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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-02031
Patent 6,407,213 B1

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Boehringer Ingelheim Pharmaceuticals, Inc. ("Petitioner" or "Boehringer") filed a Petition for an *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 67, 71, 69, 71–73, 75–78, 80, and 81 of U.S. Patent No. 6,407,213 B1 ("the '213 patent," Ex. 1001). Paper 2 ("Pet."). Genentech, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 11 ("Prelim. Resp.").

Our authority to institute an *inter partes* review is derived ultimately from 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the Petition shows "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon consideration of the Petition and Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim. Accordingly, and for the reasons set forth below, we institute *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 69, 71, 73, 75–78, 80, and 81 of the '213 patent. As also discussed below, we decline to institute *inter partes* review of claims 67 and 72 of the '213 patent.

A. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4):

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81	§ 102	Kurrle[1]

[1] Kurrle, et al., European Patent Application Publication No. 0403156, published December 19, 1990. Ex. 1071.

Ground	Claim(s)	Basis	Reference(s)
2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990[2]
3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990
4	1, 2, 4, 25, 29, 62, 64, 66, 69, 71, 73, 75–78, 80, and 81	§ 102	Jones[3]
5	73 and 77	§ 103	Kurrle, Queen 1990, and Chothia & Lesk[4]
6	63	§ 103	Jones and Riechmann[5]

In support of its patentability challenges, Petitioner relies on the Declaration of Geoffrey Hale, PhD. Ex. 1003.

B. The '213 Patent and Relevant Background

The '213 patent relates to "methods for the preparation and use of variant antibodies and finds application particularly in the fields of immunology and cancer diagnosis and therapy." Ex. 1001, 1:12–14.

A naturally occurring antibody (immunoglobulin) comprises two heavy chains and two light chains. *Id.* at 1:18–20. Each heavy chain has a variable domain (V_H) and a number of constant domains. *Id.* at 1:21–23. Each light chain has a variable domain (V_L) and a constant domain. *Id.* at

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[2] Queen, et al., International Publication No. WO 90/07861, published July 26, 1990. Ex. 1050.
[3] Jones et al., *Replacing the complementarity-determining regions in a human antibody with those from a mouse*, 321 Nature 522–525 (1986). Ex. 1033.
[4] Chothia and Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196 J. MOL. BIOL. 901–17 (1987). Ex. 1062.
[5] Riechmann et al., Reshaping human antibodies for therapy, 332 Nature 323–327 (1988). Ex. 1069.

1:23–24. The variable domains are involved directly in binding the antibody to the antigen. *Id.* at 1:36–38. Each variable domain "comprises four framework (FR) regions, whose sequences are somewhat conserved, connected by three hyper-variable or complementarity determining regions (CDRs)." *Id.* at 1:40–43. "The constant domains are not involved directly in binding the antibody to an antigen, but are involved in various effector functions." *Id.* at 1:33–34.

Before the '213 patent, monoclonal antibodies targeting a specific antigen, obtained from animals, such as mice, had been shown to be antigenic in human clinical use. *Id.* at 1:51–53. One object of the invention is "to provide methods for the preparation of antibodies which are less antigenic in humans than non-human antibodies but have desired antigen binding and other characteristics and activities." *Id.* at 4:24–28. In accordance with this goal, the Specification states that embodiments within the scope of the claims have "low immunogenicity," or are designed to "minimize the potential immunogenicity of the resulting humanized antibody in the clinic." *Id.* at 52:54–58, 61:56–61.

The '213 patent recognizes efforts to construct chimeric antibodies and humanized antibodies in the prior art. *Id.* at 1:59–2:52. According to the '213 patent, chimeric antibodies are "antibodies in which an animal antigen-binding variable domain is coupled to a human constant domain" (*id.* at 1:60–62), whereas "humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies" (*id.* at 2:32–35).

The ’213 patent also acknowledges the following as known in the prior art:

1. In certain cases, in order to transfer high antigen binding affinity, it is necessary to not only substitute CDRs, but also replace one or several FR residues from rodent antibodies for the human CDRs in human frameworks. *Id.* at 2:53–61.
2. “For a given antibody[,] a small number of FR residues are anticipated to be important for antigen binding” because they either directly contact antigen or “critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding.” *Id.* at 2:62–3:8.
3. In a few instances, a variable domain “may contain glycosylation sites, and that this glycosylation may improve or abolish antigen binding.” *Id.* at 3:9–12.
4. The function of an antibody is dependent on its three-dimensional structure, and amino acid substitutions can change the three-dimensional structure of an antibody. *Id.* at 3:40–43.
5. “[T]he antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling. *Id.* at 3:44–46.

Despite such knowledge in the field, according to the ’213 patent, at the time of its invention, humanizing an antibody with retention of high affinity for antigen and other desired biological activities was difficult to achieve using then available procedures. *Id.* at 3:50–52. The ’213 patent purportedly provides methods for rationalizing the selection of sites for substitution in preparing humanized antibodies and thereby increasing the efficiency of antibody humanization. *Id.* at 3:53–55. In one embodiment, this involves:

> a. obtaining the amino acid sequences of at least a portion of an import antibody variable domain and of a consensus variable domain;

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