IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **OUTSIDE COUNSEL EYES ONLY** **FILED UNDER SEAL**

DEFENDANT MYLAN PHARMACEUTICALS INC.'S REPLY MEMORANDUM IN SUPPORT OF MYLAN'S MOTION FOR SUMMARY JUDGMENT

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Reg. Opp.	Regeneron's Opposition to Mylan's Motion for Summary Judgment, dated May 2, 2023
'865 patent or the Formulation Patent	U.S. Patent No. 11,084,865
'572 patent	U.S. Patent No. 11,253,572
'601 patent	U.S. Patent No. 10,888,601
Dosing Patents	U.S. Patent Nos. 10,888,601 and 11,253,572
Accused Product; the BLA; YESAFILI™; YESAFILI™ BLA	The aflibercept-containing product that is the subject of Biologics License Application No. 761274
BLA	Biologic License Application
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MacMichael Opening	February 2, 2023 Opening Expert Report of Gregory MacMichael, Ph.D Regarding Invalidity of the Asserted Claims of U.S. Patent No. 11,084,865 Under 35 U.S.C. § 112 Assuming Mylan's Construction of the Claim Terms "Organic Co-solvent" and "Native Confirmation" and the Invalidity of Claims 6, 7, 12, 13, 18, 19, 22, and 23 of U.S. Patent No. 11,253,572 Under 35 U.S.C. § 112
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Trout Opening	February 2, 2023 Opening Expert Report of Bernhardt L. Trout, Ph.D.

Abbreviation	Description
Trout Responsive	March 2, 2023 Response Expert Report of Dr. Bernhardt L. Trout
FDA	Food and Drug Administration
PTO	United States Patent and Trademark Office
PTAB	Patent Trial and Appeals Board
Mylan's Motion	Defendant Mylan Pharmaceuticals Inc.'s Memorandum in Support of its Motion for Summary Judgment or Partial Summary Judgment on U.S. Patent Nos. 11,104,715 (Process Patent); 11,084,865 (Formulation Patent); and 10,888,601 & 11,253,572 (Dosing Patents) served April 20, 2023
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Dkt. 432-1, Mylan's Motion	Defendant Mylan Pharmaceuticals Inc.'s Memorandum in Support of its Motion for Summary Judgment or Partial Summary Judgment on U.S. Patent Nos. 11,104,715 (Process Patent); 11,084,865 (Formulation Patent); and 10,888,601 & 11,253,572 (Dosing Patents) served April 20, 2023
Dkt. 432-9, '572 Institution Decision	Exhibit 6 to Mylan's Motion, Institution Decision, *Apotex Inc. v. Regeneron Pharms., Inc.*, IPR2022-01524, Paper 9 (P.T.A.B. Mar. 10, 2023)
Dkt. 432-16, the '865 patent	Exhibit 13 to Mylan's Motion, U.S. Patent No. 11,084,865
Dkt. 432-17, Trout Opening	Exhibit 14 to Mylan's Motion, February 2, 2023 Opening Expert Report of Bernhardt L. Trout, Ph.D.
Dkt. 432-20, the '601 patent	Exhibit 17 to Mylan's Motion, U.S. Patent No. 10,888,601
Dkt. 432-21, the '572 patent	Exhibit 18 to Mylan's Motion, U.S. Patent No. 11,253,572
Dkt. 432-27, Yancopoulos Tr.	Exhibit 24 to Mylan's Motion, Transcript of January 18, 2023 Deposition of George Yancopoulos
Dkt. 432-29, Dixon	Exhibit 26 to Mylan's Motion, James A Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18 EXPERT OPINION ON INVESTIGATIONAL DRUGS 1573 (2009)
Dkt. 432-30, Regeneron Interrogatory No. 2 Response	Exhibit 27 to Mylan's Motion, Regeneron Pharmaceuticals, Inc.'s Objections and Responses to Defendant's First Set of Interrogatories (Nos. 1-17), served January 12, 2023
Dkt. 435, Mylan's Counterclaims	Mylan Pharmaceuticals Inc.'s First Amended Answer, Defenses, and Counterclaims to Plaintiff's Complaint
Dkt. 443, Regeneron's Response	Regeneron's Opposition to Mylan's Motion for Summary Judgment served May 4, 2023
Dkt. 443-1, Reg. SMF Resp.	Plaintiff Regeneron Pharmaceuticals, Inc.'s Response to Mylan's Statement of Uncontroverted Facts served May 4, 2023

Mylan Pharmaceuticals Inc. ("Mylan") submits its Reply in support of Mylan's Motion for Summary Judgment for claims that Regeneron Pharmaceuticals, Inc. ("Regeneron") now asserts with regard to U.S. Patent No. 10,888,601 ("the '601 patent"); 11,253,572 ("the '572 patent"), collectively the "Dosing Patents"; and U.S. Patent No. 11,084,865 ("the '865 patent").

