

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

**UNITED STATES PATENT AND TRADEMARK OFFICE**

---

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

---

*Ex parte* THIERRY VANDENDRIESSCHE,  
MARINEE CHUAH,  
STEFAN KOCHANEK, and  
GUDRUN SCHIEDNER

---

Appeal 2006-1036  
Application 10/191,760  
Technology Center 1600

---

**ON BRIEF**

---

Before ADAMS, GREEN, and LEBOVITZ, *Administrative Patent Judges*.

GREEN, *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 6, 12, 13, and 17.<sup>1</sup> Claims 6 and 13 are representative of the claims on appeal, and read as follows:

---

<sup>1</sup> Claim 1 is indicated as being allowable, and claims 2-5, 7-11, 14-16, 18, and 19 have been cancelled (Answer 2).

6. A method to obtain therapeutic levels of Factor VIII in a mammal comprising:
    - administering less than  $10^{10}$  infectious units of a recombinant high capacity adenoviral vector per kg of body weight or less than  $10^{12}$  viral particles of the recombinant high capacity adenoviral vector per kg of body weight intravenously to the mammal's liver;
      - wherein the recombinant high capacity adenoviral vector comprises:
        - an Ad5 left terminus;
        - a human or canine Factor VIII cDNA under the control of a liver specific promoter, wherein the B-domain of the Factor VIII cDNA has been deleted; and
        - an Ad5 right terminus.
  13. A method of treating hemophilia A in a mammal, comprising:
    - administering less than  $10^{10}$  infectious units of a recombinant high capacity adenoviral vector per kg of body weight or less than  $10^{12}$  viral particles of the recombinant high capacity viral vector per kg of body weight intravenously to the mammal's liver, said recombinant high capacity adenoviral vector comprising:
      - an Ad5 left terminus;
      - a human or canine Factor VIII cDNA under the control of a liver specific promoter, wherein the B-domain of the Factor VIII cDNA has been deleted; and
      - an Ad5 right terminus;
    - thus generating therapeutic amounts of Factor VIII in said mammal to substantially ameliorate the effects of hemophilia A.
- Claims 6, 12, 13, and 17 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification fails to enable the full scope of the claimed subject matter. We reverse.

## DISCUSSION

Claims 6, 12, 13, and 17 stand rejected under 35 U.S.C. § 112, first paragraph, “because the specification, while being enabling for practicing the claimed method by intravenous or local delivery to the liver of a high-capacity adenoviral vector (HC-Ad) that expresses Factor VIII (FVIII) to generic immunodeficient hemophiliac mammals; to generic immunocompetent hemophiliac mammals pre-treated with clodronate liposomes to deplete the mammal of macrophages; or specifically to hemophiliac dogs, does not reasonably provide enablement for other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims” (Answer 3-4).

The examiner asserts that the issue “is whether the specification combined with the well-known knowledge of the prior art would have enabled one to broadly practice the method at the lower doses required by the claimed invention.” *Id.* at 4. The examiner states that in the working examples, only intravenous delivery of HC-Ad was examined, and only the lowest dose was within the range required by the claims. *Id.* at 5. However, according to the examiner, “the important results were that physiologically or therapeutically relevant levels of serum FVIII were NOT obtained at doses less than  $10^{10}$  i.u. per kg of body mass in immunocompetent hemophiliac mice unless the mice were pretreated with clodronate liposomes.” *Id.* at 6.

The examiner cites Balagué<sup>2</sup> for its teaching that at the lowest dose of HC-Ad expressing full length human FVIII, serum FVIII levels were below detection in immunocompetent hemophiliac mice. *Id.* at 6-7.

VandenDriessche,<sup>3</sup> which discusses the results of Balagué, states that the result suggests a non-linear threshold effect. *Id.* at 7.

The examiner argues further that the example of treatment of a hemophiliac dog has been refuted by Brown.<sup>4</sup> *Id.* Brown, according to the examiner, “reported that a hemophiliac dog treated with HC-Ad encoding B-domain deleted cFVIII at a dose of  $5 \times 10^{11}$  viral particles per kg of body mass did not show any increase in serum FVIII or change in whole blood clotting times.” *Id.*

The examiner concludes:

In light of the evidence of record both from the prior art and the instant application, the claimed invention is inoperative for at least some immunocompetent mammals, e.g. mouse, that are treated only with the vector in the dose ranges recited by the claims. The only guidance on overcoming the apparent threshold effect is to pretreat the mammal with clodronate liposomes, ostensibly to deplete the mammal of macrophages. The specification shows successful treatment of dog without clodronate, but this contrasts with prior art findings that showed the low doses required by the claims as being inoperative.

---

<sup>2</sup> Balagué et al. (Balagué), *Sustained high-level expression of full-length factor VIII and restoration of clotting activity in hemophilic mice using a minimal adenovirus vector*, 95 Blood 820 (2000).

<sup>3</sup> VandenDriessche et al. (VandenDriessche), *Viral Vector-Mediated Gene Therapy for Hemophilia*, 1 Current Gene Therapy 301 (2001).

<sup>4</sup> Brown et al. (Brown abstract), *Heler-dependent adenovirus delivery of a canine FVIII B-domain deleted transgene in murine and canine models of hemophilia A*,” 98 Blood 695a, (2001).

Thus, the claims are not enabled for their full breadth. In light of the optimal nature of delivery targeting the liver for expression of FVIII, and the lack of guidance or working examples in the specification and prior art of record on other suitable target tissues, including effective routes of delivery to those other target tissues, undue experimentation would be required to develop the vectors and mode of administration for non-hepatic expression of therapeutic levels of FVIII.

*Id.* at 7-8.

