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Datasheet for the decision of 14 February 2022

Case Number: T 1708/18 - 3.3.04

Application Number: 07873840.8

Publication Number: 2035445

IPC: A61K38/00, C12N9/64

Language of the proceedings: EN

Title of invention:
Polynucleotides encoding novel PCSK9 variants

Patent Proprietor:
Bristol-Myers Squibb Company

Opponents:
Regeneron Pharmaceuticals, Inc.
Sanofi
Pfizer Inc.

Headword:
PCSK9 variants/BRISTOL-MYERS SQUIBB

Relevant legal provisions:
EPC Art. 54

Keyword:
Novelty - (no)

Decisions cited:
T 0189/01, T 2101/09, T 0943/93, T 0464/94

Catchword:

1. The issue of which standard of disclosure applies when assessing the legal question of novelty and the issue of which standard of proof applies when assessing evidence and factual questions are distinct and unrelated. The fact that the standard of disclosure required for a finding of lack of novelty (or for allowing an amendment to the application under Article 123(2) EPC) is the standard of a direct and unambiguous disclosure is immaterial for the question of what standard of proof applies when considering evidence and factual issues in the context of novelty (or inventive step) (see point 16).

2. The standard of proof generally applied at the EPO for deciding on an issue of fact is the balance of probabilities. According to this standard, the EPO must base its decisions on statements of fact which, based on the available evidence, are more likely than not to be true. This standard also applies when examining factual issues in the context of novelty (see point 14).

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Case Number: T 1708/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 February 2022

Appellant I: (Patent Proprietor)	Bristol-Myers Squibb Company Route 206 and Province Line Road Princeton, NJ 08543 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Appellant II: (Opponent 1)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 (US)
Appellant III: (Opponent 2)	Sanofi 54 Rue La Boétie 75008 Paris (FR)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Party as of right: (Opponent 3)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on**

3 May 2018 concerning maintenance of the European Patent No. 2035445 in amended form

Composition of the Board:

Chair	B. Claes
Members:	A. Schmitt
	R. Romandini

Summary of Facts and Submissions

I. The appeals lodged by the patent proprietor (appellant I, hereinafter "patent proprietor"), opponent 1 (appellant II, hereinafter "opponent 1") and opponent 2 (appellant III, hereinafter "opponent 2") lie from the opposition division's interlocutory decision that European patent No. 2 035 445 (patent), as amended in the form of auxiliary request 1 filed on 16 November 2017, and the invention to which it relates meet the requirements of the EPC.

Claims 4, 5 and 8 of the patent as granted read as follows:

"4. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
(a) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2; and
(b) a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:4.

5. An isolated antibody that binds specifically to the isolated polypeptide of SEQ ID NO:2 or SEQ ID NO:4.

8. The polypeptide of claim 4 for use in preventing, treating, or ameliorating a medical condition."

II. The patent, entitled "*Polynucleotides encoding novel PCSK9 variants*", was granted on the basis of European patent application No. 07 873 840.8, which had been filed as an international application under the PCT, published as WO 2008/105797.

III. Three oppositions were filed against the patent. The opposition proceedings were based on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) in Article 100(a) EPC and on the grounds in Article 100(b) and (c) EPC.

IV. In the decision under appeal, the opposition division considered sets of claims of a main request and an auxiliary request 1. Claim 5 of the main request and of auxiliary request 1 was identical to claim 5 of the patent as granted (see section I.). Auxiliary request 1 was considered to meet the requirements of the EPC.

V. With the statement of grounds of appeal, the patent proprietor submitted sets of claims of a main request and six auxiliary requests. The sets of claims of auxiliary requests 2 and 5 were identical to the sets of claims of the main request and auxiliary request 1 considered in the decision under appeal, respectively. Claim 5 of the main request and each of auxiliary requests 1 to 6 was identical to claim 5 of auxiliary request 1 underlying the decision under appeal (see section IV.).

