

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte LAWRENCE BUSH and CHANDRA WEBB

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Appeal No.1997-3511  
Application No. 08/233,663

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ON BRIEF

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Before ROBINSON, SPIEGEL, and ADAMS, Administrative Patent Judges.  
ROBINSON, Administrative Patent Judge.

REMAND TO THE EXAMINER

Our review of the record in this appeal indicates that the case is not in a condition which will permit meaningful review of the issues raised. Therefore, we vacate the examiner's rejection under 35 U.S.C. § 103 and remand the application for further consideration of the points discussed below.

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Claims 1, 9, 14, 19, and 29 are illustrative of the claims on appeal and are reproduced below:

1. A composition comprising factor IX, glycine, a cryoprotectant, and a surfactant.
9. The composition of claim 1, further comprising calcium chloride.
14. The composition of claim 1, further comprising a buffering agent.
19. A composition comprising factor IX, glycine, a surfactant, and a member selected from the group consisting of a buffering agent and a cryoprotectant.
29. The composition of claim 19, wherein said surfactant is polysorbate, wherein said cryoprotectant is sucrose and further comprising calcium chloride.

The references relied on by the examiner are listed below:

Zolton et al. (Zolton)	4,597,966	Jul. 1, 1986
Bhattacharva et al. (Bhattacharva)	5,288,853	Feb. 22, 1994
Mathews et al. (Mathews)	4,952,675	Aug. 28, 1990
Schwinn (Abstract No. 91-237793/32)	DE 4,001,451	Aug. 1, 1991

Wang et al. (Wang), "Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers," J. Parenteral Sci. and Tech., Vol. 42(S), pp S3-S26 (1988)

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### **Ground of Rejection**

Claims 1 - 9, 11 - 14, and 16 - 43<sup>1</sup> stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on an abstract of the German patent 4,001,451 to Schwinn, Wang, Zolton, Mathews, and Bhattacharva.

### **Background**

The applicants describe the invention at pages 1 and 2 of the specification as being directed to concentrated preparations of factor IX, useful as a bulk drug product, wherein the compositions are either frozen, liquid, or lyophilized and comprise factor IX, a bulking agent, such as glycine, and a cryoprotectant. Applicants state that the cryoprotectant may be a polyol such as mannitol or sucrose. Applicants also state that the composition may contain a surfactant and/or a buffering agent.

### **Discussion**

In considering the issues raised by this appeal, we have carefully considered the Examiner's Answer of September 13, 1996 (Paper No. 23) and appellants' Appeal Brief filed April 15, 1996 (Paper No. 20)<sup>2</sup>. Our consideration of these documents, as well as the

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<sup>1</sup> On the record before us, the status of claim 43 is unclear. We note the statements appearing at page 2 of the Appeal Brief and page 2 of the Examiner's Answer concerning the allowability of claim 43. However, since the examiner has included claim 43 in the list of claims rejected, we have included claim 43 in our consideration of this appeal.

<sup>2</sup> The Reply Brief, filed December 6, 1996 (Paper No. 24) was denied entry by the examiner in a letter of January 21, 1997 (Paper No. 25) and this decision by the examiner was upheld on petition under 37 CFR § 1.181. (Paper No. 28 of May 14, 1997). Therefore, we have not considered this Reply Brief in

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underlying evidence provided by both the examiner and appellants, convince us that the present record does not provide an adequate briefing of the issues raised by this appeal to permit a meaningful review for the reasons which follow.

In rejecting the claims pending in this application the examiner's principal reference is an abstract, apparently printed from a commercial data base, of a German patent. It is not readily apparent to us why no effort was made to obtain the underlying document and obtain a translation thereof. Appellants, for their part, have supplied a copy of the PCT document which is referenced as PCT/EP90/02238<sup>3</sup> (hereinafter WO 91/10439) to Schwinn (German language) and U.S. Patent 5,328,694 to Schwinn which appellants urge is the English equivalent, apparently to the abstracted German Patent 4,001,451. (Brief page 4). We would note that U.S. Patent 5,328,694 claims benefit under 35 U.S.C. § 119 to German Patent 4,001,451 and would be considered likely to correspond to some degree with that document. However, even a cursory reading of these two documents indicates that they differ in scope of disclosure in that the U. S. Patent does not describe any compositions relating to Factor IX while the German patent does describe compositions containing Factor IX.

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reviewing this appeal.

<sup>3</sup> Appellants have apparently, incorrectly identified this document, since the document supplied with the Brief is WO 91/10439 which reasonably appears to claim benefit of the earlier filing date of PCT/EP90/02238.

