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UNITED STATES DISTRICT COURT  
EASTERN DISTRICT OF CALIFORNIA

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CHIRON CORPORATION,  
Plaintiff,  
v.  
GENENTECH, INC.,  
Defendant.

NO. CIV. S-00-1252 WBS GGH

MEMORANDUM AND ORDER RE:  
INFRINGEMENT

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This lawsuit concerns Chiron's United States Patent No. 6,054,561 ("561 patent"), a patent for monoclonal antibodies that bind to a human breast cancer antigen known as HER2. Chiron moves for summary judgment on the question of whether Genentech's product, Herceptin, infringes the '561 patent. Genentech opposes Chiron's motion on the sole ground that Herceptin is not a "monoclonal antibody" as the court has defined the term.

I. Factual and Procedural Background

A. The '561 Patent

In general, the '561 patent claims monoclonal antibodies capable of binding to a human breast cancer antigen known as HER2. The science of monoclonal antibodies is discussed

1 at length in this court's Markman order of April 22, 2002.  
2 Briefly, antibodies target and attach to foreign substances in  
3 the body known as antigens. Monoclonal antibodies are  
4 homogeneous preparations of essentially identical antibodies, all  
5 of which recognize and bind to the same antigen.

6 In the early 1980s, scientists at Cetus, Chiron's  
7 predecessor, began a project to produce monoclonal antibodies  
8 capable of recognizing and binding to human breast cancer  
9 antigens but not to normal tissue. After testing thousands of  
10 monoclonal antibodies, Cetus scientists isolated several that  
11 bound to an antigen that occurred with great frequency in breast  
12 cancers, but with little frequency in normal tissue. That  
13 antigen, known today as "HER2" (Human Epidermal growth factor  
14 Receptor 2), is referred to in the '561 patent as "c-erbB-2."

15 In 1984, Cetus filed the first in a long line of patent  
16 applications that ultimately resulted in the issuance in April of  
17 2000 of the '561 patent. The '561 patent consists of thirty-one  
18 separate claims, the first twenty-five of which are at issue in  
19 this lawsuit.

20 The claims of the '561 patent fall within four broad  
21 categories. In the first category are three independent claims,  
22 claims 1, 9, and 19, which recite monoclonal antibodies that bind  
23 to a particular breast cancer antigen. Specifically, claim 1 is  
24 directed toward "[a] monoclonal antibody that binds to a human  
25 breast cancer antigen that is also bound by monoclonal antibody  
26 454 C11. . . ."; claim 9 claims "[a] monoclonal antibody that  
27 binds to a human breast cancer antigen that is also bound by  
28 monoclonal antibody 520 C9. . . ."; and claim 19 claims "[a]

1 monoclonal antibody that binds to human c-erbB-2 antigen." The  
2 patent equates the antigen bound by 454 C11 with the antigen  
3 bound by 520 C9 and c-erbB-2. ('561 patent, at 27:1-17; Claim 8,  
4 16, 18). For ease of reference, the court will refer to these  
5 claims as the "independent claims."

6 The second category of claims are dependent claims  
7 which incorporate every limitation of the independent claims, but  
8 also require that the monoclonal antibodies of the independent  
9 claims exhibit certain staining activity in an immunoassay.  
10 ('561 Patent, claims 2,4, 7, 10-12, 20, 22, 25). Claims 2 and 4  
11 are representative. Claim 2 is directed toward the monoclonal  
12 antibody of claim 1, where the monoclonal antibody exhibits  
13 strong staining on three or less identified normal tissues in an  
14 immunoassay.<sup>1</sup> Claim 4 requires strong staining on one or less of  
15 the enumerated normal tissues. The court will refer to these  
16 claims as the "staining claims."

17 The third category of claims are dependent claims  
18 directed toward the monoclonal antibodies that bind to the  
19 extracellular domain of the referenced human breast cancer  
20 antigen. Claims 3, 7, 11, 15, 21, 25 are referred to herein as  
21 the "extracellular domain claims."

22 The fourth and final category of claims in the patent,  
23 consisting of claims 5, 6, 13, 14, 23, and 24, are dependent  
24 claims that require binding to a human breast cancer cell line.