VI. With their respective statements of grounds of appeal opponents 1 and 2 each submitted two documents, including document D43 submitted by opponent 2, and provided, *inter alia*, arguments supporting their view that the subject-matter of claim 5 of the main request and auxiliary request 1 underlying the decision under appeal was not novel over the disclosure in document D3, *inter alia*.

VII. With its reply to the opponents' statements of grounds of appeal, the proprietor submitted a document and arguments, *inter alia*, to the effect that the subject-

matter of claim 5 of the main request was novel because the cited documents did not disclose an antibody that was able to specifically bind the antigen of SEQ ID NO:2 or SEQ ID NO:4 beyond doubt.

VIII. Opponents 1 and 2 both replied to the patent proprietor's appeal.

IX. The board summoned the parties to oral proceedings and issued a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion that, *inter alia*, the subject-matter of claim 5 of all the claim requests lacked novelty over the polyclonal antibody disclosed in document D3.

X. Opponent 3 did not attend the oral proceedings, as previously announced in writing. During the oral proceedings, the board decided not to admit document D43 into the appeal proceedings. At the end of the oral proceedings, the Chair announced the board's decision.

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

D3 Rashid et al. 2005, Proc. Natl. Acad. Sci 102(15), 5374-5379

D4 Amino acid sequence alignment of full-length PCSK9, full-length murine PCSK9, splice variant from D1, PCSK9b and PCSK9c

D43 Declaration by Prof. Thomas U. Schwartz

XII. The proprietor's arguments, insofar as relevant to the decision, are summarised as follows.

Main request and auxiliary requests 1 to 6 - claim 5

Claim construction
Meaning of the expression "binds specifically to"

Terms used in a claim were to be given their ordinary meaning unless the patent contained a specific definition. In the relevant technical field, the skilled person would have understood that an antibody which bound "specifically" to a protein did not have cross-reactivity with any other protein (see e.g. decision T 2101/09; points 7 and 8 of the Reasons). Therefore, antibodies that specifically bound to full-length PCSK9 could not, at the same time, also specifically bind to the PCSK9b and PCSK9c splice variants.

No other definition of the expression "binds specifically" could be derived from the patent. In particular, the definition of the expression "immunospecific binding" in paragraph [0234] of the patent could not be used for interpreting the meaning of the expression "binds specifically to" used in the claim.

It was established practice of the EPO that an antibody binding to a novel and inventive protein was also novel and inventive based on the presumption that new proteins had new epitopes that were not present in other proteins. Therefore, if a protein was novel, an antibody specifically binding to the novel protein bound to its new epitopes and was therefore also novel.

The claimed subject-matter had to be interpreted based on this notion.

Meaning of the expression "isolated polypeptide"

The expression "isolated polypeptide" did not encompass denatured polypeptides. This was evident from the fact that the PCSK9b and PCSK9c polypeptides retained at least some of the biological activity of the PCSK9 protein (see paragraphs [0102] and [0134] of the patent). Moreover, the same expression was used in claim 8 as granted. In this claim, the "isolated polypeptide" was for a particular medical use, which only made technical sense if the polypeptide was functional. Since the same interpretation of an expression had to be used throughout the entire patent, the expression "isolated polypeptide" used in claim 5 also only encompassed functional PCSK9b and PCSK9c polypeptides.

Novelty (Article 54 EPC)

Since the PCSK9b and PKSC9c polypeptides defined by SEQ ID NO:2 and SEQ ID NO:4 were novel, antibodies specifically binding to these novel polypeptides were also novel *per se*.

The correct standard for the assessment of novelty was "beyond reasonable doubt", i.e. it had to be beyond doubt, and not merely probable, that the claimed subject-matter was directly and unambiguously derivable from the prior art (see e.g. Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, I.C.4.1 and decisions T 943/93 and T 464/94 cited there).

The opponents' two-step assessment of novelty was not backed up by case law. Instead, to demonstrate that a product had inherent properties required conclusive evidence, for which the burden of proof lay with the opponents; however, no such proof had been provided.

