

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SAMSUNG BIOEPIS CO., LTD.,  
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,  
Patent Owner.

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Case: IPR2025-00176  
U.S. Patent No. 11,084,865

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**PATENT OWNER'S SURREPLY**  
**IN SUPPORT OF PRELIMINARY RESPONSE**

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**TABLE OF EXHIBITS**

| <b>Exhibit</b> | <b>Description</b>                   |
|----------------|--------------------------------------|
| 2001-2032      | <i>Previously presented</i>          |
| 2033-2034      | Reserved                             |
| 2035           | Email from D. Berl to District Court |

Lacking an answer to the multiple court decisions undermining its Petition, SB largely ignores them. SB's Reply (Paper 10) reinforces that the foundation of its Petition is hindsight and fails to show a reasonable likelihood as to any of the claim limitations addressed in Regeneron's Preliminary Response (Paper 8, "POPR"). First, no prior art suggests using an ophthalmic formulation of glycosylated aflibercept, and SB raises no challenge to the district court and Federal Circuit repeatedly finding a motivation *against* glycosylation. Second, SB has no evidence suggesting a 40 mg/mL concentration, and its theory to pluck a 4 mg dose and a 100  $\mu$ L volume misreads the references and ignores the court findings against using high concentrations of aflibercept. Third, SB relies on inherency for the 98% native conformation limitation, but the courts repeatedly have confirmed non-inherency, and SB has *no evidence* of native conformation for the Modified Fraser/Wulff formulation on which its Petition is premised. SB thus cannot show a likelihood of success as to any of these limitations, much less all three as required to institute.

SB's *Fintiv* response likewise fails. The extensive litigation on the '865 patent over the past three years—one two-week trial, three preliminary-injunction proceedings, and three adjudicated Federal Circuit decisions on validity, involving thousands of pages of briefing and expert declarations—alone warrants *Fintiv* denial. SB's delusional assertion that the litigation has been "stagnant" over the past 20 months inexplicably ignores the proceedings leading to the seven trial and

appellate court decisions. Reply 3. SB claims that its grounds and challenged claims are different, Reply 9-10, but multiple courts' holdings as to the three limitations above foreclose SB's arguments as to every challenged claim. Repeating that analysis is precisely the waste of resources that *Fintiv* intends to avert.

**I. SB's Obviousness Arguments Were Refuted by the District Court and Federal Circuit and Are Unlikely To Succeed**

**Glycosylation.** SB concedes that it cannot establish a motivation to use glycosylated aflibercept in an ophthalmic formulation, Reply 5, raising no response to multiple affirmed district court findings that independently foreclose motivation to glycosylate aflibercept. POPR 28-33. SB instead argues that Wulff "teaches that aflibercept is glycosylated." Reply 2. But Wulff nowhere mentions glycosylation; it teaches only that its (unspecified) "VEGF trap was expressed in CHO cells." Ex.1016, 2798. The district court and Federal Circuit have refuted repeatedly the notion that expression in CHO cells implies glycosylation. *Contra* Reply 5.

First, the district court found that the prior art expressly taught that CHO cells may or may not glycosylate. *In re Aflibercept Pat. Litig.*, 2024 WL 3422971, at \*25-26 (N.D.W. Va. June 24, 2024) ("*SB PI Decision*") (finding that VEGF Trap proteins could be "made in *E. coli* or mutant CHO cells and not glycosylated"); Daly (Ex.1039), ¶38. The Federal Circuit affirmed, agreeing that Daly "states that mutant cell lines may be used, 'which either eliminate glycosylation or modify the extent of glycosylation.'" *Regeneron Pharm. v. Mylan Pharm.*, 2025 WL 324288, at \*7 (Fed.

Cir. Jan. 29, 2025) (“*Formycon*”) (quoting Ex.1039, ¶38). Second, the court in *Mylan* found that “even if a protein contains amino acid sequences that may be glycosylated, a given protein may not be glycosylated.” *Regeneron Pharm. v. Mylan Pharm.*, 714 F. Supp. 3d 652, 741 (N.D.W. Va. Jan. 31, 2024) (“*Mylan*”); POPR at 35 n.3. SB responds to none of these findings, which refute its assertion that CHO cell expression indicates glycosylation. Reply 5.