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25  
26 <sup>1</sup> Claim 2 reads: "The monoclonal antibody of claim 1,  
27 wherein the monoclonal antibody exhibits strong staining  
28 intensity as determined in an immunoassay with three or less of  
the normal tissues and blood cells selected from the group  
consisting of pancreas, esophagus, lung, kidney, colon, stomach,  
brain, tonsil, liver, heart, ovary, skin, breast, platelets, red  
cells, lymphocytes, monocytes and granulocytes."

1 These claims are referred to herein as the "cell line claims."  
2 The court held a Markman hearing, and issued an order on April  
3 22, 2002 construing a number of the terms in the above claims.

4 B. Herceptin

5 The accused product, Herceptin, is a drug used in the  
6 treatment of breast cancer. Herceptin is the product of years of  
7 research and development by Genentech scientists that began in  
8 the mid 1980s. (Slikowsky Decl. Ex. A at 2.) Like scientists at  
9 Cetus, scientists at Genentech were interested in identifying  
10 antibodies capable of binding to human breast cancer for the  
11 purpose of developing a breast cancer drug. In the late 1980s,  
12 they discovered a murine (mouse) monoclonal antibody named "4D5."  
13 (Id. at 3.) In addition to binding strongly to HER2, 4D5 stops  
14 or reduces the growth of breast tumors that overexpress HER2.  
15 (Id.) This "antiproliferative effect" results from the binding  
16 of 4D5 to the HER2 antigen. (Id.)

17 After it identified 4D5, Genentech sought to "humanize"  
18 the murine antibody. Genentech scientists identified portions of  
19 4D5's amino acid sequence and used those as a "blueprint" for  
20 creating a synthetic amino acid chain that had the binding  
21 properties of 4D5. This chain was combined with chains of amino  
22 acids modeled after human antibodies to create a "humanized"  
23 antibody. (Id. at 4.)

24 Humanization was an important step in producing  
25 antibodies that could be used as effective therapeutics against  
26 breast cancer. Repeated doses of antibodies derived from animal  
27 sources provoked an adverse immune response in some human  
28 patients, as their bodies rejected the presence of non-human

1 elements. Humanized antibodies, however, reduced the potential  
2 for this response by surrounding animal-derived binding sites  
3 with human DNA. (Id.) Genentech succeeded in humanizing 4D5 in  
4 1992. (Crotty Decl. Ex. 7, 1992 Carter article). The humanized  
5 antibody was called "HuMAb4d5-8," short for "Humanized Monoclonal  
6 Antibody 4D5-variant 8."

7           A variant of HuMAb4d5-8 known as "trastuzumab" is the  
8 active ingredient in Herceptin. (Sliwowski Dep. at 39; Crotty  
9 Decl. Ex. 3, Herceptin® Product Insert.) Trastuzumab is produced  
10 by "transfecting," or introducing, heavy and light chains of the  
11 HuMAb4d5-8 antibody into a Chinese Hamster Ovary cell. ("CHO  
12 cell"). (Sliwowsky Decl. Ex. A at 5.) CHO cells do not produce  
13 antibodies naturally; however, once transfected with HuMAb4d5-8,  
14 they produce additional HuMAb4d5 antibodies, as well as molecular  
15 variants of HuMAb4d5-8. (Harris Decl. ¶ 5.)

16           The HuMAb4d5-8 variants include molecules with  
17 different "glycosylation" structures, which essentially are  
18 sugars attached to the amino acid chain of the antibody. (Id. ¶  
19 14.) They also include molecules with slightly different amino  
20 acid structures, which can result from partial "deamidation"  
21 (change in amino-acids) or partial "isomerization" (conversion  
22 into a different structural arrangement) at particular positions  
23 in the amino acid chain. (Id. ¶¶ 9-13.) These amino acid  
24 variants constitute approximately 26% of the overall antibody  
25 composition of Herceptin. (Id. ¶ 9.) Each of these variants  
26 have between 99.8% and 99.9% homology, or similarity in amino  
27 acid sequence, with HuMAb4d5-8. (Id. Ex. A at 243.) According  
28 to a paper published by Genentech scientists, the variants in the

1 antibody population of Herceptin do not have a significant effect  
2 on Herceptin's potency. (Id. Ex. A at 243.)

