858 F.2d 731
United States Court of Appeals,
Federal Circuit.

In re Jack R. WANDS, Vincent R. Zurawski, Jr., and Hubert J.P. Schoemaker.

No. 87–1454.
|
Sept. 30, 1988.

Inventors of method to create immunoassay of hepatitis B surface antigen using monoclonal antibodies sought patent. The Board of Patent Appeals and Interferences denied the patent on grounds it was not enabling. On appeal, the Court of Appeals, Edward S. Smith, Circuit Judge, held that: (1) determination of enablement is reviewed as question of law; (2) while deposit of living cells can be used to satisfy enabling requirement, it is not necessary; (3) undue experimentation was not necessary to produce art for method of immunoassay of hepatitis B surface antigen using monoclonal antibodies; and (4) enablement of patent involving living microorganisms is not precluded by necessity of some experiments such as routine screening.

Reversed.

Pauline Newman, Circuit Judge, concurred in part and dissented in part with opinion.

Attorneys and Law Firms

***732** Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein, Washington, D.C., argued for appellant. With him on the brief was Henry N. Wixon, Washington, D.C.

John H. Raubitschek, Associate Sol., Com'r of Patents and Trademarks, of Arlington, Va., argued for appellee. With him on the brief were Joseph F. Nakamura, Sol. and Fred E. McKelvey, Deputy Sol., Washington, D.C.

Before SMITH, NEWMAN, and BISSELL, Circuit Judges.

Opinion

***733** EDWARD S. SMITH, Circuit Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM Antibodies," which was filed September 19, 1980.[1] The rejection under 35 U.S.C. § 112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

1 *In re Wands,* Appeal No. 673–76 (Bd.Pat.App. & Int. Dec. 30, 1986).

I. *Issue*

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

II. *Background*

A. *The Art.*

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an *antigen.* The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure to an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected

experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as regents for sensitive diagnostic tests (*e.g.,* to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay.*

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes.* Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. These are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are *lymphocytes.* Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to ***734** their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture. Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma cells that are all progeny of a single cell) are called monoclonal antibodies. [2]

[2] For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1368–71, 231 USPQ 81, 82–83 (Fed.Cir.1986), *cert. denied,* 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987).

B. *The Claimed Invention.*

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. § 112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.

The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25–27 are for chemically modified (*e.g.,* radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

> 1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
>
> contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
>
> determining the presence of said substance in said sample;
>
> wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

Certain claims were rejected under 35 U.S.C. § 103; these rejections have not ***735** been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25–27 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti–HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. *Analysis*

A. *Enablement by Deposit of Microorganisms and Cell Lines.*

[1] The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention." [3] A patent need not disclose what is well known in the art. [4] Although we review underlying facts found by the board under a "clearly erroneous" standard, [5] we review enablement as a question of law. [6]

3 *W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed.Cir.1983), *cert. denied,* 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984).

4 *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.,* 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed.Cir.1984).

5 *Coleman v. Dines,* 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed.Cir.1985).

6 *Moleculon Research Corp. v. CBS, Inc.,* 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed.Cir.1986), *cert. denied,* 479 U.S. 1030, 107 S.Ct. 875, 93 L.Ed.2d 829 (1987); *Raytheon Co. v. Roper Corp.,* 724 F.2d 951, 960 n. 6, 220 USPQ 592, 599 n. 6 (Fed.Cir.1983), *cert. denied,* 469 U.S. 835, 105 S.Ct. 127, 83 L.Ed.2d 69 (1984).

[2] Where an invention depends on the use of living materials such as microorganisms or cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues. [7] Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112. [8] A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. [9] Even when starting materials are available, a deposit has been necessary where it would require undue experimentation

to make the cells of the invention from the starting materials. [10]

7 *In re Argoudelis,* 434 F.2d 1390, 1392–93, 168 USPQ 99, 101–02 (CCPA 1970).

8 *In re Lundak,* 773 F.2d 1216, 227 USPQ 90 (Fed.Cir.1985); *Feldman v. Aunstrup,* 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), *cert. denied,* 424 U.S. 912, 96 S.Ct. 1109, 47 L.Ed.2d 316 (1976); Manual of Patent Examining Procedure (MPEP) 608.01(p)(C) (5th ed. 1983, rev. 1987). *See generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement,* 67 J.Pat. Trademark Off. Soc'y 569 (1985).