I. INTRODUCTION.

Regeneron concedes summary judgment and/or has withdrawn certain claims raised in Mylan's summary judgment Motion. (Dkt. 433 at 1-2). For the remainder, Regeneron's response (1) raises new untimely claim construction theories; (2) remains vague about whether it contends visual acuity claim language in claims 1 and 16 of the '572 patent is still enforceable; and (3) argues that the Court should avoid invalidating the remaining '572 patent claims based on terms that cannot confer separate patentability. Since Regeneron's responsive arguments raise no genuine issues of material fact, Mylan respectfully requests that its Motion be granted.

II. CLAIM 18 OF THE '865 PATENT SAYS, "DOES NOT CONTAIN PHOSPHATE" WITHOUT EQUIVOCATION; [redacted]

Claim 18 states, "The vial of claim 5, wherein said formulation does not contain phosphate." (Dkt. 443-1, Reg. SMF Resp. ¶ 17). Regeneron concedes that it never tested for phosphate in the Accused Product, YESAFILI™, [redacted] Despite this Court scheduling *Markman* proceedings and construing the claims, Regeneron untimely proposes new constructions to try to salvage its infringement case; none work.

Regeneron proposes that the claimed "formulation" that "does not contain phosphate" is not the "end product" in the vial, but an (unexpressed) something else. (Dkt. 443, Reg. Opp. at 5). That construction is inconsistent with the '865 patent's description of formulations; and Regeneron's discovery and expert opinions in this case. (*See* Section II.A). Regeneron tries to construe "formulation" to a component list or "purposeful" excipients (Dkt. 443, Reg. Opp. at 6-

7), to discount phosphates *within* these same components or excipients. This has the same infirmities as above; [redacted] (*See* Section II.B). Regeneron urges construing "does not contain phosphate" as "consisting of," to ignore [redacted] (Dkt. 443, Reg. Opp. at 8). Regeneron could have, but didn't, use "consisting of" claim language, and it can't rewrite its claims now. (*See* Section II.C).

Regeneron also proposes that the summary component list it relies on is akin to a legally binding "specification" under *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013). It isn't, rendering its last theory a failure as well. (*See* Section II.D).

Since Regeneron's arguments are ultimately legal, and not factual, summary judgment for Mylan on claim 18 is proper, as discussed in more detail below.

A. The record nowhere supports Regeneron's new claim construction that the '865 patent's "formulation" differs from the contents of the vial.

1. A new "formulation" claim construction is unnecessary and untimely.

Regeneron states that whether YESAFILI™, when sold, has phosphate is the "wrong question." (Dkt. 443, Reg. Opp. at 5). But that is the only *relevant* question. For a product under pending FDA review, "[w]hat is likely to be sold, or, preferably, what will be sold, will ultimately determine whether infringement exists." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997). Regeneron admits that it never tested the product accused of infringement for which FDA approval is sought—YESAFILI™—to determine whether it contains phosphate. (Dkt. 443-1, Reg. SMF Resp. ¶ 23). That justifies summary judgment for Mylan.

Though claim 18 requires the "vial of claim 5, wherein said formulation does not contain phosphate," (Dkt. 443-1, Reg. SMF Resp. ¶ 17), Regeneron seeks a new "formulation" construction that means a component list, not the product in the vial; so that Regeneron can look

only at what it calls the "operative document governing the infringement inquiry," to the exclusion of the product to be sold. (Dkt. 443, Reg. Opp. at 5-6).

First, the '865 patent does not limit the term "formulation" to a component list—it uses "formulation" broadly, including to describe the contents of a vial for intravitreal injection into the eye. (*See* Dkt. 432-16, '865 patent at Abstract ("Ophthalmic formulations" of the drug "are provided suitable for intravitreal administration to the eye"); *id*. at col. 1, ll. 45-46 (same); *id*. at col. 5, ll. 23-25 ("The invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration")). Regeneron's new claim construction cannot be right, because it directly conflicts with the intrinsic record. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1324 (Fed. Cir. 2005) (en banc) (noting that a court's construction may not "contradict claim meaning that is unambiguous in light of the intrinsic evidence").