3 In 1998, after several years of clinical trials, the  
4 FDA approved Herceptin to treat certain forms of breast cancer.  
5 (Id. Ex. 8, FDA Approval Letter). Genentech has made, sold, and  
6 offered to sell Herceptin in the United States since that time.  
7 (Crotty Decl. Ex. 10.)

## 8 II. Discussion

9 The court must grant summary judgment to a moving party  
10 "if the pleadings, depositions, answers to interrogatories, and  
11 admissions on file, together with the affidavits, if any, show  
12 that there is no genuine issue as to any material fact and that  
13 the moving party is entitled to judgment as a matter of law."  
14 Fed. R. Civ. P. 56(c). The party adverse to a motion for summary  
15 judgment may not simply deny generally the pleadings of the  
16 movant; the adverse party must designate "specific facts showing  
17 that there is a genuine issue for trial." Fed. R. Civ. P. 56(e);  
18 see Celotex Corp. v. Catrett, 477 U.S. 317 (1986). Simply put,  
19 "a summary judgment motion cannot be defeated by relying solely  
20 on conclusory allegations unsupported by factual data." Taylor  
21 v. List, 880 F.2d 1040, 1045 (9th Cir. 1989). The non-moving  
22 party must show more than a mere "metaphysical doubt" as to the  
23 material facts. Matsushita Elec. Indus. Co. v. Zenith Radio, 475  
24 U.S. 574, 587 (1986).

25 According to section 271(a) of the Patent Act, "whoever  
26 without authority makes, uses, offers to sell or sells any  
27 patented invention within the United States . . . infringes the  
28 patent." 35 U.S.C. § 271(a). Determining whether a patent is

1 infringed requires a two step analysis. First, the court must  
2 construe the disputed terms of the patent. See Markman v.  
3 Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (en  
4 banc), aff'd, 517 U.S. 370 (1996). Second, the court must  
5 compare the properly construed claims to the accused product.  
6 Id. at 976. A product literally infringes the patent if each and  
7 every limitation of the properly interpreted claim is found in  
8 the accused product. See Transmatic, Inc. v. Gulton Indus.,  
9 Inc., 53 F.3d 1270, 1277 (Fed. Cir. 1995).

10 The court has already construed the terms of the  
11 patent, and Genentech admits to making, offering to sell, and  
12 selling Herceptin in the United States. Thus, the only issue for  
13 the court to decide is whether Herceptin contains all of the  
14 limitations of the claims as construed by the court. Whether  
15 Herceptin infringes the '561 patent is a question of fact.  
16 Rheox, Inc. v. Entact, Inc., 276 F.3d 1319, 1324 (Fed. Cir.  
17 2002).

18 One limitation that appears in all of the claims in the  
19 '561 patent is that the antibody must be a "monoclonal antibody."  
20 The court has construed the term "monoclonal antibody" to mean:

21 An antibody composition having a homogeneous  
22 (essentially identical) antibody population. The term  
23 is not limited regarding the species or source of the  
24 antibody, nor is it limited by the manner in which it  
25 is made. For example, the term includes monoclonal  
26 antibodies produced by a methodology other than  
27 hybridoma which results in monoclonal antibodies no  
28 matter how subcategorized, e.g., hybrid, altered,  
chimeric, or humanized. The term includes variants  
that naturally arise during the production of  
monoclonal antibodies. The term includes whole  
immunoglobulins.

(April 22, 2002 Order, at 38) (emphasis added). Genentech argues

1 that Herceptin does not infringe any of the claims in the '561  
2 patent because Herceptin does not have a homogenous antibody  
3 population.<sup>2</sup>

4           It is undisputed that approximately 26% of Herceptin's  
5 antibody composition has a different amino acid structure from  
6 HuMAb4d5-8, and that some of the antibodies within the population  
7 are also glycosylated. However, the definition of monoclonal  
8 antibody allows for "variants that naturally arise during the  
9 production of monoclonal antibodies," as long as the antibodies  
10 in the resulting preparation are "essentially identical." If the  
11 variants in Herceptin's antibody population arise naturally  
12 during Herceptin's production and are essentially identical, then  
13 Herceptin infringes the patent.

