection raised by the examining division exclusively related to the definition of variants of this antibody.

5. A first question that needs to be addressed is whether it is unusual to define antibody compositions by percentage of oxidised or deamidated variants of a completely defined amino acid sequence.

5.1 Document D8 aims at identifying modification sites in recombinant antibodies. The modifications assessed included asparagine deamidation and methionine oxidation (see title and abstract). For a given antibody, treatment conditions resulted in increased deamidation at light chain (LC)-Asn92 from 8% to 25%. Oxidation was also reported in terms of percentages (see page 330, right-hand column, second and last paragraphs as well as Tables 1 and 2).

Document D5 concerns antibody compositions characterised by a low percentage of acidic variants (see paragraph bridging pages 1 and 2). It discloses antibody compositions which are, *inter alia,* defined in terms of the percentage of deamidation variants (see page 33, third paragraph). For example, deamidation variants of adalimumab may occur at Asn393 or Asn329 (see page 5, third paragraph).

Document D7 concerns defining the quality attributes, or product profile, relevant for the therapeutic application of a given antibody composition (see abstract). This profile refers in particular to the presence of antibody variants such as deamidated and oxidised variants. Deamidation was studied in three

antibody compositions. The rates of deamidation differed between different asparagine amino acid positions, with two of the tested compositions presenting 23% deamidation at Asn384 (see paragraph bridging pages 504 and 505).

Document D10 concerns antibody structure and formulations for stabilising antibodies in compositions for therapeutic use (see abstract). An overview of antibody variants in antibody compositions includes a composition of antibody OKT3 showing 90% deamidation at Asn386 and compositions of antibody rhuMab HER2 showing oxidation variants at levels 10%, 17% and 52% (see Table 2).

5.2 Thus, documents D5, D7, D8 and D10 show examples of antibody compositions characterised by a percentage of deamidated or oxidised antibody variants. The board concludes that such structural definitions were not uncommon in the technical field of antibody production.

6. The examining division pointed out that the known antibodies to IL-5 were not defined by means of the parameters in claim 1. Accordingly, the examining division objected to the parameters for being unusual in the definition of anti-IL-5 antibodies. The board understands that the examining division's objections relate to the difficulties in assessing novelty of subject-matter defined in ways not used in the prior art on file disclosing anti-IL-5 antibody compositions. However, claim 1 at issue provides a structural characterisation of the antibodies of the claimed composition. As set out above, this structural characterisation is not uncommon for defining antibody compositions. This situation is to be distinguished from definitions by means of a parameter which has no

recognised meaning for the skilled person and which is only defined in the description.

7. A second question that needs to be addressed is whether methods for measuring a percentage of deamidated variants and a percentage of oxidised variants were known and whether they should be included in the claim.

7.1 In the patent, deamidated and oxidised variants were determined by trypsin peptide mapping coupled with liquid chromatography and mass spectrometry (LC-MS/MS). This same analytical technique is used for characterising antibody variants, and specifically deamidated variants, in document D6 (see point 3.3, in particular sentence bridging pages 94 and 95). Document D3 is a textbook. It discloses that site-specific detection of deamidated and oxidised variants uses LC-MS/MS (see, respectively, page 298, third paragraph, last sentence and page 299, second paragraph, last sentence). In document D8, the percentage of deamidation or oxidation of a given amino acid in the antibody was analysed by tryptic peptide mapping followed by LC-MS/MS (see page 328, left-hand column, second paragraph and page 336, right-hand column, second paragraph to page 337, left-hand column, second paragraph). Also document D5 discloses analysing variants using digestion and peptide mapping by LC/MS (see page 134, second paragraph, lines 6 to 9). Document D7 provides an overview of the analytical techniques available to study the quality of antibody compositions and discloses that the choice depends on whether site-specific information is needed or whether whole molecule changes are to be monitored instead. For the former purpose, it discloses RP-HPCL peptide mapping with mass spectrometry identification (see page 505, right-hand column, second paragraph, lines 6

to 11). The reference to RP-HPLC, i.e. reversed-phase chromatography, is no difference to the analytical technique mentioned in documents D5, D6 and D8 because it is the most commonly used type of HPLC for analysing organic compounds.

7.2 The examining division considered that the claim should define the method of measurement for the variants essentially because the method did not belong to the common general knowledge.

7.3 However, in the current case, the board takes the view that it is not justified to require that the claim make reference to the method of measurement. As set out above, the textbook document D3, as well as various scientific articles addressing antibody heterogeneity, discloses in detail a method of measurement. There is no evidence of several alternative methods of measurement. The fact that a method of measurement is disclosed in the description does not necessarily lead to the requirement to include it in the claim. This is especially the case if the measurement method was the one commonly used in the technical field (see also decision T 1156/01) and was not merely one of several alternative methods resulting in different measured values (that was the situation underlying decision T 1497/08).

8. In conclusion, the board does not consider the features in claim 1 to amount to unusual parameters and does not see a justification for requiring that the method of measuring them be included in the claim.

Remittal of the case to the examining division

9. The decision under appeal dealt solely with clarity of claim 1. As set out above, the board concludes that claim 1 is clear (Article 84 EPC). The appeal is thus allowable, and the decision under appeal is to be set aside.

10. Under Article 111(1) EPC, following the examination as to the allowability of the appeal, the board shall decide on the appeal. It may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case to that department for further prosecution. Under Article 11 RPBA, the board shall not remit a case for further prosecution to the department whose decision was appealed unless special reasons present themselves for doing so.

11. The appellant requested that the board remit the case for assessment of the further requirements of the EPC. The decision under appeal does not assess clarity for the other claims or the remaining requirements of the EPC. Since the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner as expressed in Article 12(2) RPBA, the board decides to remit the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division for further prosecution on the basis of the main request filed with the statement of grounds of appeal.

The Registrar: The Chairman:

A. Chavinier B. Rutz

Decision electronically authenticated