

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 26

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte THERESA M. SILER-KHODR

Appeal No. 1996-2468
Application 08/091,899

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1 through 13, which are all of the claims pending in this application.

We reverse.

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

1. A method for regulating placental cell production of thromboxane and PGF₂, comprising treating placental cells with a pharmacologically effective amount of insulin-like growth factor I sufficient to inhibit thromboxane and prostaglandin F₂ production without affecting prostacyclin or prostaglandin E₂ production.

Appeal No. 1996-2468
Application 08/091,899

References of record regarding issues of enablement include:

Vane et al. (Vane), "The contribution of prostaglandin production to contractions of the isolated uterus of the rat," Br. J. Pharmac., Vol. 48, pp. 629-39 (1973)

Zuckerman et al. (Zuckerman), "Inhibition of Human Premature Labor by Indomethacin," The American College of Obstetricians and Gynecologists, Vol. 44, No. 6, pp. 787-92 (Dec. 1974)

Johnson et al. (Johnson), "Pharmacologic control of uterine contractility: In vitro human and in vivo monkey studies," Am. J. Obstet. Gynecol., Vol. 123, No. 4, pp. 364-75 (Oct. 1975)

Demers et al. (Demers), "Placental prostaglandin levels in pre-eclampsia," Am. J. Obstet. Gynecol., Vol. 126, No. 1, pp. 137-39 (Sept. 1976)

Valenzuela et al. (Valenzuela), "Effect of pregnancy-induced hypertension upon placental prostaglandin metabolism: Decreased prostaglandin F_{2α} catabolism with normal prostaglandin E₂ catabolism," Am. J. Obstet. Gynecol., pp. 255-56 (Jan. 1980).

Mäkilä et al. (Mäkilä), "Increased Thromboxane A₂ Production But Normal Prostacyclin By The Placenta In Hypertensive Pregnancies," Prostaglandins, Vol. 27, No. 1, pp. 87-95 (Jan. 1984)

Walsh, "Preeclampsia: An imbalance in placental prostacyclin and thromboxane production," Am. J. Obstet. Gynecol., Vol. 152, No. 3, pp. 335-40 (June 1985)

Murphy et al. (Murphy), "Uterine Insulin-Like Growth Factor-1: Regulation of Expression and Its Role in Estrogen-Induced Uterine Proliferation," Endocrine Reviews, Vol. 11, No. 3, pp. 443-53 (1990)

Siler-Khoder et al. (Siler-Khoder), "IGF-I Inhibits Human Placental Prostaglandin F and Thromboxane B₂ Production," Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, The 38th Annual Meeting of the Society for the Study of Reproduction, Abstract #513, p. 179 (1992)

Rall, "Oxytocin, Prostaglandins, Ergot Alkaloids, and other Drugs; Tocolytic Agents," The Clinical Use Of Drugs That Inhibit Uterine Motility, Section IX, Chapter 39, pp. 949-53 (1990)

Appeal No. 1996-2468
Application 08/091,899

Geisthovel et al. (Geisthovel), "Insulin-like growth factors and thecal-granulosa-cell function," Human Reproduction, Vol. 5. No. 7, pp. 785-99 (1990)

OPINION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the above-noted rejection, we make reference to the Examiner's Answer (Paper No. 18½, mailed October 31, 1995) for the examiner's complete reasoning in support of the rejection, and to the appellant's Brief (Paper No. 18, filed July 24, 1995) and Reply Brief (Paper No. 19, filed December 4, 1995) for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

DECISION ON APPEAL

Claims 1-13 stand rejected under 35 U.S.C. § 112, first paragraph for failing to teach how to use the claimed invention.¹

The examiner has admitted on the record that utility of the claimed invention has been established. Examiner's Answer, page 5. Therefore, we interpret the examiner's position of lack of enablement to be that there are no concerns of inoperability or utility,

¹ A rejection under 35 U.S.C. § 101 has been withdrawn. Examiner's Answer, page 5.

however, the specification does not teach “how to use” the claimed invention within the entire claim scope. We limit our review to the question of whether the specification teaches how to use the invention within the scope of the claims.

An analysis of whether the claims under appeal are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the appealed claims as to enable one skilled in the pertinent art to make and use the claimed invention. The first paragraph of Section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification. Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

In order to establish a prima facie case of non-enablement, the examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of

35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See

In re Marzocchi, 439 F.2d at 224, 169 USPQ at 370 (CCPA 1971). As stated by the court,

it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement.

It is the examiner's position that the claims, as written encompass both in vitro and in vivo methods. The examiner alleges that "the specification does not set forth any use for the in vitro methods." Examiner's Answer, page 8. The examiner admits that the "specification enables the in vitro administration of IGF-1 to placental tissue and demonstrates the changes in thromboxane and PGF₂", [but] the specification does not tell how to use the in vitro methods in a patentable manner." Examiner's Answer, page 8. The examiner further argues that the in vitro test results are "deemed to provide information for further scientific research in this area, particularly in vivo, but do not enable using IGF-I in vivo to inhibit labor or inhibit placental cell production of thromboxane and PGF₂" in vivo." Examiner's Answer, page 9. Thus, the examiner appears ultimately to argue that the in

vivo method is not enabled, i.e., the specification fails to teach the “how to use” component of the in vivo method because the in vitro model is not predictive of in vivo activity.