SB bears the burden to prove the POSA’s motivation to use a glycosylated form of aflibercept in an ophthalmic formulation with a reasonable expectation of success. *Otsuka Pharm. v. Sandoz*, 678 F.3d 1280, 1298 (Fed. Cir. 2012); POPR 33. Yet SB does not even attempt such a showing: Wulff, the only reference discussed specifically in SB’s Reply (at 4-5), nowhere discusses glycosylation or any ophthalmic formulation or use. Rather, it involved subcutaneous administration of a VEGF antagonist in monkeys to study ovarian function, Ex.1016, 2798-99, and thus sheds no light on the considerations that, per the district court and Federal Circuit, motivated *against* using glycosylated aflibercept ophthalmically. See POPR 29-33 (findings regarding retinal penetration, systemic half-life, and inflammation). With no contrary evidence on motivation, SB cannot show a reasonable likelihood of success as to any challenged claim. *Otsuka*, 678 F.3d at 1298; see *Regeneron Pharm. v. Mylan Pharm.*, 127 F.4th 896, 912 (Fed. Cir. 2025) (“*SB*”) (rejecting SB’s attempt to “bypass[] the focused factual analysis of motivation” to modify).

**40 mg/mL.** SB points to no teaching of a 40 mg/mL ophthalmic formulation of aflibercept and instead contrives that concentration through a hindsight-driven selection of a 4 mg dose and a 100  $\mu$ L volume. Reply 5-6. But as the district court found, the prior art taught away from 40 mg/mL: Genentech tried that concentration of ranibizumab, and it caused “extremely concerning” ocular inflammation. POPR 37-39; *Mylan*, 714 F. Supp. 3d at 738. SB offers no reason why the POSA would ignore the sole teaching of a 40 mg/mL intravitreal formulation of a VEGF antagonist. There is none. See *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998); POPR 39-43.

SB’s argument separately fails because the prior art supports selecting neither a 4 mg dose nor a 100  $\mu$ L volume. Reply 6. First, SB identifies no reason to select 4 mg from among the 6 tested doses in the 2006 Presentations. Reply 6. The presentations provide no data at all for the 4 mg dose. They report positive clinical data only for the 0.5 and 1.0 mg doses, which SB inexplicably ignores. Ex.1011, 16-21; Ex.1012, 21; Ex.1013, 23; POPR 23, 44-45. Even at a 50  $\mu$ L volume, those doses translate to concentrations of 10 and 20 mg/mL, not 40.

In contrast, nothing in the 2006 Presentations suggests selecting the highest 4 mg dose. Instead, they teach that “[a]dditional studies to determine [the] optimal dose and interval” were still to be done. Ex.1011, 22. While the 2006 Presentations report no particular side effects at *any* dose, e.g., Ex.1011, 14, that hardly provides

motivation to select the highest dose. As explained in the POPR (at 46), and as SB does not dispute, higher doses may require higher concentrations, which cause a “greater risk of aggregation” and associated inflammation and toxicity. *Mylan*, 714 F. Supp. 3d at 737. Moreover, “[b]ecause of its higher potency, *less* aflibercept is needed to inhibit the same amount of VEGF as compared to ranibizumab,” *id.* (emphasis added), which achieved maximum VEGF inhibition at only 10 mg/mL with a 0.5 mg dose, *i.e.*, one of the two doses with reported data in the 2006 Presentations, Ex.1068 (Gaudreault), 727, 732. SB addresses none of these issues. SB’s proposed 4 mg dose disregards both the affirmative teachings of the 2006 Presentations highlighting the 0.5 and 1.0 mg doses and the multiple district court findings based on prior art teaching away from the higher concentrations that a 4 mg dose would require. Such hindsight reasoning cannot establish obviousness. *Sanofi-Aventis v. Dr. Reddy’s Labs.*, 933 F.3d 1367, 1378-80 (Fed. Cir. 2019).

