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# Datasheet for the decision of 10 December 2009

**Case Number:** T 1653/07 - 3.3.04

**Application Number:** 98110526.5

**Publication Number:** 0893450

**IPC:** C07K 16/06

**Language of the proceedings:** EN

**Title of invention:**
Chromatographic method for high yield purification and viral inactivation of IgG

**Patentee:**
BAYER CORPORATION

**Opponent:**
Octapharma AG

**Headword:**
Purification of IgG/BAYER

**Relevant legal provisions:**
EPC Art. 56

**Relevant legal provisions (EPC 1973):**
-

**Keyword:**
"Main request - inventive step (yes)"

**Decisions cited:**
-

**Catchword:**
-

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**Case Number:** T 1653/07 **-** 3.3.04

# D E C I S I O N
## of the Technical Board of Appeal 3.3.04
## of 10 December 2009

**Appellant**: (Opponent)
Octapharma AG
Seidenstrasse 2
CH-8853 Lachen (CH)

**Representative**:
von Kreisler Selting Werner
Patentanwälte
Deichmannhaus am Dom
Bahnhofsvorplatz 1
D-50667 Köln (DE)

**Respondent**: (Patent Proprietor)
BAYER CORPORATION
100 Bayer Road
Pittsburgh
PA 15205-9741 (US)

**Representative**:
Burkert, Frank
Bayer Schering Pharma Aktiengesellschaft
Law and Patents
Patents and Licensing
Building Q 18
D-51368 Leverkusen (DE)

**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 11 July 2007 rejecting the opposition filed against European patent No. 0893450 pursuant to Article 102(2) EPC 1973.**

**Composition of the Board:**

**Chair:** U. Kinkeldey
**Members:** R. Gramaglia
R. Moufang

## Summary of Facts and Submissions

I. European patent No. 0 893 450 (application No. 98110526.5), having the title "Chromatographic method for high yield purification and viral inactivation of IgG" was granted with 9 claims, of which claim 1 read as follows:

"1. A method of preparing a purified, virally inactivated IgG preparation from a starting solution comprising IgG and contaminants, the method comprising the steps of:

(a) adjusting the pH of the starting solution to 3.8 to 4.5 to produce an intermediate solution;

(b) adding caprylate ions to the intermediate solution and adjusting the pH to form a supernatant solution comprising antibodies and a precipitate;

(c) separating the supernatant solution from the precipitate;

(d) incubating the supernatant solution under conditions of caprylate ion concentration, time, pH and temperature such that the titer of active enveloped virus is reduced by at least 2 log units or to an undetectable level, to produce a virally inactivated solution;

e) contacting the virally inactivated solution with at least one anion exchange resin and optionally with two different anion exchange resins under conditions that allow binding of contaminants to the resin while not

allowing significant binding of IgG to the resin, wherein a purified, virally inactivated IgG preparation is produced."

Dependent claims 2 to 9 related to specific embodiments of the method according to claim 1.

II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of Article 100(a) EPC on the grounds that the claims did not fulfil the requirements of Article 56 EPC.

III. The opposition division rejected the opposition and maintained the patent as granted.

IV. The appellant (opponent) filed an appeal against the decision of the opposition division.

V. Oral proceedings were held on 10 December 2009.

VI. The following documents are cited in the present decision:

D1 Habeeb A.F.S.A et al., Preparative Biochemistry, Vol. 14, No. 1, pages 1-17 (1984);

D3 EP-A-0374625;

D5 Prin C. et al., Biochimica Biophysica Acta, Vol. 1243, pages 287-290 (1995).

VII. The submissions by the appellant, insofar as they are relevant to the present decision, can be summarized as follows:

*Inventive step (Article 56 EPC)*

– The closest prior art was represented by document D1. This document already disclosed a process for preparing a purified IgG preparation including steps (a), (b), (c) and (e) of claim 1, which process already achieved high IgG purity and yield. The only problem left to be solved by the patent in suit was thus to provide a further viral inactivation step to the process described in document D1. However, since document D3 taught that this problem could be solved by addition of caprylate, it would have been obvious for the skilled person to combine the teachings of documents D1 and D3 and thereby arrive at the claimed invention.

– In view of the poor caprylic acid solubility in water (0.69 g/l), the skilled person would understand that the teaching by document D1 to add 15 ml caprylic acid to 600 ml solution was an error and that a dilute caprylic acid solution should have been added, as prescribed by document D3.

– The distinction made by the respondent between caprylic acid and caprylate in solution was artificial because these species reached an equilibrium.

– Furthermore, a pH shift to 5.0-5.2 was an essential step which was missing from the claims, and thus claim 1 failed to solve the problem posed.

VIII. The submissions by the respondent (patentee) can be summarized as follows:

Inventive step (Article 56 EPC)

– Combining the teachings of documents D1 and D3 did not result in the process according to present claim 1 because there were fundamental differences between the claimed process and the one described in document D1. These lay in the use of caprylate ions (claimed process) instead of caprylic acid (document D1) and in the pH of the starting solution. Fig. 2 of document D5 showed that IgA went in solution at a lower pH. There was thus no incentive to lower the pH.