The examiner’s first point of contention is that “the specification does not establish that the placental perfusion [sic] model is representative of the effects of IGF-I in vivo.” Examiner’s Answer, page 10. The examiner states that the placental perfusion model does not address the role of insulin-like growth factor binding proteins (IGF-BP) that would have been known to modulate the activity of IGF-I in vivo. Examiner’s Answer, page 10 and Geisthovel. The examiner supposes that IGF-I would have been known to exert a variety of other biological effects in vivo not accounted for in the placental perfusion model. In our opinion, the examiner raises legitimate issues with respect to the predictive ability of the placental perfusion model and arguably presents a prima facie case of lack of enablement.

Once the examiner has established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on the appellant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the disclosure as a guide. See In re Brandstadter, 484 F.2d 1395, 1406, 179 USPQ 286, 294 (CCPA 1973).

The appellant responds to the argument that the placental perfusion model is not representative of the effects of IGF-I in vivo, with the submission of four publications which the appellant indicates are evidence of the acceptability of the in vitro placental perfusion

model as representative of in vivo results to those of ordinary skill in the art. In particular, the appellant argues that Walsh establishes the acceptability of the in vitro placental perfusion model as a predictor of in vivo activity, in a similar context. Walsh discloses the use of the placental perfusion model to establish the ability of indomethacin to inhibit thromboxane. (Indomethacin has been shown and is known to inhibit $\text{PGF}_{2^{\alpha}}$ and premature labor in vivo. See Zuckerman.) Demers evidences the use of the placental perfusion model to show increased levels of PGF are associated with pre-eclampsia. Demers, Figure 2. Valenzuela evidences the use of the placental perfusion model to show decreased metabolism of $\text{PGF}_{2^{\alpha}}$ by placental tissue is associated with toxemia. Valenzuela, Table II.

The examiner takes issue with several of the publications submitted to support the predictive value of the placental perfusion model, indicating some differences exist between the performance steps of the placental perfusion model in the references and the placental perfusion model as used in the specification. These differences, however, fail to negate the evidenced acceptability and routine use of the placental perfusion model by those of ordinary skill in the art. In addition, it appears clear from the record that there are constraints, and legal and ethical considerations which prohibit scientific experimentation directly on pregnant humans. Appellant believes that the best possible system available for demonstrating the claimed method, the human placental perfusion model has been used. Appeal Brief, page 27.

Moreover, the appellant submits Zuckerman to show that indomethacin has been shown to inhibit the activity of prostaglandins and stop uterine contractions in in vivo clinical trials of women in premature labor. It is argued that in view of “the demonstrated effect of IGF-I on placental production of prostaglandin PGF₂” and thromboxane, in view of the art recognized action of PGF₂ for labor regulation previously described using indomethacin, establish a reasonable correlation between the use of IGF-I and the inhibition of labor.” Brief, page 27.

The examiner responds to this argument, arguing indomethacin has a different pharmacologic profile than indomethacin. We believe, however, that the evidence of record adequately supports agreement in activity of IGF-I and indomethacin, at least with respect to inhibition of prostaglandin and thromboxane.

We also find there to be literal support in the specification for the in vivo “how to use” requirement. Example 7 of the specification demonstrates “that IGF-I specifically inhibits vasoconstrictive prostanoid production by human placental explants in a dose related manner, and that the active doses are well within the physiological range. Therefore, appropriate doses of IGF-I may be determined for human use in the inhibition of labor using standard pharmacological parameters known to those of skill in the art to provide the described inhibition of thromboxane and prostaglandin F₂ by placenta in vivo.” Specification, p. 51. Appellant appears to have adequately demonstrated extrapolation of the in vitro model to in vivo use as it pertains to

prostaglandin inhibition. This showing is uncontroverted by the examiner. Thus, it would reasonably appear that the “how to use” requirement of 35 U.S.C. § 112, first paragraph is satisfied by the above disclosure.

In vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. It is not urged, that there is an invariable exact correlation between in vitro test results and in vivo test results. Cross v. Iizuka, 753 F.2d 1040, 1044, 224 USPQ 739, 742 (Fed. Cir. 1985); Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (1980). It is appellant's position that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful. On the facts before us, we agree.

Based upon the relevant evidence as a whole, we find there to be a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. Cross v. Iizuka, supra; Nelson v. Bowler, supra.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND AND FOURTH PARAGRAPHS

Appeal No. 1996-2468
Application 08/091,899

Claim 2 stands rejected under 35 U.S.C. § 112, second paragraph, for failing to distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 6 stand rejected under 35 U.S.C. § 112, fourth paragraph, as being in improper dependent claim form.

The appellant attempted to cancel claims 2, 4, 5, 6 and 9 in an amendment after final rejection submitted February 23, 1995, which the examiner did not enter. Appellant subsequently filed an amendment with the appeal, requesting cancellation of claims 2, 4 and 6, which the examiner did not enter.

No arguments have been presented with respect to claims 2, 4 and 6. It appears clear from the record that it is appellant's intention to cancel claims 2, 4 and 6, which would obviate the rejections of record. Until such claims are canceled, the rejections of claims 2, 4 and 6 is affirmed.

Appeal No. 1996-2468
Application 08/091,899

CONCLUSION

The rejection of the claims under 35 U.S.C. § 103 for obviousness is reversed. The rejections under 35 U.S.C. § 112, second and fourth paragraphs are affirmed.

REVERSED

)	
Sherman D. Winters)	
Administrative Patent Judge)	
)	
)	
)	BOARD OF PATENT
William F. Smith)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
)	
Demetra J. Mills)	
Administrative Patent Judge)	

Appeal No. 1996-2468
Application 08/091,899

DJM/cam

Denise L. Mayfield, Esq.
Vinson & Elkins, LLP
2300 First City Tower
1001 Fannin Street
Houston, TX 77002-6760