Second, no prior art teaches a 100  $\mu$ L injection volume for a VEGF antagonist. The art teaches 50  $\mu$ L for ranibizumab, the leading VEGF antagonist at the time, *Mylan*, 714 F. Supp. 3d at 692, and 90  $\mu$ L for Macugen<sup>®</sup>. Ex.2022, 1051-52; Ex.1045, 1-2. SB thus relies on references having nothing to do with VEGF or aflibercept to urge a 100  $\mu$ L volume that those references do not deem desirable. First, SB cites (at 6) Jaffe, which generally refers to “a small volume (such as 0.10 mL or less),” Ex.1049, 106, for a small molecule that activates the P2Y<sub>2</sub> receptor,

not VEGF, *id.*, 97. But SB ignores that Jaffe specifically teaches that this molecule “is administered [intravitreally] ... *at a volume of 0.05 mL.*” *Id.* (emphasis added). Second, SB cites an editorial about the corticosteroid Kenalog<sup>®</sup>. Reply 6. Although the editorial states that “0.1 mL is the maximum volume most eyes can tolerate,” it notes uses of higher 0.2 and 0.4 mL volumes, and never suggests 100 µL as preferred. Ex.1048, 932. SB’s reliance on non-VEGF references that do not even promote use of 100 µL is again emblematic of hindsight. *Sanofi*, 933 F.3d at 1380.

Thus, although SB’s asserted 40 mg/mL concentration requires selections of *both* 4 mg and 100 µL from the ranges of at least 6 possible doses and injection volumes spanning at least 50-100 µL (with other volumes also specifically tested, Ex.1049, 932), the prior art supports neither. SB’s arguments come nowhere close to overcoming the established prior art teach-away from a 40 mg/mL concentration.

**98% native conformation.** SB cites not a scintilla of data regarding the native conformation of the Modified Fraser/Wulff formulation after 2 months’ storage and thus cannot meet inherency’s high bar. POPR 49-51. Its Reply (at 6-8) instead improperly inverts the standard of proof and irrelevantly points to a different patent.

Unlike SB’s absence of evidence for its contrived formulation, courts have held repeatedly that the claimed 98% native conformation is not inherent, including because an actual formulation (SS195) did not possess 98% native conformation even at time zero but otherwise fell within the scope of claim 1. POPR 47-48; *SB*

*PI Decision*, 2024 WL 3422971, at \*29; *Regeneron Pharm. v. Mylan Pharm.*, 2025 WL 706079, at \*3 (Fed. Cir. Mar. 5, 2025) (“*Celltrion*”); Ex.2024, ¶10. SB argues (at 8) irrelevantly that the SS195 study involved different storage conditions: SS195 “possessed less than 98% native conformation by SEC even at time zero, before any storage,” and as in the district court, “SB does not dispute that a formulation starting with less than 98% native conformation could not possess 98% native conformation after 2 months’ storage.” *SB PI Decision*, 2024 WL 3422971, at \*29; POPR 53; Reply 6-8. SB also complains that it had no “opportunity to respond” to these data. Reply 8. Not so: SB twice addressed the SS195 data in its motion to strike Dr. Graham’s declaration and in its reply, and the district court specifically addressed and rejected SB’s arguments. 2024 WL 3422971, at \*29-30.

Although SB agrees that the SS195 formulation meets claim 1, SB argues that it does not “match[] the Modified Fraser/Wulff formulation.” Reply 8. But as Regeneron explained and SB does not dispute, POPR 49-56, *no actual formulation* “matches” SB’s hypothetical, hindsight-derived formulation. SS195 undisputedly is a formulation within claim 1 that lacks 98% native conformation and thus refutes SB’s premise that all formulations falling within “ranges” of the ’865 patent and Dix necessarily have 98% native conformation. *Contra* Pet. 43-45; Reply 8; POPR 54.

Unable to prove inherency, SB inverts the burden of proof, to require that Regeneron prove that SB’s *nonexistent* Modified Fraser/Wulff formulation would

*not possess* 98% native conformation after 2 months’ storage. Reply 7-8. But the petitioner, not the patentee, bears the “burden to demonstrate that the claimed limitation is indeed inherent. Simply saying it is so” does not suffice. *Cytiva v. JSR*, 122 F.4th 876, 889 n.15 (Fed. Cir. 2024); *In re Magnum Oil Tools*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (petitioner’s burden “to prove ‘unpatentability by a preponderance of the evidence,’ 35 U.S.C. § 316(e),” “never shifts to the patentee”); *Crown Ops. v. Solutia*, 289 F.3d 1367, 1377 (Fed. Cir. 2002).

