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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PDL BIOPHARMA, INC., a Delaware corporation, Plaintiff, v. MERCK SHARP & DOHME CORP., a New Jersey corporation, Defendant.	Civil Action No. _____ **COMPLAINT FOR: PATENT INFRINGEMENT** **DEMAND FOR JURY TRIAL**

Pursuant to Local Civil Rule 10.1, the address of Plaintiff PDL BioPharma, Inc. ("PDL") is 932 Southwood Boulevard, Incline Village, Nevada 89451. The address of Defendant Merck Sharp & Dohme Corp. ("Merck") is 1 Merck Drive, Whitehouse Station, New Jersey 08889. PDL, by its undersigned attorneys, for its Complaint against Merck alleges as follows:

NATURE OF THIS ACTION

1. This is an action for patent infringement arising under 28 U.S.C. § 1331 and the United States Patent Act, 35 U.S.C. § 100 *et seq.*

PARTIES

2. PDL is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 932 Southwood Boulevard, Incline Village, Nevada.

3. PDL pioneered the humanization of recombinant antibodies (*i.e.*, therapeutic antibodies created in a laboratory through genetic engineering to have certain human characteristics so as not to be rejected as a foreign substance by the human immune system). This groundbreaking technology widely enabled the discovery of a new generation of targeted treatments for cancer and immunologic diseases. PDL owns certain foundational patents in the United States and overseas relating to humanized antibodies and methods of making such humanized antibodies, commonly referred to as the "Queen Patents" (after Cary Queen, the lead inventor on the patents and the co-founder of PDL). PDL has broadly licensed the Queen Patents to many pharmaceutical and biotechnology companies that have utilized PDL's inventions to create blockbuster drug therapies, sales of which have generated many billions of dollars in revenues. In exchange for those licenses, PDL contracted to receive royalty payments on products whose manufacture, use, or sale would, absent the licenses, infringe PDL's patents.

4. PDL is informed and believes, and on this basis alleges, that Defendant Merck Sharp & Dohme Corp. is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at 1 Merck Drive, Whitehouse Station, New Jersey.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States of America, 35 U.SC. § 1 *et seq.* This Court has federal question jurisdiction under 28 U.S.C. § 1331 and 28 U.S.C. § 1338(a) because it is a civil action arising under the Patent Act.

6. PDL is informed and believes, and on this basis alleges, that this Court has personal jurisdiction over Merck because Merck has availed itself of the legal protections of the State of New Jersey by, among other things, incorporating in and maintaining its principal place of business in New Jersey. This Court also has personal jurisdiction over Merck because Merck has availed itself of the legal protections of the State of New Jersey by, among other things, asserting claims and admitting jurisdiction in lawsuits filed in the United States District Court for the District of New Jersey. *See, e.g.*, *Merck Sharp & Dohme Corp. v. Sandoz Inc.*, No. 2:12-cv-6077, Complaint ¶ 2 & Reply to Counterclaims ¶¶ 4, 7 (D.N.J. Sept. 27, 2012 & May 29, 2013); *Merck Sharp & Dohme Corp. v. Fresenius Kabi USA, LLC*, No. 14-cv-04989, Complaint ¶¶ 1, 12 & Reply to Counterclaims ¶ 5 (D.N.J. Aug. 7 & Sept. 19, 2014); *Merck Sharp & Dohme Corp. v. Actavis Labs. FL, Inc.*, No. 3:15-cv-06075, Complaint ¶¶ 2, 15 & Reply to Counterclaims ¶ 5 (D.N.J. Aug. 6 & Oct. 19, 2015).

7. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c) because Merck resides in this District and because Merck is subject to personal jurisdiction in this District.

BACKGROUND FACTS

8. PDL's Queen Patents relate to humanized immunoglobulins, including humanized antibodies, and methods of making such humanized immunoglobulins, including humanized antibodies. Antibodies are produced by cells of the immune system and represent an important component of the immune system in its fight against foreign microbes and pathogens. Antibodies bind to parts of foreign agents called antigens.