14           Genentech argues that because CHO cells do not  
15 naturally produce antibodies, any variants that arise from a  
16 population of antibodies produced by a transfected, or as  
17 Genentech puts it, "genetically manipulated," CHO cell are not  
18 "natural." This argument is inconsistent with both the patent  
19 and the understanding of those skilled in the art.

20           The patent explains that some variants will arise  
21 during the production of monoclonal antibodies, and includes  
22 these within the definition of "monoclonal antibody":

23           Antibodies are normally synthesized by lymphoid cells  
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25           <sup>2</sup> Chiron contends that Genentech should be precluded from  
26 raising the argument that Herceptin is non-homogenous and  
27 therefore does not infringe the '561 patent, because Genentech  
28 failed to identify this theory in its responses to Chiron's  
interrogatories. See Fed. R. Civ. Proc. 26(e), 37(c)(1).  
Chiron, however, has not shown or even alleged any prejudice  
resulting from Genentech's purported failure to supplement its  
interrogatory responses. The court refuses to preclude a  
substantive defense on a mere technicality.

1 derived from B lymphocytes of bone marrow. Lymphocytes  
2 derived from the same clone produce immunoglobulin of a  
3 single amino acid sequence. Lymphocytes cannot be  
4 directly cultured over long periods of time to produce  
5 substantial amounts of their specific antibody.  
6 However, Kohler et al (1975) Nature 256: 496-497,  
7 demonstrated that a process of somatic cell fusion,  
8 specifically between a lymphocyte and a myeloma cell,  
9 could yield hybrid cells which grow in culture and  
10 produce a specific antibody called a "monoclonal  
11 antibody" . . . . The resulting hybrid cell was called  
12 a "hybridoma." A monoclonal antibody belongs to a  
13 group of antibodies whose population is substantially  
14 homogeneous, i.e. the individual molecules of the  
15 antibody population are identical except for naturally  
16 occurring mutations.

17 ('561 Patent at 1:39-54) (emphasis added). Genentech interprets  
18 this language to mean that "the 'mutations' or variants  
19 contemplated [by the patent] are those that arise from cells such  
20 as lymphocytes of bone marrow that naturally produce antibodies."  
21 (Genentech Opp'n at 3.) However, nothing in the language cited  
22 by Genentech suggests that it is the lymphocyte cells that must  
23 produce these mutations. In fact, the expert testimony in the  
24 record suggests that the variations referred to occur because the  
25 monoclonal antibodies are produced in a host cell, i.e. something  
26 other than a lymphocyte, such as a hybridoma. (Mar. 6, 2002  
27 Markman Tr. at 34 (testimony of Dr. Lanier that "if you produce  
28 antibodies in different host cells, they may suddenly change the  
29 sugar attached to the antibody," resulting in a "naturally  
30 occurring mutation."))

31 At the Markman hearing, Chiron's expert Dr. Lanier was  
32 asked about what he understood the patent to mean by "naturally  
33 occurring mutations." He testified that the term meant small,  
34 minor variations in antibody composition, and that glycosylation,  
35 deamidation and isomerization would all be examples of naturally

1 occurring mutations. (Id. at 34-35.) He also testified that  
2 each of these types of naturally occurring mutations were known  
3 to occur in 1984, when the first patent application leading to  
4 the '561 patent was filed. (Id. at 35; see also Lanier Reply  
5 Decl. ¶¶ 8-10.) Glycosylated variants, and variants resulting  
6 from deamidation and isomerization are the variants of HuMAb4d5-8  
7 in Herceptin. Given the plain language of the patent, the  
8 court's claim construction, and Dr. Lanier's expert testimony,  
9 Genentech's argument that the variants in Herceptin do not arise  
10 naturally from its production rings hollow.

11           Moreover, the logic of Genentech's argument dictates  
12 that no one could ever make a homogeneous preparation of  
13 antibodies having "natural" variants from a hybridoma, which is  
14 inconsistent with the way this court has defined a monoclonal  
15 antibody. Hybridomas do not exist in nature - they are produced  
16 in the laboratory by fusing a myeloma with a lymphocyte. Like a  
17 CHO cell, a myeloma will not produce antibodies unless it is  
18 "manipulated." Variants that are produced from a hybridoma are  
19 therefore no more "natural" by Genentech's definition than  
20 variants produced by CHO cells. Similarly, because humanized  
21 monoclonal antibodies do not occur in nature, any variants that  
22 would arise from trying to make a humanized monoclonal antibody  
23 would not be "natural" according to Genentech's interpretation.  
24 This court, however, has already found that the term "monoclonal  
25 antibody" encompasses both humanized antibodies and hybridoma-  
26 derived antibodies.