Document D3 described a polyclonal antibody against murine PCSK9, which had an amino acid sequence that was different from human PCSK9 (see document D4). Document D3 did not demonstrate that this antibody cross-reacted with human PCSK9, let alone with the PCSK9b and PCSK9c polypeptides. Cross-reactivity was possible; however, this was not sufficient to deny novelty, which required a direct and unambiguous disclosure.

Furthermore, the PCSK9b and PCSK9c polypeptides were novel proteins which might have assumed a shape that was different from that of human PCSK9. Due to the particular folding of a protein, not every linear sequence within a protein could form an antigenic epitope. Consequently, the presence of a common amino acid stretch in different proteins was not sufficient evidence to conclude that these proteins shared a similar shape or common epitopes. Instead, it had to be assessed experimentally whether or not these polypeptides shared the PCSK9 epitope to which the antibody in document D3 bound. Wet-lab experiments would therefore have been required to prove that the known antibody bound to the PCSK9b or the PCSK9c polypeptides. In the absence of such experimental evidence, novelty had to be acknowledged.

XIII. The opponents' arguments, insofar as relevant to the decision, are summarised as follows.

Main request and auxiliary requests 1 to 6 - claim 5

Claim construction
Meaning of the expression "binds specifically to"

The binding specificity of an antibody was defined by the epitope to which it bound (see e.g. decision T 189/01; point 14 of the Reasons). Therefore, if the recognised epitope was present in another protein, the antibody also specifically bound to this other protein. The expression "binds specifically to" therefore did not exclude cross-reactivity with a protein comprising the same epitope, as was also evident from paragraphs [0234] and [0245] of the patent.

The notion that providing a novel protein justified a claim to an antibody to this novel protein did not apply to closely related proteins, which shared most of the epitopes of a known protein. This was the case for the PCSK9b and PCSK9c splice variants, which only differed from the PCSK9 protein on account of few amino acids. The subject-matter of claim 5 was hence not restricted to antibodies binding to epitopes which differed between PCSK9 and its splice variants PCSK9b and PCSK9.

Meaning of the expression "isolated polypeptide"

The expression "isolated polypeptide" not only referred to the native, functionally folded form of the polypeptide. The medical use recited in claim 8 as granted was an additional functional limitation of the isolated polypeptide in claim 8 over that in claim 5

and therefore could not be used to interpret the meaning of the expression "isolated polypeptide" in claim 5. Features which were only disclosed in the description, such as the catalytic activity of PCSK9b and PCSK9c mentioned in paragraphs [0102] and [0134] of the patent, could not be read into a claim either. The claimed subject-matter therefore also encompassed antibodies which bound to a linear epitope which was present in the isolated polypeptide of SEQ ID NO:2 or SEQ ID NO:4 and was accessible in a non-native unfolded or linearised form of the polypeptides.

Novelty (Article 54 EPC)

Novelty was a matter of two questions. An assessment had to be made both as to what matter was known in the art and how the properties of the known matter compared with the claimed subject-matter.

Document D3 disclosed a polyclonal antibody raised against specific peptides and recognising PCSK9 in an immunoblot. What had to be assessed was whether this antibody also bound to the PCSK9b and/or PCSK9c polypeptides which shared the amino acid sequence of the peptide against which the antibody had been raised.

The specific binding capability of an antibody was an objective measurable property inherent to the antibody. For such an inherent property, the correct assessment was based on the balance of probabilities, which did not necessarily require experimental evidence. It was a factual assessment of whether or not the PCSK9b and PSCK9c polypeptides formed similar epitopes as the PCSK9 protein, which did not have to be proved experimentally. It was commonly known that the same amino acid sequences would generate similar shapes when

folded, especially in a modular protein such as PCSK9. The skilled person therefore expected that PCSK9, PCSK9b and PCSK9c had similar shapes. Moreover, the antibody used in the experimental section of the patent recognised all three proteins and therefore demonstrated that a commonality of epitopes existed between these molecules. All the available evidence therefore pointed towards a similar structure of these proteins and therefore towards shared epitopes.