9. Antibodies are Y-shaped proteins composed of four chains of linked amino acids (which are the building blocks of all proteins). Each antibody consists of two identical heavy chains and two identical light chains. The heavy and light chains are so named because the heavy

chain is a longer amino acid chain with a higher molecular weight. Figure 1 below illustrates the two identical heavy chains (blue) and two identical light chains (green).

Figure 1.

10. Each chain is structurally divided into two regions that are responsible for distinct functions: a variable region that varies significantly between different antibodies and allows antibodies to recognize a wide variety of foreign antigens, and a constant region which activates other immune system components. Figure 2 below illustrates the light chain variable regions (dark green), heavy chain variable regions (dark blue), light chain constant regions (light green), and heavy chain constant regions (light blue).

Figure 2.

11. The variable region of each heavy and light chain determines an antibody's ability to recognize and bind to a particular antigen. In addition, the variable region contains three sub-regions that have a particularly high degree of variability in amino acid sequence and three-dimensional structure, called complementarity-determining regions ("CDRs"). The CDRs are

primarily responsible for binding to the antigen. The remaining part of the variable region is called the framework. The framework positions and aligns the CDRs to form the antigen binding site.

12. The advent of monoclonal antibody technology in the mid-1970s for the first time gave researchers and clinicians access to essentially unlimited quantities of monoclonal antibodies—nearly identical antibodies capable of binding to a predetermined antigen. Monoclonal antibodies are generally produced in mice. To produce such an antibody, a mouse is immunized with the antigen of interest, so that the mouse's immune system begins to produce antibodies to that antigen. The cells responsible for producing antibodies are then removed from the mouse and fused with a type of cancer cell to create hybridomas. These hybridomas each continue to produce multiple, nearly identical copies of a single antibody. Monoclonal antibodies were thought to hold great promise in, for example, the removal of harmful cells from the body.

13. Unfortunately, the development of appropriate therapeutic products based on monoclonal antibodies was severely hampered by a number of drawbacks inherent in monoclonal antibody production. The most significant drawback was that the monoclonal antibodies were nonhuman (generally mouse or rat, *i.e.*, "murine") and therefore contained substantial stretches of amino acid sequences that a human's immune system recognized as foreign. Accordingly, when injected into human patients, these antibodies elicited immune responses in which the patient's immune system attacked the antibodies as though they were foreign antigens. The degree to which the antibodies elicited that negative reaction is called "immunogenicity."

14. Researchers tried to address the immunogenicity problem with the production of "chimeric" antibodies, in which, through application of genetic-engineering techniques, the

constant regions of the human immunoglobulin (antibody) molecule were combined with mouse variable regions. As the mouse variable regions typically came from a monoclonal antibody—which, as discussed above, could be produced to target a specific antigen—these chimeric antibodies could be engineered to target an antigen of interest. Maintaining a human constant region lowered the immunogenicity of these antibodies because a higher percentage of the antibodies were human—*i.e.*, not recognized by the patient's immune system as foreign. In addition, the human constant regions could more effectively interact with the human immune system's machinery. However, a significant immunogenicity problem remained because of the mouse sequences in the variable regions.

15. Thereafter, researchers used recombinant DNA technology to produce "humanized" antibodies with variable regions composed of human framework regions combined with CDRs from a donor mouse or rat immunoglobulin in a process sometimes called "CDR-grafting." Figure 3 below illustrates the differences between mouse, human, chimeric, and humanized antibodies, with red denoting mouse elements and green denoting human elements.