– By using caprylate ions in the claimed process instead of caprylic acid (document D1), considerably less caprylic acid (under its ionized form) was required in order to achieve high IgG purity and yield. Prior to the present invention, nobody adopted this approach. Document D1 did not suggest that lower levels of caprylate would have successfully precipitated proteins. On the contrary, the teaching by document D1 that the conditions described therein were optimum conditions would have discouraged the skilled person from using caprylate at a much lower concentration.

– A pH shift to 5.0-5.2 was not an essential step. In any case, the addition of caprylate salt would increase the pH.

IX. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 893 450 be revoked.

The respondent (patentee) requested that the appeal be dismissed.

## Reasons for the Decision

*Inventive step (Article 56 EPC)*
*Closest prior art*

1. The process according to present claim 1 and that described in document D1 are based on the known phenomenon that caprylic acid forms insoluble complexes with α- and β-globulins whereas γ-globulins (= IgGs) are not precipitated (i.e., they remain in solution). Document D1 discloses (see pages 2 and 3) a method of preparing a purified IgGs preparation from a starting solution comprising IgGs and contaminants, the method comprising the steps of:

(a) adjusting the pH of the starting solution to 4.8 to produce an intermediate solution;

(b) adding caprylic acid to the intermediate solution to form a supernatant solution comprising antibodies and a precipitate;

(c) separating the supernatant solution from the precipitate;

(e) contacting the supernatant solution after caprylic acid precipitation with an anion exchange resin (DEAE-cellulose) under conditions that allow binding of contaminants to the resin while not allowing significant binding of IgG to the resin, wherein a purified IgG preparation is produced.

Therefore, document D1 is considered by both parties and by the board as the closest prior art.

2. It is argued by the appellant that the process described in document D1, including steps (a), (b), (c) and (e) of claim 1, achieved IgGs purity and yield comparable to those reported in the patent in suit. The only problem left to be solved by the patent in suit vis-à-vis document D1 was, in the appellant's view, to provide a further viral inactivation step (step (d) in claim 1) to the prior art process. But since document D3 taught that this problem could be solved by addition of caprylate, it would have been obvious for the skilled person to combine the teachings of documents D1 and D3 and thereby arrive at the process according to present claim 1.

3. It is true that the method disclosed in document D1 differs from the method claimed by the absence of a step of viral inactivation (d). However, the board notes two further differences in step (a), relating to the pH of the starting solution (claimed process: pH = 3.8-4.5; process according to document D1:

pH = 4.8) and in step (b), as explained in more detail below.

4. As regards step (b), document D1 (see page 2, under the heading "Treatment of Plasma With Caprylic Acid") teaches the addition of 15 ml caprylic acid to 600 ml of diluted plasma solution (200 ml plasma + 400 ml buffer). As emphasized by the appellant in the submission dated 12 November 2007 (see page 2, second full paragraph), the non-ionized form of caprylic acid is poorly soluble in water (0.68 g/l corresponding to 0.068 g/100 g water (assuming 100 ml water = 100 g) or 0.068 weight percent (wt %); see also document D3, page 3, lines 35-36). Therefore, these 600 ml solution are able to only solubilise about 0.07 g/100 g x 6 = 0.43 g caprylic acid, while most of the insolubilized 15 ml (= about 13.5 g) of the added caprylic acid forms a biphasic system with the 600 ml diluted plasma solution.

5. The appellant argues that the skilled person would understand that the teaching by document D1 to add an excess (15 ml) of insoluble caprylic acid to 600 ml solution was an error and that a dilute caprylic acid solution should have been added, as suggested by document D3.

6. It is true that document D3 suggests the use of dilute caprylic acid solutions, however, in the board's opinion, this is done in the context of inactivating lipid-coated viruses. It is indeed stated on page 3, lines 39-43 of this document that 0.001 to 0.07 wt % caprylic acid achieve almost instantaneous virus inactivation. If ionized caprylate is used, its

concentration should be kept at 0.1 wt % at pH = 4.8 (see page 4, line 34), in order to achieve the same result.

However, insofar as document D3 relates to precipitation of contaminant proteins with caprylic acid (see the passage from page 2, line 13 to page 3, line 7, under the heading "Prior Art"), it is stated that caprylic acid, when used as precipitating agent, has to be present in an amount considerably above its maximum solubility in water, "commonly about 0.86 - 2.5 wt %" (see page 3, lines 3-5 of document D3), thus leading to a biphasic system. The "biphasic" way to proceed described in document D1 is thus in keeping with the passage in document D3 cited above (also compare the term "emulsion" on page 3, lines 7 and 37 of document D3 with the wordings "suspension" and "suspended particles" on page 2 of document D1, under the heading "Treatment of Plasma With Caprylic Acid").

7. In contrast to the "biphasic" approach disclosed in document D1 and further dealt with by document D3, the process according to granted claim 1, part (b) involves the addition to the dissolved immunoglobulins of **a miscible solution of caprylate ions** (e.g., 40% w/v sodium caprylate in water: see page 4, line 13 of the patent).