Second, Regeneron did not limit the term "formulation" this way in its prior discovery responses, infringement contentions, or expert reports—it instead applied the "formulation" term to mean the substance injected into the eye. (Dkt. 432-30, Regeneron's Responses to Mylan's Interrogatories at No. 2 (in "developing the drug product formulation for EYLEA—it sought to develop a formulation that stabilized aflibercept and that was suitable for intravitreal injection"); Ex. 28, Regeneron '865 Contentions at 4 (alleging YESAFILI™ is a "formulation" because it "is being developed as a biosimilar product to Eylea®" and is a "sterile solution intended for intravitreal administration supplied in a single-use vial"); 25 (same)); Dkt. 432-17, Trout Opening ¶ 49 ("M710 comprises 'an ophthalmic formulation suitable for intravitreal injection' because it is 'a sterile solution ***intended for intravitreal administration***.'") (emphasis in original)).

[redacted]

[redacted]

Thus, Regeneron has no basis to limit the term "formulation" to just a component list.

2. The component list is not a representation that no other compounds exist *in the listed components*.

Even assuming that Regeneron's proffered summary table,[redacted] (Dkt. 443, Reg. Opp. at 6). That is a strawman choice, and wrong.

By name and nature, the Summary Table is an "overview" of the top-line ingredients in YESAFILI™ (denoted as M710 DP) and Regeneron's Eylea®. FDA does not stop its review at the Summary Table. FDA comprehensively analyzes each component.

[redacted]

[1] Regeneron calls this the "operative document," but it is not the same one cited in its contentions and in Dr. Trout's expert report to describe formulation ingredients. (Ex. 28, Regeneron '865 Contentions at 5-6; Dkt. 432-17, Trout Opening ¶ 42). Mylan nevertheless uses it here.

[redacted]

The cases Regeneron cites explain why: "impurities normally associated with" a chemical component "are implicitly adopted by the ordinary meaning of the components themselves." *Conoco, Inc. v. Energy & Environmental Intern., L.C.*, 460 F.3d 1349, 1361 (Fed. Cir. 2006); *see also Otsuka Pharm. Co. v. Lupin Ltd.*, 2022 WL 2952759 at *4 (D. Del. July 26, 2002) ("the presence of impurities is 'implicit[]' in the ordinary meaning of the recited components"). The Summary Table uses this well-known convention [redacted] Thus, the Summary Table does not compel concluding the formulation "does not contain phosphate."

B. Regeneron's effort to distinguish between "purposeful" excipients and "unwanted" impurities also fails.

[redacted] the

[redacted] Regeneron did not craft claim 18 to say the formulation does not contain "phosphate buffers," "high phosphate levels," or "intentional phosphate." Regeneron used clear and unequivocal "does not contain phosphate" language that excludes phosphate, of any kind, source, amount, or purpose. Regeneron may regret this today, but how patentees claim their invention is the claim drafter's choice and the Federal Circuit "has consistently adhered to the proposition that courts cannot alter what the patentee has chosen to claim as his invention." *DSW, Inc. v. Shoe Pavilion, Inc.*, 537 F.3d 1342, 1347 (Fed. Cir. 2008).

Regeneron insists that it can construe "does not contain phosphate" to mean, does not contain intentionally-added phosphates, under *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339 (Fed. Cir. 2004). (Dkt. 443, Reg. Opp. at 7). Not so. In *Glaxo*, the claims required cefuroxime axetil with "a purity of at least 95% aside from residual solvents." *Id*. at 1343. The excipients-versus-impurities debate arose because Apotex argued it could avoid the claimed cefuroxime axetil purity limit by co-precipitating cefuroxime axetil with zinc salts, which then rendered the drug only 90% "pure." *Id*. at 1343, 1346. The Federal Circuit focused on the zinc salt's purpose ***because the specification defined an impurity*** as "an unwanted reaction product formed during synthesis." *Id*. at 1347. Apotex purposefully adding zinc salts "to enhance the performance" of the drug plainly could not meet the specification's "unwanted" impurity definition. *Id*. The Federal Circuit never suggested the zinc salts, or impurities in cefuroxime axetil, were not part of the *formulation*. Thus, *Glaxo* does not justify limiting the scope of claim 18 phosphates so it can cover YESAFILI™. Nor does *Conoco*, 460 F.3d at 1360; or *Otsuka*, 2022 WL 2952759 at *3, help Regeneron. As next discussed, both cases' claims used "consisting of," not "does not contain phosphate" like claim 18,

which also changes the analysis.