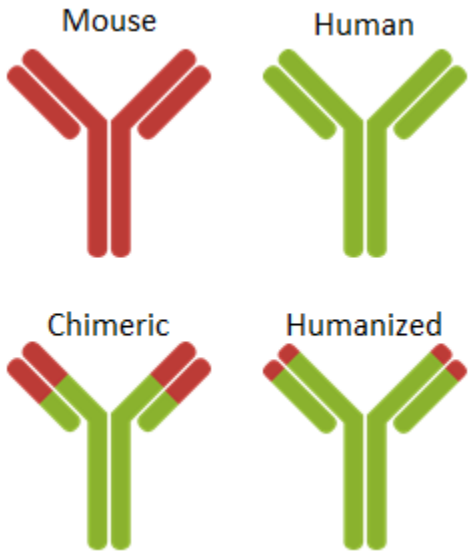

Figure 3.

16. However, a major problem with these CDR-grafting humanization procedures was loss of affinity for the antigen of interest. Affinity refers to the strength of the interaction between the antibody and the antigen. A high affinity antibody more avidly binds its antigen than a low affinity antibody. Loss of any binding affinity is undesirable. At the least, it means that more of the humanized antibody will have to be injected into the patient, at higher cost and greater risk of adverse effects. Even more critically, an antibody with reduced affinity may have poorer biological functions and thus poorer therapeutic efficacy.

17. It was against this background that U.S. Patent No. 5,693,761 (the "'761 patent") issued. The approach set forth in the '761 patent addressed the significant problems faced in the prior art by setting forth a method for creating humanized immunoglobulins, including humanized antibodies, that were substantially non-immunogenic in humans yet retained high affinity for their antigen.

COUNT I

(INFRINGEMENT OF U.S. PATENT NO. 5,693,761)

18. PDL re-alleges and incorporates the allegations in Paragraphs 1 through 17 as if fully set forth herein.

19. On December 2, 1997, the United States Patent and Trademark Office duly and legally issued the '761 patent titled "Polynucleotides Encoding Improved Humanized Immunoglobulins." The '761 patent expired on December 2, 2014. A true and correct copy of the '761 patent is attached hereto as Exhibit 1.

20. Cary L. Queen, Man Sung Co, William P. Schneider, and Harold E. Selick are the sole and true inventors of the '761 patent. By operation of law and as a result of written

assignment agreements, PDL obtained the entire right, title, and interest in the '761 patent and maintained the entire right, title, and interest throughout the period of Merck's infringement.

21. The '761 patent includes 37 claims. By way of example, claim 1 of the '761 patent recites:

> First and second polynucleotides respectively encoding heavy and light chain variable regions of a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chain frameworks, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least about 10^8 M^{-1} and no greater than about four-fold that of the donor immunoglobulin, wherein the sequence of the humanized immunoglobulin heavy chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin heavy chain variable region framework and comprises at least 70 amino acid residues identical to those in the acceptor human immunoglobulin heavy chain variable region framework.

22. Keytruda® (pembrolizumab) is a humanized monoclonal IgG4 antibody manufactured by Merck that is directed against human cell surface receptor PD-1. The U.S. Food and Drug Administration ("FDA") granted approval to Keytruda® on September 4, 2014, for treatment of patients with advanced and unresectable melanoma who are no longer responding to other drugs. On October 2, 2015, the FDA approved Keytruda® for the treatment of patients with metastatic non-small cell lung cancer ("NSCLC") whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

23. PDL is informed and believes, and on this basis alleges, that the humanization of murine antibody hPD-1.09A to obtain the humanized antibody H409A11 is described in U.S. Patent No. 8,952,136, assigned to Merck Sharpe & Dohme B.V., titled "Antibodies to Human

Programmed Death Receptor PD-1." PDL is informed and believes, and on this basis alleges, that Keytruda® includes the humanized antibody H409A11.

24. PDL is informed and believes, and on this basis alleges, that Keytruda® is manufactured using first and second polynucleotides respectively encoding the variable regions of the heavy and light chains of the humanized antibody H409A11.

25. PDL is informed and believes, and on this basis alleges, that H409A11 is a humanized antibody comprising a humanized heavy chain, 109A-H, and humanized light chain, K09A-L-11.