Moreover, the binding properties of an antibody raised against a specific short peptide were fully determined by the primary sequence of this peptide. Such an antibody hence bound to a linear epitope within this short peptide. This inherent property of the antibody could be taken into account and substantiate a lack of novelty. Indeed, if an antibody had been raised against a short peptide and the same short peptide was present in another protein, the antibody also necessarily bound to this other protein, at least when it was denatured.

The polyclonal antibody in the study reported in document D3 had been raised against two peptides consisting of amino acids 163 to 188 and 220 to 240 of murine PCSK9 (see page 5375, left-hand column, third full paragraph) and was shown to bind full-length and mature murine PCSK9 in a Western blot (see Figure 2). The peptide defined by amino acids 220-240 of murine PCSK9 was also comprised in the human PCSK9, PCSK9b and PCSK9c polypeptides, as was evident from the sequence alignment presented in document D4. An antibody raised against this peptide therefore also specifically bound to each of these human proteins comprising the identical peptide sequence under the non-native conditions of a Western blot.

XIV. The parties' requests, insofar as relevant to the decision, were as follows:

Appellant I (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the set of claims of the main request or, alternatively, on the basis of the set of claims of one of the auxiliary requests 1 to 6, all requests submitted with the statement of grounds of appeal (auxiliary request 5 being equivalent to requesting that the appeals of opponents 1 and 2 be dismissed); and that document D43 not be admitted.

Appellant II (opponent 1) and appellant III (opponent 2) requested that the decision under appeal be set aside and the patent be revoked. Appellant III further requested that the main request and auxiliary requests 1, 3 and 4 submitted with the patent proprietor's statement of grounds of appeal not be admitted into the proceedings and that document D43 be admitted.

Opponent 3, a party as of right in the appeal proceedings, did not formulate any requests.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Parties not represented at the oral proceedings

2. Opponent 3, a party as of right, was not represented at the oral proceedings, as announced previously. In accordance with Rule 115(2) EPC and

Article 15(3) RPBA 2020, the board decided to continue the proceedings in its absence.

Admittance of document D43 (Article 12(4) RPBA 2007)

3. The board decided not to admit document D43, submitted by opponent 2, into the appeal proceedings (see section X.). In view of the board's conclusions regarding novelty, it is not necessary to provide reasons for this decision.

Main request and auxiliary requests 1 to 6 - claim 5

Claim construction
Meaning of the expression "binds specifically to"

4. The independent claim is for an isolated antibody that binds specifically to one of two isolated polypeptides defined by their sequence, i.e. SEQ ID NO:2 or SEQ ID NO:4 (see sections I. and V.).

5. The opposition division decided that, in line with decision T 2101/09, the expression "antibody that binds specifically to" a polypeptide used in the claim limited the claimed subject-matter to antibodies that bound to epitopes which are unique for this polypeptide. Therefore, the claimed subject-matter was limited to antibodies "*reactive with those epitopes of PCSK9b (or PCSK9c) that discriminate PCSK9b (or PCSK9c) from other structurally related sequences in the art*".

6. The interpretation of a claim is a question of law. The meaning of the technical terms used in the claim, in this case the expression "antibody that binds specifically to" a polypeptide, depends on the specific factual context of the individual case, and more

precisely, how the skilled person would understand a particular claim on the relevant date in light of the specific context. This context includes the common general knowledge, the other claims of the patent or application, and the description. Therefore, even if, in another earlier decision, a board has come to the conclusion that a specific term has a specific meaning to the skilled person, this does not mean that the same understanding may, or even must, apply when considering another patent in which similar or identical technical expressions are used. This conclusion also applies in the field of antibodies to an expression such as "binds specifically to" or cognate expressions.