SB’s burden argument relies solely on *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977), Reply 7-8, which held that the PTO may “require an applicant” during prosecution to show non-inherency. But SB cites no case (and we are aware of none) applying *Best* outside of examination. And “burden-shifting framework[s]” like in *Best* that apply during prosecution do “not apply in the adjudicatory context of an IPR,” *Magnum Oil*, 859 F.3d at 1375, consistent with § 316(e). SB also suggests that a prior institution decision trumps Regeneron and the Federal Circuit’s view, but that too is wrong. Reply 8 n.2 (citing Ex.1130, 39-40). There, the Board addressed whether *Best* was “limited to ... single-reference obviousness” or applied to “non-prior art data,” neither of which are at issue here. Ex.1130, 39-40.

Finally, SB boldly asserts that an institution decision involving a *different patent, different claims, and different arguments* is somehow “more relevant” than the court decisions addressing *the same patent claims* that SB challenges here. Reply

6-7. That makes no sense. As SB notes (at 7), the '992 patent proceeding addressed Fraser's formulation, but here SB relies on a "modified" formulation altering virtually every aspect of Fraser. POPR 26. There, Regeneron did not dispute whether the limitation was inherent, Ex.1130; here Regeneron does, including in view of courts' holdings that 98% native conformation in the '865 patent claims is not inherent based on the uncontroverted SS195 evidence not presented in the '992 proceeding. *SB PI Decision*, 2024 WL 3422971, at \*29; Ex.2024, ¶10.

## II. The Board Should Deny Institution Under *Fintiv*

***Parallel Litigation.*** *Fintiv* warrants denial of SB's Petition, which invites retreading the same issues already decided by courts. SB's *Fintiv* arguments lack merit. Reply 8-10. First, challenging unasserted claims does not favor institution, as the nonoverlapping claims do not "differ significantly in some way," and SB does not argue "it would be harmed" by noninstitution. *Next Caller, Inc. v. TrustID, Inc.*, IPR2019-00961, Paper 10 at 14 (P.T.A.B. Oct. 16, 2019). The Petition's failures as to glycosylation, 40 mg/mL, and 98% native conformation apply to *all* challenged claims; neither party, for example, raised any argument specific to "challenged claims reciting a PFS." Reply 10; POPR 63. Second, precise identity between IPR grounds and prior decisions is not required; the courts' findings are "substantially similar" to the Petition's arguments, so the investment in those decisions is relevant. *Apple v. Fintiv*, IPR2020-00019, 2020 WL 2126495, at \*6 (P.T.A.B. Mar. 20, 2020);

POPR 6-15. And SB’s belated *Sotera* stipulation cannot “mitigate ... concern of duplication” or “outweigh the substantial investment in the” court proceedings. *Motorola Sols. v Stellar*, IPR2024-01205, Paper 19 at 4 (P.T.A.B. Mar. 28, 2025).

***SB’s Delay.*** SB waited a full year after being sued to file its Petition. POPR 10. SB excuses its delay based on an assertion of service in October 2024, Reply 10, but that ignores nearly a year of *litigating an entire preliminary injunction and appeal*. SB erroneously conflates 35 U.S.C. §§ 315(b) and 314(a), the latter of which, relevant here, has nothing to do with complaint service. *Apple Inc. v. Seven Networks*, IPR2020-00156, 2020 WL 3249313, at \*4 (P.T.A.B. June 15, 2020).

***Trial Date.*** The current lack of a scheduled trial date does not outweigh the massive overlap with and investment in the parallel proceedings. *Mylan Labs. v. Janssen Pharm.*, IPR2020-00440, 2020 WL 5580472, at \*6-11 (P.T.A.B. Sept. 16, 2020). SB’s position appears tribunal-dependent: its pending proposal to the district court seeks a trial in March 2026, POPR 15-16; Ex.2008, but it pledges here not to “seek a trial date ... before the FWD is due.” Reply 9. Regardless, all parties recently requested a district court conference to address the case schedule. Ex.2035. Even if trial is scheduled after the FWD is due, the *Fintiv* factors still strongly favor denial. *Fintiv*, 2020 WL 2126495, at \*4; *Arthrex, Inc. v. Medshape, Inc.*, IPR2025-00053, Paper 11 at 10, 15 (P.T.A.B. Apr. 25, 2025).

For the foregoing reasons and those in the POPR, institution should be denied.

Date: May 7, 2025

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**CERTIFICATE OF SERVICE**  
**(37 C.F.R. § 42.6(e))**

The undersigned hereby certifies that on May 7, 2025, I caused true and correct copies of the following materials:

- Patent Owner's Surreply in Support of Preliminary Response
- Patent Owner's Exhibit List
- Exhibit 2035

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