26. PDL is informed and believes, and on this basis alleges, that each of the six CDRs from the murine antibody hPD-1.09A were combined with human acceptor immunoglobulin heavy and light chain frameworks resulting in the humanized heavy and light chains of H409A11.

27. PDL is informed and believes, and on this basis alleges, that the heavy chain framework encoded by GenBank® accession #AB063829 was selected to build the heavy chain 109A-H.

28. PDL is informed and believes, and on this basis alleges, that the light chain framework encoded by GenBank® accession #M29469 was selected to build the light chain K09A-L-11.

29. PDL is informed and believes, and on this basis alleges, that H409A11 specifically binds to an antigen, PD-1, with an affinity constant of $3.41 \times 10^{10} M^{-1}$, which is no greater than about four-fold that of hPD-1.09A (which has an affinity constant of $4.55 \times 10^{10} M^{-1}$).

30. PDL is informed and believes, and on this basis alleges, that the sequence of the heavy chain variable region framework of H409A11 is at least 65% identical to the sequence of the heavy chain variable region framework of hPD-1.09A.

31. PDL is informed and believes, and on this basis alleges, that the sequence of the heavy chain variable region framework of H409A11 comprises at least 70 amino acid residues identical to those in the human immunoglobulin heavy chain variable region framework encoded by GenBank® accession #AB063829.

32. PDL is informed and believes, and on this basis alleges, that Merck has infringed one or more claims of the '761 patent, including at least claim 1, in violation of 35 U.S.C. § 271, literally and/or under the doctrine of equivalents, by, among other things, making Keytruda® without license or authority from PDL.

33. Merck's infringement has damaged PDL, which is entitled to recover from Merck the damages resulting from Merck's wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

34. PDL is informed and believes, and on this basis alleges, that Merck has known about the '761 patent for many years prior to the expiration of the patent and was well aware long before the filing of this action that making Keytruda® amounted to infringement of the '761 patent. In 2005, Merck & Co., Inc. entered into a License Agreement with PDL (then known as Protein Design Labs, Inc.) to secure rights to the '761 patent, among other Queen Patents, for a variety of potential products—but not for Keytruda®. PDL is informed and believes, and on this basis alleges, that Merck Sharp & Dohme Corp. is a subsidiary of Merck & Co. Inc. and that Merck Sharp & Dohme Corp. is and has at all relevant times been aware of PDL's License Agreement with Merck & Co. Inc. regarding the '761 patent, as well as the content and scope of

the claims in the '761 patent. Accordingly, PDL is informed and believes, and on this basis alleges, that despite Merck's knowledge of the '761 patent and its infringement thereof, Merck willfully, wantonly, and deliberately engaged in acts of infringement of the '761 patent.

35. PDL is informed and believes, and on this basis alleges, that Merck's willful, wanton, and deliberate infringement of the '761 patent justifies an award to PDL of increased damages under 35 U.S.C. § 284, and attorneys' fees and costs incurred under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, PDL prays for relief as follows:

A. Judgment that Merck has infringed one or more claims of the '761 patent;

B. An award of damages pursuant to 35 U.S.C. § 284;

C. A declaration that Merck's infringement was willful and deliberate, and an increase to the award of damages of three times the amount found or assessed by the Court, in accordance with 35 U.S.C. § 284;

D. An award for an accounting of damages from Merck's infringement;

E. An award to PDL of its costs and reasonable expenses to the fullest extent permitted by law;

F. A declaration that this case is exceptional pursuant to 35 U.S.C. § 285, and an award of attorneys' fees and costs; and

G. An award of such other and further relief as the Court may deem just and proper.

JURY DEMAND

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, PDL hereby demands trial by jury of all issues so triable by a jury in this action.

Dated: January 22, 2016

/s/ Thomas R. Curtin

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Plaintiff, by its undersigned counsel, hereby certifies pursuant to Local Civil Rule 11.2 that the matters in controversy are not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: January 22, 2016

/s/ Thomas R. Curtin

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