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We would, additionally, note that the appellants have described the issues raised by this appeal as being whether the claimed compositions are non-obvious over the seven references identified at page 3 of the Brief. The examiner notes at page 2 of the Examiner's Answer that only the five listed references are relied on. Since we find no further discussion of the remaining two references, we assume this is the correct statement of the rejection before us. However, it serves as further evidence of the confusion which exists on this record.

Since the filing of the Examiner's Answer, translations of both German 4,001,451<sup>4</sup> and WO 91/10439<sup>5</sup> have become available. (Copies Attached). The issues raised by rejections of obviousness are a fact-intensive inquiry, both as to what is claimed and what the state of the art is relative to the claimed invention. It stands to reason that full text documents, whether they be English language translations of foreign language documents or the full text English documents, will provide more facts. It is not apparent why the examiner and appellants have satisfied themselves with attempting to determine patentability under 35 U.S.C. § 103 on less than a complete factual record.

As stated in Gechter v. Davidson, 116 F.3d 1454, 1457, 43 USPQ2d 1030, 1033 (Fed. Cir. 1997):

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<sup>4</sup> Provided to the USPTO by The Ralph McElroy Translation Co. in August of 2001.

<sup>5</sup> Provided to the USPTO by Schreiber Translations, Inc. in June 2001.

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For an appellate court to fulfill its role of judicial review it must have a clear understanding of the grounds for the decision being reviewed, (citation omitted) . . . [which requires that] [n]ecessary findings must be expressed with sufficient particularity to enable . . . [the] court, without resort to speculation, to understand the reasoning of the Board, and to determine whether it applied the law correctly and whether the evidence supported the underlying and ultimate fact-findings.

Like the court in Gechter, this Board requires a clear understanding of the grounds for the decision being reviewed. In this case, we find it impossible to ascertain whether the evidence, upon which the examiner relies, reasonably supports the underlying fact findings for the rejection under 35 U.S.C. § 103.

The Board cannot examine, in the first instance, all applications which come before it in an ex parte appeal under 35 U.S.C. § 134. As we have stated, it has been the experience of the Board that full text documents are always more fact filled than abstracts of these documents. Here, for example, the abstract of German Patent 4,001,451 merely describes a stable injectable solution of factor VIII or IX suitable for human therapy which contains a defined amount of a natural or synthetic disaccharide which may be sucrose and at least one amino acid which may be lysine or glycine. The abstract, also, provides that the solution may contain CaCl<sub>2</sub>. When we review the translation of the underlying document we find that example 3 describes a concentrated solution of Factor IX which includes sucrose, lysine and CaCl<sub>2</sub>. Whether this supports or hurts the examiner's case, it

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remains that one obtains a clearer picture of the prior art relative to the claimed invention when one reviews the full text document.

In addition, we would note that the translation of German Patent 4,001,451, at page 2, would appear to make a distinction between the use of cryoprecipitates of VIII and solutions of IX. It is not clear that either the examiner or appellants have considered the relevancy of this information. What is clear from the present record, however, is that neither the examiner or appellants have had the opportunity to review and consider the translations of the documents most relevant to the determination of the obviousness of the present claimed invention. Therefore, we remand this application, with copies of these documents and the translations, to the examiner for full consideration of whether one or both form the proper basis for questioning the patentability of the present claims under 35 U.S.C. § 103. In so doing we offer the following remarks which we hope will be helpful and provide guidance in considering the issues raised by this appeal.

The examiner has taken the position that the '451 abstract describes a composition of the type claimed except for the presence of the buffering agent or the surfactant. (Answer, page 4). The examiner offers Wang as teaching that "[i]t is well known in the art that to stabilize proteins the use of stabilizers that prevent denaturation is routine." (Id.). The examiner urges that Wang "disclose[s] that of the factors that contribute to denaturation, pH, detergents or physical stress are some factors that contribute to

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instability during processes such as filtration. (Id.). The examiner further urges that Wang teaches the use of polysorbate surfactants, such as Tween<sup>®</sup>, to inhibit denaturation.

(Answer, page 5). The examiner acknowledges that Wang does not teach the use of histidine as the buffering agent. (Id.). However, Wang talks only in terms of proteins, in general, and does not explicitly describe any formulations of coagulation factor proteins which could reasonable be said to relate to factor IX of the present claims.

