

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Patent No. 10,464,992

Inter Partes Review No. IPR2023-00462

**PATENT OWNER'S SUR-REPLY TO PETITIONER'S PRE-INSTITUTION
REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE¹**

¹ Authorized by the Board via email on May 4, 2023

Petitioner requested a reply “directed to Patent Owner’s arguments that ‘VEGF Trap,’ ‘VEGF Trap R1R2,’ or ‘R1R2’ refer to a genus of proteins.”

Petitioner now agrees that the prior art “may have used the terms ‘VEGF Trap’ and ‘R1R2’ when referring to more than one protein,” i.e., those terms to refer to genera, but maintains that the prior art used “VEGFTrap_{R1R2}” to refer to only one protein, aflibercept. Reply, 3. That argument does not survive the concession that the other two names were generic. As the evidence Regeneron presented in its preliminary response demonstrates, the term VEGFTrap_{R1R2} was used in the same generic way and was not equated with a single protein sequence. POPR 19-27. The prior art discloses multiple proteins within that genus. *Id.*

Moreover, Petitioner must show that the references that it relies on for the claimed formulation (*Fraser* and *Wulff*) involve the **same** protein as in *Dix*. Petitioner has not done so, and indeed fails to mention *Dix* in its Reply at all. Petitioner attempts to find the specificity lacking in *Fraser* and *Wulff* in unrelated publications. But it fails to explain why those publications are determinative of what *Fraser and Wulff* disclose, and none equates the term VEGFTrap_{R1R2} with the protein discussed in *Dix* (referred to as “VEGF trap protein,” not VEGFTrap_{R1R2}) or with aflibercept. Thus, institution should be denied.

A. Petitioner Fails to Show *Fraser* and *Wulff* Involve the Same Protein as *Dix*

Petitioner argues that the stability-related requirement in every challenged

claim is inherent based on *Dix*, which is not prior art. Pet. 24 n.3. Petitioner does not dispute that its inherency argument depends on showing the fusion protein used in each of *Fraser* and *Wulff*—referred to as “VEGF Trap_{R1R2},” “R1R2,” “VEGF R1R2,” “VEGF Trap R1R2,” or just “VEGF Trap” in the publications²—was the same, specific protein in *Dix*. POPR 18-19.

Instead of addressing that question, Petitioner argues that *Fraser* and *Wulff* both describe administering “a single protein” (and that *Holash*, which does not describe a formulation, also uses the term VEGFTrap_{R1R2} to refer to a single protein). Reply, 1-2. That issue is not in dispute. Petitioner fails to address Regeneron’s actual point, which is that both that term and the other descriptions of the proteins used in the prior art are not specific enough to convey *which* protein that was, or that it was the *same* as the *Dix* protein. POPR 27-32.

Both *Fraser* and *Wulff* describe the protein they administered in general terms by function (it traps VEGF) and the domains it includes—VEGF-R1 domain 2 (“R1”) and VEGF-R2 domain 3 (“R2”). Ex.1009, 1115; Ex.1016, 2798. The moniker “R1R2” reflects this general structure-based description. Ex.1029, 59:6-7.

² Ex.1016, 2797-98, 2800-06; Ex. 1009, 1114, 1115, 1118. Thus, Petitioner’s attempt (Reply, 1-3) to contrast the term “VEGF Trap_{R1R2}” with “R1R2” or “VEGF Trap” (which it admits can refer to genera, *id.* at 3) is belied by the prior art itself.

Petitioner does not dispute that there are many different proteins that contain these domains and “trap” VEGF.³ But neither *Fraser* nor *Wulff* provide the nucleic or amino acid sequence for the protein they used, making it impossible to show that either reference is *necessarily* using the same protein as described in *Dix*.