8. The appellant argues that the differences in pH of the starting solution (step (a)) and in the use of caprylate ions instead of caprylic acid (step (b)) between the claimed process and that described in document D1 are trivial, once taking into account the equilibrium equation between caprylic acid and

caprylate, as reported on page 4, lines 11-15 of document D3 (wherein a double arrow (<->) showing equilibrium between caprylic acid and caprylate is apparently missing).

9. The board agrees that upon mixing the ingredients, the concentrations of not only caprylic acid and caprylate (as the appellant points out), but also of $OH^-$ and $H_3O^+$ (pH) reach an equilibrium. Nevertheless, the claimed process, represents an approach fundamentally different from that described in the prior art. This is because upon addition of a miscible solution of caprylate ions to the dissolved immunoglobulins, a technical effect turns up, as illustrated by the fact that about ten fold less caprylic acid (under its ionized form) is required in order to achieve similar IgG yields after step (b). This technical effect is indeed shown by comparing the 15 mM to 25 mM (0.22 to 0.36 wt %) referred to in paragraph [0022] of the patent with the 0.15 M (= 150 mM or 2.16 wt %) undissociated caprylic acid used in the process according to document D1 (see the comment on "Habeeb et al." (= document D1) in document D3). As regards the similar IgG yields after step (b), the comparison should be made between the averaged 82% in Table I of document Dl with the 84% ("Post CLM Treatment") in the Table on page 5 of the patent. The technical effect above suggests that the precipitation mechanism or kinetics underlying the "caprylate" approach is fundamentally different from the "biphasic" approach described in document D1.

*Problem to be solved*

10. Starting from document D1 as closest prior art, the problem to be solved can be seen in the provision of an alternative process for preparing purified IgGs from a starting solution comprising IgGs and contaminants. As regards the question whether or not the solution to this problem proposed in claim 1 follows from the prior art in an obvious way, the board observes that document D1 did not suggest that lower levels of undissociated caprylic acid, let alone of ionized caprylate would have successfully precipitated contaminant proteins, while leaving IgGs in solution. Rather, this document taught that its conditions were optimum conditions (see page 14, line 4). This would have discouraged the skilled person from using much lower concentrations of undissociated caprylic acid, let alone ionized caprylate. In fact nobody attempted the "caprylate" approach before the authors of the patent in suit. In conclusion, the board views the changes recited in steps (a) and (b) of claim 1, compared to steps (a) and (b) of the process described in document D1, as non obvious rather than trivial modifications.

11. Therefore, the appellant's line of argument relying on the combination of the teachings of documents D1 and D3 for questioning the inventive step of the process of present claim 1, is not convincing.

12. But assuming, for the sake of argument, that the skilled person would have modified the process according to document D1 by using ionized caprylate at a pH of 3.8-4.5, the skilled person, when turning to document D3, would be taught that high caprylic acid

concentrations (0.86-2.5 wt %) were required for precipitation and low concentrations (0.001 to 0.07 wt % caprylic acid or 0.1 wt % ionized caprylate at pH = 4.8) were required to kill viruses (see point 6 supra). Therefore, the skilled person coming across document D3 would merely obtain confirmation by this document that virus inactivation had implicitly taken place. Hence document D3 did not provide to the skilled person any incentive to either use lower concentrations of caprylic acid, let alone of ionized caprylate, in order to precipitate IgG (see point 10 supra), or to introduce a further virus inactivation step, in order to kill enveloped viruses.

13. The board must conclude that combining the teachings of documents D1 and D3 would not have resulted in or led to the process according to present claim 1.

14. Finally, the appellant argues that a pH shift to 5.0-5.2 is an essential step (see paragraph [0016] of the patent specification) which is missing from the claims, and that hence claim 1 fails to solve the problem posed.

15. The board firstly agrees with the respondent that the addition of caprylate salt would increase the pH from its starting value of 3.8 to 4.5 recited in step (a) of claim 1. This can be derived from the Henderson-Hasselbalch equation on page 4, line 20 of document D3, upon increasing "[ionized form]" in the formula (i.e., the concentration of caprylate in the present case).

Moreover, during the oral proceedings before the first instance (see points 14.1 and 14.2 of the "minutes"),

technical experts from both parties expressed the opinion that the final pH range had in any case to be optimized to achieve a compromise between yield and purity. These experts also expressed the view that at higher or lower pHs than 5-5.2, the invention would also work, however, the yield or purity would be lower. The board adheres to the experts' view above and also considers that, unlike the features recited in steps (a) and (b) in claim 1, a pH shift to 5-5.2 merely represents an optimal value rather than an essential feature of the invention. The subject-matter of present claim 1 thus solves the problem posed by virtue of the distinguishing features recited in steps (a) and (b) of claim 1, not of a pH shift to 5-5.2.

16. Claim 1 and dependent claims 2 to 9, relating to specific embodiments of the method according to claim 1, are thus found to satisfy the requirements of Article 56 EPC.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: Chair:

P. Cremona U. Kinkeldey