Further, it does not appear that the examiner fully appreciates the complete disclosure of this reference. At page S12, column 1, 4th full paragraph, in discussing the use of cryoprotectant with proteins the reference states "[w]ithout elaborative research, it is difficult to delineate the true mechanism of stabilization in any particular circumstance." Further, at pages S20-21, the reference discusses the "Special Considerations" relating to stability of proteins under freezing conditions and lyophilization and in column 1 of page S21 states that "proper selection of a buffer system is extremely important." At column 2, of page S21, last full paragraph, the reference states that:

Knowledge of the mechanisms for aggregation makes it easier to understand the stabilization observed. Molecules of surfactants composed of a hydrophilic end group and long hydrocarbon moieties, form a hydrophobic core of micelles in which the protein molecule can be sheltered from interaction with another protein molecule. The presence of surfactant also reduces the concentration of protein at the interface.

In addition, at column 1 of page S22, Wang provides a discussion of the important role that pH plays in the stabilization of a protein or peptide. These portions of Wang would appear

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relevant to the issues raised by this appeal and particularly to arguments made by appellants relating to the lyophilization of protein compositions.

While Wang does not specifically relate to factor IX, the remaining references, relied on by the examiner, are more closely related to this aspect of the claimed subject matter. For example Zolton, relied on by the examiner as disclosing the use of glycine and histidine, describes the stabilization of plasma proteins. Since factor IX is a plasma glycoprotein (Specification, page 1, lines 10-11), this reference would be relevant to the claimed subject matter. Both Mathews and Bhattacharva describe compositions relating to factor VIII and describe the incorporation of substances such as calcium chloride, sugars, buffers, surfactants with this protein for stabilization during isolation and purification. The examiner has urged that “stabilizers for Factor IX would also be considered stabilizers for Factor VIII or vice versa . . . .” (Answer, page 6). However, even where the examiner has shown that each component of the claimed composition has been combined with a protein, even a closely related protein, there must be a suggestion or direction to be found in the prior art which would have led one of ordinary skill in the art to bring all components required by the claim into a single combination. It is not enough that the individual components have been used in combination with other proteins for various purposes. As set forth in Ecolochem Inc. V. Southern California Edison, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000) “[a] rejection cannot be predicated on the mere identification . . . of the individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of

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the claimed invention, would have selected these components for combination in the manner claimed.” There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the modifications required. That knowledge can not come from the applicants' invention itself. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 678-79, 7 USPQ2d 1315, 1318 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). We leave it to the examiner, in the first instance, to determine whether the prior art would have reasonably suggested bringing the components of the presently claimed composition together.

In this regard, we would note that appellants urge that (Brief, page 13):

**immunoglobulin** and **factor VIII**, are chemically/structurally distinguishable from Appellants' **factor IX**. Such generic disclosures are not relevant, must less predictive, of effectively stabilizing compositions for lyophilization of factor IX and provide no reasonable expectation of success. [Emphasis in the original].

In rebuttal, the examiner appears to assume that, since the primary reference relates to factor IX, it is sufficient for purposes of establishing a prima facie case that Wang and Zolton generically relate to proteins, including plasma proteins. (Answer, page 9).

However, it is not readily apparent, from the present record, that all such proteins should be

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regarded as equivalent in this manner in the absence of a teaching to be found in the prior art or sound scientific reasoning which would support this position.

For appellants' part we would note initially, as the examiner did through out the Examiner's Answer, that the claims are not directed to a method of lyophilizing a composition or to a lyophilized composition. Appellants acknowledge at page 10 of the Appeal Brief that the claimed composition is "inherently" stable to both lyophilization and prolonged storage in the freeze-dried state. Thus, any compositions containing these ingredients which are established by the examiner as old or obvious would also be expected to inherently be stable to lyophilization. As correctly pointed out by the examiner the motivation to combine the ingredients of the presently claimed composition need not be the same as that which motivated appellants to make the combination. See In re Kemps, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996).

Similarly, arguments to the affect that "[r]elevant disclosures are only those relating to factor IX formulations that protect factor IX from stresses associated with lyophilization and that provide factor IX stability in a freeze-dried state (in the presence of little water)" (Brief, page 11) would inappropriately limit the scope of review of the prior art on the part of the examiner.

### **SUMMARY**

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To summarize, the rejection of claims 1 - 9, 11 - 14, and 16 - 43 under 35 U.S.C. § 103 is vacated and the application is remanded to the examiner for consideration of the documents supplied herewith. If upon review of these documents, the examiner remains of the opinion that the claims on appeal are unpatentable, she should issue an appropriate Office action which sets forth the facts and reasons in support of such a rejection and provide appellants with the appropriate opportunity to respond thereto. We would note that we are not authorizing a supplemental Examiner's Answer to address the issues raised by this decision.

**VACATED and REMANDED**

Douglas W. Robinson	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
Carol A. Spiegel	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
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