7. In the case underlying decision T 2101/09, the patent did not define the meaning of an antibody "specifically reactive with" a (novel) polypeptide and no evidence was available for a commonly accepted meaning of this term either (see points 7 and 8 of the Reasons). In the case at hand, however, it is explicitly stated in paragraph [0234] of the patent that the term "*antigenic epitope ... is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen*" and that "*[i]mmunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens*". In the context of antibody-antigen interactions, "immunospecific" binding is the same as "specific" binding because the prefix "immuno" only indicates that the definition relates to components of the immune system, i.e. a property inherent to antibodies binding to their antigens. The teaching in paragraph [0234] is moreover confirmed in paragraph [0245] of the patent, which specifically includes cross-reactive antibodies within the ambit of the invention. The case at hand is

therefore different from that underlying decision T 2101/09.

8. The definition of the term "immunospecific binding" in paragraph [0234] of the patent and the explicit inclusion of cross-reactive antibodies within the ambit of the invention in paragraph [0245] of the patent are in line with the assessment of the specificity of an antibody provided in decision T 189/01. In this decision, it was held that since an antibody was specific for an epitope and not for a protein, "specificity" did not exclude the fact that an antibody might cross-react with polypeptides other than those against which it has been raised. Accordingly, cross-reactivity was a feature of the antigenic epitope, which could be present on several different molecules (see point 14 of the Reasons).

9. In view of these considerations, the subject-matter of claim 5 encompasses antibodies that bind to epitopes shared by the isolated polypeptide of SEQ ID NO:2 (PCSK9b) or SEQ ID NO:4 (PCSK9c) and the PCSK9 protein. Indeed, such an antibody "specifically binds to" the PCSK9b or PCSK9c polypeptide on the one hand, since they bind to an antigenic epitope of this polypeptide, and "cross-react" with the PCSK9 protein which contains the same antigenic epitope on the other hand.

Meaning of the expression "isolated polypeptide"

10. The expression "isolated polypeptide", as commonly understood in the art, refers to a polypeptide removed from its original environment, i.e. a polypeptide which is, to some extent, purified. This interpretation is confirmed by paragraph [0075] of the patent, in which the term "isolated" is explained as referring "*to*

material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state". Consequently the "isolated polypeptide" referred to in claim 5 does not need to be in its active native form, but could also be in a denatured or linearised form provided that it has been isolated from its natural environment.

11. The disclosure in paragraphs [0102] and [0134] of the patent and claim 8 as granted (see section I.) does not change this interpretation. Paragraphs [0102] and [0134] disclose that the PCSK9b and the PCSK9c polypeptides retain "*the catalytic triad of the wild-type PCSK9 polypeptide*"; however, this information has no bearing on the interpretation of the expression "isolated polypeptide" in the claim because the claim neither requires the polypeptide to be functional nor requires it to be in its native conformation. Claim 8 as granted concerns an "isolated polypeptide" for use in preventing, treating, or ameliorating a medical condition, i.e. contains an additional functional limitation of the recited "isolated polypeptide" which is absent from claim 5 and therefore cannot be used to restrict the subject-matter of this claim.

12. In view of the above considerations on the meaning of the expressions "binds specifically to" and "isolated polypeptide", the board concludes that the subject-matter of claim 5 encompasses antibodies binding to an epitope shared by the full-length or mature PCSK9 protein and one or both of the PCSK9b and PCSK9c polypeptides, including linear epitopes and epitopes accessible only in denatured forms of the polypeptides.

Novelty (Article 54 EPC)

13. The opposition division considered that the subject-matter of claim 5 was novel over the disclosure of each of the documents cited by the opponents, including document D3, irrespective of the interpretation of the expression "binds specifically to". According to the opposition division, the opponents "*did not show beyond doubt that one of the antibodies disclosed in documents D3, D5, D6, ... or D35 is able to bind the antigen of SEQ ID NOs:2 or 4*". At least the commercially available antibodies could have been tested experimentally to demonstrate a specific binding.

14. The board disagrees with this assessment. The question of whether or not a given known antibody binds to a particular polypeptide is a question of fact. It is correct that the inherent binding property of the antibody concerned must be demonstrated by the party making the allegation, i.e., in the case at hand, the burden to prove that the antibody disclosed in document D3 binds to the PCSK9b and/or PCSK9c polypeptides lay with the opponents; however, the standard of proof generally applied at the EPO for deciding on an issue of fact is the balance of probabilities. According to this standard, the EPO must base its decisions on statements of fact which, based on the available evidence, are more likely than not to be true (see also the decisions summarised in Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019 ("CLBA"), III.G.4.3 and III.G.4.3.1). This standard also applies when examining factual issues in the context of novelty.