9 *In re Jackson,* 217 USPQ 804, 807–08 (Bd.App.1982) (strains of a newly discovered species of bacteria isolated from nature); *Feldman,* 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); *In re Argoudelis,* 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); *In re Kropp,* 143 USPQ 148, 152 (Bd.App.1959) (newly discovered microorganism isolated from soil).

10 *In re Forman,* 230 USPQ 546, 547 (Bd.Pat.App. & Int.1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); *In re Lundak,* 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the prima facie date of invention, ***736** [11] and to satisfy the requirement under 35 U.S.C. § 114 that the PTO be guaranteed access to the invention during pendency of the application. [12] Although a deposit may serve these purposes, we recognized, in *In re Lundak,* [13] that these purposes, nevertheless, may be met in ways other than by making a deposit.

11 *In re Lundak,* 773 F.2d at 1222, 227 USPQ at 95–96; *In re Feldman,* 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis,* 434 F.2d at 1394–96, 168 USPQ at 103–04 (Baldwin, J. concurring).

12 *In re Lundak,* 773 F.2d at 1222, 227 USPQ at 95–96; *In re Feldman,* 517 F.2d at 1354, 186 USPQ at 112.

13 *In re Lundak,* 773 F.2d at 1222, 227 USPQ at 95–96.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. *Undue Experimentation.*

[3] **[4]** **[5]** Although inventions involving microorganisms or other living cells often can be enabled by a deposit, [14] a deposit is not always necessary to satisfy the enablement requirement. [15] No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. [16] Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case. [17]

14 *In re Argoudelis,* 434 F.2d at 1393, 168 USPQ at 102.

15 *Tabuchi v. Nubel,* 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

16 *Id.* at 1186–87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co.,* 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J.1967); *Guaranty Trust Co. v. Union Solvents Corp.,* 54 F.2d 400, 403–06, 12 USPQ 47, 50–53 (D.Del.1931), *aff'd,* 61 F.2d 1041, 15 USPQ 237 (3d Cir.1932), *cert. denied,* 288 U.S. 614, 53 S.Ct. 405, 77 L.Ed. 987 (1933); MPEP 608.01(p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

17 *In re Jackson,* 217 USPQ at 807; *see In re Metcalfe,* 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

[6] Appellants contend that their written specification fully enables the practice of their claimed invention because the monoclonal antibodies needed to perform

the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980.[18] The sole issue is whether, in this particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies.

18 *Hybritech,* 802 F.2d at 1384, 231 USPQ at 94.

[7] Enablement is not precluded by the necessity for some experimentation such as ***737** routine screening.[19] However, experimentation needed to practice the invention must not be undue experimentation.[20] "The key word is 'undue,' not 'experimentation.' "[21]

19 *Id.; Atlas Powder Co. v. E.I. DuPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed.Cir.1984); *In re Angstadt,* 537 F.2d at 502–504, 190 USPQ at 218; *In re Geerdes,* 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *Mineral Separation, Ltd. v. Hyde,* 242 U.S. 261, 270–71, 37 S.Ct. 82, 86, 61 L.Ed. 286 (1916).

20 *Hybritech,* 802 F.2d at 1384, 231 USPQ at 94; *W.L. Gore,* 721 F.2d at 1557, 220 USPQ at 316; *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).

21 *In re Angstadt,* 537 F.2d at 504, 190 USPQ at 219.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* [448 F.2d 872, 878–79; 169 USPQ 759, 762–63 (2d Cir.1971), *cert. denied,* 404 U.S. 1018, 92 S.Ct. 680, 30 L.Ed.2d 666 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * *.[22]

22 *In re Jackson,* 217 USPQ at 807.

[8] The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.[23] Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data.

23 *See Hybritech,* 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder,* 750 F.2d at 1576, 224 USPQ at 413.

[9] Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *In re Forman.*[24] They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.[25]

24 *In re Forman,* 230 USPQ at 547.

25 *Id.; see In re Colianni,* 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer,* 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells,

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