The examiner bears the initial burden of showing that a claimed invention is nonenabled. “[A] specification disclosure which contains a teaching of the manner and process of making and using the 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 in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). “When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.” *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). “[E]nabled requires that the specification teach those in the art to make and use the invention without ‘undue experimentation.’ . . . That some experimentation may be required is not fatal; the issue is whether the

amount of experimentation required is ‘undue.’” *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

In this case, the examiner has done a thorough and commendable job of explaining the reasons for believing that practicing the claimed method would have required undue experimentation. The examiner has also provided evidence to support that position and clearly explained the relevance of the evidence to the claimed method. Notwithstanding the examiner’s diligence, however, we conclude that the rejection is based on an improperly stringent legal standard and must be reversed.

The examiner’s rejection as it relates to the use of immunocompromised mice or mice pretreated with clodronate has been considered, but we do not agree with the examiner’s reasoning that the claim is only enabled for methods of administration in which the mammal is immunocompromised, as there is an example in the specification that uses a model that is not immunocompromised, and that is example 8, which is a canine study.

As noted by the abstract of Connelly,<sup>5</sup> of record, the canine model closely mimics the human disease, and later states on that same page that canine hemophilia A “has been thoroughly characterized as a model of hemophilia A in humans.” In addition, Brown 2004<sup>6</sup> states that “murine

---

<sup>5</sup> Connelly et al. (Connelly), *Complete Short-Term Correction of Canine Hemophilia A by In Vivo Gene Therapy*, 88 Blood 3846, (1996)

<sup>6</sup> Brown et al. (Brown 2004), *Helper-dependent adenoviral vectors mediate therapeutic factor VIII expression for several months with minimal accompanying toxicity in a canine model of severe hemophilia A*, 103 Blood 804, 805 col. 1 (2004).

models do not necessarily predict treatment outcomes in higher order mammals,” and “it is important that HD vectors be tested in a large animal model before future clinical trials are carried out.” Brown, page 805

The examiner discounted the arguments and evidence presented by appellants, such as the Chuah declaration, that the hemophiliac dog model is predictive for treatment parameters of human hemophilia (Answer 12-14). We find that the statements made by Connelly make clear that at the time of invention, the canine model was an art accepted model. The examiner references the statement in Brown 2004 at page 809, column 2, that “[w]e do not believe that current HD technology is ready for the treatment of human monogenic disease, especially in light of the relatively small therapeutic index and the significant interindividual variability of toxicity seen in this project.” Thus, Appellants have provided evidence that the claimed method is enabled for treating hemophilia in a mammal as claimed.

Moreover, requiring that a pharmaceutical invention be ready for clinical testing in humans is not the proper standard. “Usefulness in patent law, and in particular the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” *In re Brana*, 51 F.3d, 1560, 1568 34 USPQ2d 1436, 1442-43 (Fed. Cir. 1995) (citations omitted). While the *Brana* court referred to “usefulness,” the rejection on appeal was for nonenablement. *See id.* at 1564, 34 USPQ2d at 1439.

Example 8 of the Specification illustrates that an intravenous injection corresponding to a dose of  $3 \times 10^{11}$  v.p./kg, which is within the claimed

dosage levels, was effective in reducing whole blood clotting time from 15 minutes prevaccination to 7-9 minutes 72 hours after vaccination (Br. 9).

We also do not find that the examiner's assertions based on the Brown abstract that Example 8 is not predictive of canine studies, and thus treatment of mammals generally, to be convincing. The portion of the Brown abstract relied upon merely states that “[e]arly results from a single dog injected with  $5 \times 10^{11}$  vp/kg did not show any increase in FVIII levels or a change in whole blot clot times.”

As noted by Appellants, the portion of the Brown abstract relied upon by the Examiner was later refuted by a 2004 article by Brown (Brown 2004), which corrects the earlier finding and supports the enablement of the claims (Br. 8). The examiner, however, did not agree that the Brown 2004 reference refuted the earlier Brown abstract. The examiner first notes that only Dog A had been treated with a dose of HC-Ad that was within the dose permitted by the claims (Answer 9). The examiner then points to Figure 1B, lowest line, which is asserted to show that no FVIII expression is seen in Dog A at most time points.

As noted by Appellants (Br. 9), however, and not refuted by the examiner, the Brown 2004 authors themselves stated in the abstract that “[l]ow-level increases in FVIII activity were detected in all 3 HD-HNF-cFVIII-treated dogs [which would include Dog A], which corresponded with decreased whole blood clotting times.” Moreover, the Brown 2004 reference reports in the paragraph bridging pages 806 and 807 that “[a]ll hemophilic dogs in this colony experience about 5 spontaneous bleeding episodes per year,” but that “[n]o clinical bleeding events were observed in

any of the dogs . . . subsequent to treatment with the Hd-Ad vector.” Thus, the reduction in bleeding events provides evidence that a therapeutic effect was achieved.

## SUMMARY

Because we found that the evidence of record as a whole supported the enablement of the claimed methods at the claimed dosages, we reverse the enablement rejection under 35 U.S.C. § 112, first paragraph.

## REVERSED

DONALD E. ADAMS                  )  
Administrative Patent Judge      )  
                                      )  
                                      )  
                                      )  
                                      ) BOARD OF PATENT  
LORA M. GREEN                     )  
Administrative Patent Judge      ) APPEALS AND  
                                      )  
                                      ) INTERFERENCES  
RICHARD M. LEBOVITZ             )  
Administrative Patent Judge      )

LMG/jlb

Appeal No. 2006-1036  
Application No. 10/191,760

Trask Britt  
P.O. Box 2550  
Salt Lake City, UT 84110