15. The board is not persuaded by the arguments of the opposition division and the patent proprietor that, by way of exception, a higher standard must apply in the present case. The opposition division considered that "[t]*he argument from the Os* [opponents] *that because the prior art discloses antibodies binding to epitopes of the human wild type PCSK9 identical to epitopes of PCSK9b or PCSK9c, which makes it "reasonable to assume" or highly likely*" [sic] *that they also recognize the latter protein, is not sufficient to argue that the prior art directly and unambiguously discloses an antibody binding to the antigens of SEQ ID NOs: 2 or 4*."

16. However, in this reasoning, the opposition division appears to mix up two issues which are distinct and unrelated: i) the issue of which *standard of disclosure* applies when assessing the legal question of novelty, and ii) the issue of which *standard of proof* applies when assessing evidence and factual questions. The fact that the standard of disclosure required for a finding of lack of novelty (or for allowing an amendment to the application under Article 123(2) EPC) is the standard of a direct and unambiguous disclosure is immaterial to the question of which standard of proof applies when considering evidence and factual issues in the context of novelty (or inventive step).

17. The board is also not persuaded by the patent proprietor's argument that, *inter alia*, decisions T 943/93 and T 464/94 supported the notion that a higher standard of proof than that of the balance of probabilities applied when examining novelty.

18. In decision T 943/93, the deciding board arrived at the conclusion that the skilled person operating a

semiconductor laser amplifier "*according to the conventional rule ... would automatically work outside the claimed wavelength region*" (see point 2.4 of the Reasons). No evidence had been provided that an experimental adaptation necessary for operating within the claimed wavelength region "*was disclosed in a prior art document or was realised in practice before the priority date of the patent under appeal*". There was therefore only a "*hypothetical possibility of operating within the claimed region*", which was considered as "*not sufficient to destroy the novelty of this region*" (see point 2.5 of the Reasons).

19. Therefore, in this board's understanding, in T 943/93 the deciding board considered that the abstract possibility that an operator, by experimentally adapting the wavelength, could work within the wavelength region mentioned in the claims of the patent, without evidence that such an adaptation had in fact been put into practice or disclosed in another form before the critical date, was not sufficient for considering the claimed subject-matter to be anticipated. Therefore, the deciding board neither dealt with the standard of proof nor contended that the balance of probability would not apply when determining factual issues relevant for the question of novelty. Decision T 943/93 is hence not relevant for the case in hand.

20. In the case underlying decision T 464/94, a cited document reported on experiments for stably transforming cells but was inconclusive on whether this goal had actually been achieved. In fact, the authors of the document themselves expressed doubts that the observed results reflected a stable cell transformation. Nonetheless, the opposition division

considered it "probable" that the process described in the document resulted in a stable cell transformation, i.e. that the document disclosed a stable cell transformation in a reworkable manner. Based on this finding the patent was revoked for lack of novelty. On appeal, however, the deciding board held that it was not admissible to decide on the question of novelty on the basis of probabilities. The board stated (see point 16 of the Reasons):

"*Nach Auffassung der Kammer ist es nicht gerechtfertigt, bei der Beurteilung der Neuheitsschädlichkeit einer Druckschrift Wahrscheinlichkeitsüberlegungen anzustellen. Wenn ein Patent wegen mangelnder Neuheit widerrufen wird, muß sich die entscheidende Instanz, nach Würdigung aller in dem Verfahren vorgebrachten Argumente und Tatsachen, sicher sein, daß diese einen Widerruf des Patents rechtfertigen. Im Zweifel muß eine weitere Aufklärung des Sachverhalts erfolgen, ansonsten kann das Patent nicht wegen fehlender Neuheit widerrufen werden*".