27           Genentech has also failed to present any evidence that  
28 the variants in Herceptin are not "essentially identical" to

1 HuMab4d5-8 and to each other so as to make Herceptin a non-  
2 homogeneous preparation.<sup>3</sup> To the contrary, it is undisputed that  
3 the variants are at least 99.8% homologous to trastuzumab, and  
4 have no significant impact on the purity or potency of Herceptin.

5 Finally, the testimony of experts for both Chiron and  
6 Genentech overwhelmingly confirms that Herceptin is a homogeneous  
7 preparation of antibodies. Genentech's expert, Dr. Deborah  
8 French, testified at her deposition that "Herceptin is a  
9 humanized antibody which as a product is a homogeneous  
10 population." (French Dep. at 59.) Dr. John Adair, another  
11 Genentech expert, similarly testified that trastuzumab is sold as  
12 a homogeneous preparation antibody in the drug Herceptin. (Adair  
13 Dep. at 195.) Dr. Jay Unkeless, also testifying on Genentech's  
14 behalf, confirmed that if Genentech made Herceptin in a  
15 recombinant cell line, it would be an antibody composition having  
16 a homogeneous population. (Unkeless Dep. at 120; see also  
17 Slikowsky Dep. at 45 (responding affirmatively when asked if  
18 Herceptin contains a "substantially pure population of  
19 antibodies"); Lanier Reply Decl. ¶ 12 (concluding that Herceptin  
20 is a homogeneous preparation of antibodies).) Significantly,  
21 neither of the experts upon whose testimony Genentech relies for  
22 purposes of opposing Chiron's motion, Drs. Sliwkwosky and Harris,  
23

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24 <sup>3</sup> At oral argument, Genentech suggested that because not  
25 all of the antibodies in Herceptin are identical, there could be  
26 no literal infringement of the '561 patent. Genentech argued  
27 that the proper question for the court was therefore whether  
28 Herceptin infringes under the doctrine of equivalents. However,  
the claims themselves, as the court has construed them, do not  
require a completely identical population of antibodies. A  
product will literally infringe the patent if it is a preparation  
of "essentially identical" antibodies. (See April 22, 2002 Order,  
at 38) (emphasis added).

1 have attested that Herceptin is not a homogeneous preparation of  
2 antibodies.

3 In light of the language of the patent, this court's  
4 claim construction, and the undisputed expert testimony in the  
5 record, no reasonable jury could conclude that Herceptin is a  
6 non-homogeneous antibody population. The undisputed facts  
7 clearly establish that Herceptin is a "monoclonal antibody" as  
8 this court has construed the term. It is further undisputed that  
9 Herceptin binds to the same antigen as 454 C11, 520 C9, and to c-  
10 erbB-2.<sup>4</sup> Therefore, Herceptin literally infringes all of the  
11 independent claims of the patent. Because Genentech does not  
12 dispute that Herceptin also meets all of the limitations in the  
13 dependent claims of the patent, Chiron is entitled to summary  
14 judgment that Herceptin infringes all of the claims of the '561  
15 patent at issue in this case.

16 IT IS THEREFORE ORDERED that Chiron's Motion For  
17 Summary Judgment Re: Infringement be, and the same hereby is,  
18 GRANTED. The court determines as a matter of law that  
19 Genentech's product, Herceptin, infringes claims 1 through 25 of  
20 United States Patent No. 6,054,561.

21 DATED: June 24, 2002

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WILLIAM B. SHUBB  
UNITED STATES DISTRICT JUDGE  
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<sup>4</sup> Genentech "does not advance a non-infringement position  
on th[e] basis" that Herceptin does not "bind" to HER2, and has  
come forward with no evidence to refute Chiron's evidence on this  
point. (Genentech Opp'n To Mot. S.J. Re: Infringement at 1 n.3.)