Petitioner insists that “VEGF Trap” and “R1R2” are “more general terms” than “VEGFTrap_{R1R2}” because *Fraser* and *Wulff* use the latter term to refer to the administered “protein in the singular,” but both references employ the term “VEGF Trap” the same way. Compare Ex.1009, 1114 (“Animals were given a single, iv injection of a potent, receptor-based VEGF antagonist, the VEGF Trap”); *id.*, 1118 (referencing “macaques treated with VEGF Trap”); Ex.1016, 2798 (referring to marmosets “treated with VEGF trap”) with Reply, 1-2. Petitioner *admits* that “VEGF Trap” may “refer[] to more than one protein” Reply, 3, and it follows that the same is true of “VEGFTrap_{R1R2},” which *Fraser* and *Wulff* use the same way.

B. Regeneron’s Post-Priority Statements to the Patent Office Do Not Supply the Disclosures Missing from the Prior Art

Petitioner argues that Regeneron’s position is contrary to statements Regeneron made to the PTO, long after the priority date, but its argument is based on selective quotation. Reply, 4. Quoted in full, Regeneron told the PTO that,

³ Thus, Petitioner does not dispute the central point made by Dr. Klibanov’s declaration, so the Board need not assess the weight to be given to it. Reply, 5.

“[t]he name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}.” Ex.1020, 2. Missing from this statement is any assertion that aflibercept is the *only* protein known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}. Indeed, as noted above, Petitioner concedes that “VEGF trap” can refer to a genus, so the same is true of VEGF-TRAP_{R1R2}.⁴ See also POPR 33-34.

Regeneron’s subsequent statement that “aflibercept is described in [*Holash*] as VEGF Trap_{R1R2}” simply provides additional (post-priority) specificity about the identity of a protein *Holash* describes more ambiguously as VEGF Trap_{R1R2}; the statement would be unnecessary if (as Petitioner contends) VEGF Trap_{R1R2} were not a genus and was instead a known synonym of aflibercept. Moreover, the use of post-priority date information to establish the identity of a prior art compound is prohibited. See POPR 34 (citing *Endo Pharms. Sols., Inc. v. Custopharm, Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018)).

⁴ Petitioner is incorrect that the Board previously concluded otherwise in IPRs. Reply, 4-5. The portion Petitioner cites comes from the Board’s summary of *one of the petitioner’s arguments*, which was not about whether aflibercept and VEGFTrap_{R1R2} were synonymous. IPR2021-00880, Paper 89, 53.

C. The '309 Publication Does Not Cure the Deficiencies in the Prior Art

Petitioner continues to attribute significance to '309 Publication's statement that "VEGFR1R2-FcΔC1(a) 'is also termed VEGFTrap_{R1R2}'." Reply, 3. But (as with the previously-discussed statement that aflibercept "is also known as . . . VEGF trap," a conceded genus term) the '309 Publication does not say that the *only* protein called VEGFTrap_{R1R2} is VEGFR1R2-FcΔC1(a). Petitioner concedes that *Amgen v. Alexion* holds that where the prior art uses an equivocal term that does not necessarily meet the claim requirements, it cannot anticipate. Reply, 4 (citing IPR2019-00741, 2019 WL 4132685, at *9-10 (P.T.A.B. Aug. 30, 2019)⁵). Regardless, Petitioner's Reply fails to address the fact that the '309 Publication is not cited by *Fraser*, *Wulff*, *Holash*, or the '319 Publication, and that the '309 Publication pertains to any entirely different field. POPR 35-37. Thus, Petitioner has not demonstrated why *any* statement from the '309 Publication would be imported into *Fraser* or *Wulff*, let alone interpreted as narrowly as Petitioner does to support its inherency argument. *Id.*; see also *Amgen*, 2019 WL 4132685, at *11 (declining to import information from non-cited references regarding identity of prior art antibody).

⁵ The term at issue there was "eculizumab" (singular), but the Board still concluded that it referred to a "category of antibodies, not a single antibody structure." *Id.*

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Dated: May 16, 2023

Respectfully submitted,

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Certificate of Service (37 C.F.R. § 42.6(e)(4))

I hereby certify that the attached PATENT OWNER'S SUR-REPLY TO PETITIONER'S PRE-INSTITUTION REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE was served as of the below date on the Petitioner via email (by agreement) to the following counsel of record:

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