(Translated into English (adapted from CLBA, I.C.4.1): "In the board's view, it is not justifiable to decide whether a document is prejudicial to novelty on the basis of probability. When a patent is revoked for lack of novelty, the department concerned has to be sure, having taken all the facts and arguments put forward during the proceedings into consideration, that the revocation is justified. In case of doubts, further clarification of the factual situation must be carried out; otherwise, the patent cannot be revoked for lack of novelty".)

21. First, this board notes, however, that it is not clear whether the deciding board was referring in this

statement to the assessment of legal issues in the context of novelty, such as the question of whether the skilled person would have directly and unambiguously derived a specific piece of information from a document, or to the assessment of factual questions, such as whether particular information was published on a specific date, whether a given process resulted in a particular product or whether the product concerned had a specific property. This board is therefore not persuaded that the board in decision T 464/94 indeed adopted an approach to the assessment of factual questions that was different from that which this board intends to follow.

22. Second, even if the deciding board in the above-cited passage also had questions of fact in mind, it had not provided any reason or argument in support of the notion that a higher standard of proof than that of the balance of probabilities applies when examining novelty. Against this background, this board sees no reason not to follow the general principles of established case law set out above (see point 14.) and not to apply the balance of probability to decide on the factual questions relevant for assessing novelty in the case at hand.

23. The factual question to be decided upon in the present case is whether it is more likely than not that a known PCSK9 antibody would bind specifically to the PCSK9b and/or the PCSK9c polypeptide. In assessing this question, any evidence submitted by the parties is considered by the board and such evidence does not necessarily have to be in the form of "wet lab" experiments, as argued by the patent proprietor. The question must be answered in the affirmative in the

board's opinion, for the reasons set out in the following.

24. Document D3 discloses a polyclonal antibody raised against two short murine PCSK9 peptides (see page 5375, right-hand column, third full paragraph). When an antibody is raised against a short peptide, the antibody recognises an epitope within this peptide. It is also demonstrated in document D3 that the polyclonal antibody binds to full-length and mature murine PCSK9 in an immunoblot after denaturing gel electrophoresis ("SDS-PAGE") (see Figures 2A and 6A), i.e. it binds to the peptide in a denatured form. The binding properties of the polyclonal antibody disclosed in document D3 are therefore determined by the linear amino acid sequence of the peptides against which it was raised.

25. One of the peptides used for immunisation in document D3 consists of amino acids 220 to 240 of murine PCSK9. An identical amino acid sequence is present in human PCSK9 (amino acids 217 to 237), PCSK9b and PCSK9c (amino acids 48 to 68), surrounded by amino acid sequences that are also almost identical in each of these four PCSK9 forms (see the boxed sequence in the sequence alignment of document D4). Therefore, the linear amino acid sequence, which contains the epitope to which the antibody binds, is fully contained within the PCSK9b and PCSK9c polypeptides.

26. Thus, the polyclonal antibody disclosed in document D3 recognises an epitope determined by the linear sequence of a peptide (see point 24. above), which is fully contained within the PCSK9b and PCSK9c polypeptides (see point 25. above). In view of this factual assessment, the board considers that it is more likely than not that this antibody, the availability of which

had not been questioned, also specifically binds to the PCSK9b or PCSK9c polypeptides, at least in a so-called "Western blot", i.e. an immunoblot of proteins separated by denaturing gel electrophoresis. Consequently, the board concludes that, based on the applicable standard of proof, the polyclonal antibody disclosed in document D3 also specifically binds to the PCSK9b and PCSK9c polypeptides comprising the same peptide.

27. The subject-matter of claim 5 in each of the claim requests on file therefore lacks novelty over the polyclonal antibodies disclosed in document D3 (Article 54 EPC).

Main request and auxiliary requests 1, 3 and 4
Admittance (Article 12(4) RPBA 2007)

28. Since the subject-matter of claim 5 of each of these requests lacks novelty (see points 13. to 27. above), it is not necessary to decide on the admittance of these requests into the appeal proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated