

The opinion in support of the decision being entered today was *not* written for publication and is *not* binding precedent of the Board.

Paper No. 13

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WILLIAM R. ALONSO

Appeal No. 2001-1485
Application No. 08/532,211

HEARD: MAY 22, 2003¹

Before WILLIAM F. SMITH, ADAMS and MOORE, *Administrative Patent Judges*.

MOORE, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1 - 24, which are all of the claims pending in this application.

1 A request for oral hearing was made within the notice of appeal dated December 18, 1996. Although the appellant appears to have been charged the appeal and oral hearing fees on January 16, 1997, the request for oral hearing was not acted upon by the USPTO. As a historical note, we observe that at the time the request was filed, 37 CFR 1.194 (b) (1993) read "If appellant desires an oral hearing, appellant must file a written request . . ." 37 CFR 1.194 (b) (1997) now reads "If appellant desires an oral hearing, appellant must file, in a separate paper, a written request for such hearing . . ." Such oversights are now more easily avoided. We sincerely apologize for the delay in discovering the oral hearing request.

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REPRESENTATIVE CLAIM

Claim 1 is representative of the claims on appeal and reads as follows:

1. A method of treating a solution of antibodies which may have virus activity, the method comprising:
 - a) contacting the solution with a trialkylphosphate and a detergent under conditions sufficient to substantially reduce any virus activity and resulting in an increased level of anticomplement activity; and
 - b) then incubating the solution of step a) under conditions of controlled time, pH, temperature, and ionic strength, such that the increased anticomplement activity of the solution is reduced to an acceptable level suitable for intravenous administration.

The References

In rejecting the claims under 35 U.S.C. § 103(a) the examiner relies upon the following references:

Tenold (Tenold)	4,396,608	Aug. 02, 1983
Neurath et al. (Neurath)	4,540,573	Sep. 10, 1985
Mitra et al. (Mitra)	4,762,714	Aug. 09, 1988

Joy Yang, Y.H. et al., "Antibody Fc Functioning Activity of Intravenous Immunoglobulin Preparations Treated with Solvent-Detergent for Virus Inactivation," Vox Sang, 1994; 67:337-344 (Joy Yang).

The Rejections

Claims 1-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tenold in view of Neurath, Mitra, and Joy Yang.

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The Invention

The invention is directed to a method for treating a solution of antibodies which may have viral activity by a two-step process of first contacting the solution with a trialkylphosphate and detergent under conditions which reduce viral activity and increase anticomplement activity, then incubating the solution under controlled time, pH, temperature, and ionic strength to reduce the increased anticomplement activity. (Claim 1).

Discussion

The § 103 Rejection of Claims 1-24 over Tenold in view of Neurath, Mitra, and Joy Yang

The examiner has found that Tenold teaches the modification of immune serum globulin (ISG) to reduce anticomplement activity (ACA) in order that the serum may be administered safely. (Examiner's Answer, page 4, lines 15-17). The resulting ISG product is then maintained at a controlled pH, temperature, ionic strength, and tonicity so as to generate a monomeric solution of antibodies with a reduced ACA rendering the solution safe for intravenous administration (Id., page 5, lines 7-11).

The examiner has also found that Neurath discloses a method for inactivating infectious virus present in blood or blood derived solutions (including ISG) while maintaining the activity of proteins contained in the composition. This is accomplished by treating the solution with a trialkylphosphate and a detergent

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followed by removal of the inactivating agents and further optional processing of the product. (Id., page 5, line 19 - page 6, line 7).

The examiner has additionally found that Mitra teaches the need to produce virus-free ISG to prevent viral infection in patients. Mitra also recognizes the historic need to reduce the ACA to obtain safe ISG. (Id., page 6, lines 8-14).

The examiner has further found that Joy Yang discloses an ISG with a deliberate virus inactivation step followed by retention of complement activity. (Id., page 6, line 15 - page 7, line 8).

The examiner thus concludes that it would have been obvious to one of ordinary skill at the time the invention was made to modify Tenold to pretreat for viral reduction as taught by Neurath, Mitra, and Joy Yang to both ensure reduction of viruses and low ACA. (Id., page 7, lines 6-11). As to the incubation step of Claim 1(b), the examiner explains that the "antibody solution [of Tenold] is stored for up to six months under the defined controlled parameters," citing Tenold, column 4, line 24 - column 8, line 54).

The appellant, on the other hand, asserts that there is no suggestion or motivation to require a step (b) which reduces the increased ACA level as no one was aware of the "surprising" increase. Consequently, no one could have expected the increased ACA level, much less found a way to counter it. (Appeal Brief,

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page 4, lines 4-34).

The appellant also asserts that the Tenold and Mitra references do not teach a decrease in ACA, and Tenold blames the increase of ACA on aggregation of the monomers. (Id., page 5, lines 1-11). Mitra, it is urged, fails to disclose a lowering of ACA due to incubation conditions. (Id., page 5, lines 12-18).

We observe that it is not in dispute that the appellant's process combines two relatively well-known steps to accomplish known functions. Neurath is known to provide acceptable viral inactivation (Neurath, column 4, lines 1-18), and Tenold to provide ISG solutions with low ACA (Tenold, column 8, lines 8-10). Indeed, that is the basis for the examiner's rejection - inactivation of viruses and a low ACA are required for intravenous preparations - therefore it would have been obvious to pretreat the Tenold starting material to eliminate viruses. (Examiner's Answer, page 9, lines 1-20).

The examiner notes that none of the applied prior art teaches an increase in ACA activity after viral inactivation by treatment with trialkylphosphate and detergent, but also asserts that it was art-standard knowledge that the level of ACA must be low for the serum globulin to be injected intravenously (Examiner's Answer, page 8, lines 4-8).

However, the claimed subject matter requires that the inactivation step result in an increase in ACA levels, and a

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reduction in that claimed increase by the incubation step to a point where the solution is suitable for intravenous use. The appellant argues that there is no motivation to require an incubation step (b) as the increase in ACA caused by using the solvent-detergent method was unexpected. (Appeal Brief, page 4, lines 8-10). The examiner has admitted that the prior art is silent on this claimed increase in ACA.

It is clear to us that the problems of viral presence in antibody solutions and the problems of reducing ACA to an acceptable level were well known, as discussed in the cited references. The solvent-detergent method of Neurath inactivates viruses, and the Tenold ACA reduction process reduces ACA. The appellant has admitted that the combination of the Neurath and Tenold procedures "may have been an obvious step" (Appeal Brief, page 4, lines 4-5) but that such combination "would only result in step (a)" (Id., page 4, lines 6-7).

The appellant has discovered that Neurath's process results in elevated ACA levels (Specification, page 17, last 2 lines). Although the ACA increase was unrecognized, Neurath alone therefore inherently meets step (a) of the process. Neurath also suggests "further processing" (column 9, lines 19-24). The question then presented is whether one of ordinary skill in the art would be taught to follow with the Tenold process and whether the instantly claimed results would be obtained.

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Tenold discloses a method for reducing ACA in ISG to the point that the ISG is suitable for IV administration. This is accomplished by solubilizing an ISG to yield a solution with a certain protein concentration. The pH and ionic strength of the solution is adjusted to the point where the monomer content of the ISG is greater than about 90% and the actual and latent ACA is such that the ISG product is IV injectable. (Tenold, column 4, lines 30-41). The examiner states that Tenold differs from the instant claims in that the starting material is not pre-treated to inactivate infectious agents (Examiner's Answer, page 5, lines 16-18). The appellant urges that Tenold already has a low ACA and consequently cannot reduce ACA. (Appeal Brief, page 5, lines 3-6).

Tenold also discloses storing the solutions at an ionic strength of 0.001, a pH of 4.2, at room temperature, and for a six-month period of time. (Tenold, column 9, lines 12-21). The specification reveals that the incubation is conducted at an ionic strength of 0.001, a pH of 4.25, at 20-27°C (room temperature), at not less than 21 days (Specification, page 9, lines 4-12). Thus, Tenold would appear to disclose the values required by step (b) to obtain the desired ACA goal.

Viewed alone, the relied upon teachings of the applied prior art may perhaps be said to support a conclusion of prima facie obviousness.

However, the specification establishes the following:

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(1) Solvent detergent viral inactivation results in an increase in ACA (See Table 1, Specification, Page 11).

(2) Using the solvent detergent process to treat ISG and subsequently treating that product according to Tenold does not result in a product having acceptable ACA levels when measured immediately. (Specification, paragraph bridging pages 2 and 3 and Table 5).

(3) In contrast, holding ("incubating") the solvent-detergent inactivated samples results in marked lowering of ACA (Specification, page 12, Table 3).

(4) The ACA results do not appear to correlate to the monomer content (Specification, page 17, table 8).

(5) Tenold's basic process (starting with non-solvent detergent inactivated solutions) results in a 25 ACA (CH₅₀/mL). (Specification, page 11, table 1).

From this, it is apparent that the problem being addressed places the question of whether a prima facie case of obviousness exists in a different light. First, one must question whether the teachings and results of Tenold can be combined with Neurath successfully. See, for example, the paragraph bridging pages 2 and 3 of the specification. Tenold starts with an unmodified human ISG (Tenold, column 4, lines 65-66) initially having an ACA which is unacceptable for intravenous injection (although the actual ACA level is not specifically described) (Tenold, Column 1,

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lines 23-27). The ACA level is lowered such that the final product has an ACA which is acceptable immediately, without appreciable change in the monomer content after 6 months (Column 8, lines 8-10). From the evidence provided by the appellants, this ACA can initially be 25 (Specification, page 11, Table 1).

If one of skill in the art starts with the Neurath solvent detergent modified ISG, and further treats that product by the Tenold process, the ISG would apparently still have an unacceptable ACA level. (See specification, table 3, page 12).

The examiner does not dispute the data in the specification showing that simply treating a solvent detergent virally inactivated ISG solution obtained by way of the Neurath process will not have an acceptable ACA level immediately or shortly after being further treated by the procedure described in Tenold. Rather, the examiner relies upon the data reported after containers of the Tenold treated ISG had been stored for six months.

Specifically, Tenold states at column 9, lines 15-30 that initial results indicated that a monomer level of 99% had been achieved. That level of monomer content had been maintained for six months. How does the Tenold data compare with the data in the present specification? Not well.

The appellants state that they treated solvent detergent virally inactivated ISG obtained by way of the Neurath process

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with the Tenold ACA lowering procedure and that the resulting product did not have an initially acceptable ACA level. This is in direct contrast to Tenold's statements that the process initially provides an acceptable ACA. Confronted with this anomaly, why would one of ordinary skill in the art then further incubate the solvent detergent treated ISG having an unacceptable ACA after the Tenold process?² On this record we find no reason to do so.

The six-month data in Tenold only shows that an initial acceptable ACA level can be maintained upon six months storage. Importantly, Tenold does not teach that the initially high ACA level may be lowered merely by storing the ISG for six months. Assuming the examiner is correct, and that one of skill in the art would measure ACA after Neurath's solvent detergent treatment, that person would presumably discover what the appellants did; the ISG has a higher ACA level than expected. Why, then would one skilled in the art know that simply treating the solvent detergent ISG by way of Tenold would not lower the ACA to an acceptable level, but rather a significant incubation step would be needed? Again Tenold only indicates that six months storage maintains, not lowers, the ACA level.

² Although not discussed in the Examiner's Answer or the Brief, we observe that Mitra teaches a Cohn fractionated ISG, when stored, shows a reduction in the AIDS virus. (Column 6, lines 42-54 and column 7, line 1 to column 8, line 25). However, this storage does not occur after a solvent detergent inactivation step, and does not reveal the effect on the ACA of the ISG solution.

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"Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

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We think this is the case here. Once appellants did what the prior art would reasonably appear to suggest doing, they found they did not obtain the expected results. It was only after obtaining the anomalous results did they understand the problem and discover its solution.

The decision of the examiner is reversed.

Summary of Decision

The rejection of claims 1-24 under 35 U.S.C. §103(a) as being unpatentable over Tenold in view of Neurath, Mitra, and Joy Yang is reversed.

REVERSED

WILLIAM F. SMITH)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
DONALD E. ADAMS)	
Administrative Patent Judge)	APPEALS AND
)	
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