C. "Does not contain phosphate" should not be construed to have the same meaning as "consisting of" to exclude phosphate "impurities."

Regeneron's next claim construction argument is that 1) "does not contain phosphate" is a "closed" term analogous to "consisting of"; 2) the latter phrase can avoid impurities; thus, 3) [redacted] (Dkt. 443, Reg. Opp. at 7-9). Regeneron cannot rewrite its claims. Regeneron *chose not to use* "consisting of" language. It cannot now interpret claim 18 as if it did. *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, No. CIV.A. 2:05CV421, 2006 WL 1314413, at *7-8 (E.D. Va. May 11, 2006) (refusing to equate "substantially free" to "consisting essentially of" when considering isomer and other impurities because patentee chose not to use the latter term).

Moreover, "consisting of" denotes precise ingredients or components to *include* to meet the invention's goals. The routine additive in the accused water-alcohol mixture did not frustrate them in *Conoco*. 460 F.3d at 1360. Amorphous composites "consisting of" drug and HPC excipient could not accept a solvent in the role of excipient; but could if just an impurity. *Otsuka*, 2022 WL 2952759, at *3. But, "does not contain phosphate" is a negative term of exclusion. The exclusionary purpose is lost when phosphate of any amount or kind, is present.

D. The component list in the Summary Table is not a "specification" under the FDA regulations for purposes of *Sunovion*.

Regeneron also proposes that it can ignore [redacted] because the Summary Table is a specification under *Sunovion*, 731 F.3d at 1278. (Dkt. 443, Reg. Opp. at 9). The fatal flaw in this theory is that the Summary Table is not a "specification" under FDA standards. Legally, they

are ***not*** the same, and a mere component list does not meet the standard.[2]

Further, *Sunovion*'s patent claims required eszopiclone "in the form of its dextrorotatory isomer and essentially free of its levorotatory isomer," construed to mean under 0.25% of levo-isomer. 731 F.3d at 1273-74. Defendant Reddy asked FDA to approve its generic product with a drug specification test for levorotatory isomer set to "[n]ot less than 0.3% and [n]ot more than 1.0%," but FDA rejected that. *Id*. at 1274-75. FDA would only approve the product if Reddy changed its eszopiclone specification to *require* a test result for levorotatory isomer that met a "0.0-0.6%" range—which permitted infringement. *Id*. at 1278.

Regeneron identifies no test specification in the YESAFILI™ BLA, or for aflibercept, requiring that either *not* contain phosphate. [redacted] Most critically to

[2] *See Bayer AG v. Elan Pharmaceutical Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000) (specification defined by 21 C.F.R. § 314.50(d)(1)(i)). 21 C.F.R. § 314.50(d)(1)(i) specifications describe "the identity, strength, quality, and purity of the drug substance" using "tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form." For biologics, FDA requires "a complete and thorough CMC section that provides the necessary and appropriate information (e.g., characterization, adventitious agent safety, process controls, and specifications) to support that the manufacturing process consistently delivers a product with the intended quality characteristics." (Ex. 34, May 2019 Guidance at 6).

[redacted]

show the inapplicability of *Sunovion*, FDA never required Mylan or anyone else to affirm the YESAFILI™ BLA product does not contain phosphate, or risk rejection of the application.

Thus, Mylan's motion for summary judgment for claim 18 should be granted.

III. MYLAN SHOULD RECEIVE SUMMARY JUDGMENT ON THE REMAINING DOSING PATENT ISSUES.

A. Regeneron concedes it will not assert direct infringement by Mylan.

Regeneron will not contend that Mylan directly infringes, but objects that entering summary judgment is an improper "advisory" opinion. (Dkt. 443, Reg. Opp. at 3, 12). Mylan's Counterclaims seek a declaration of no direct infringement. (Dkt. 435 at ¶¶ 120 ("Mylan … will not directly … infringe… the '601 patent"); 184 (same, for '572 patent)). Summary judgment is appropriate because it resolves live counterclaims.

B. The '601 patent.

Aside from the direct infringement issue above, Regeneron's invalidity stipulations resolve Mylan's summary judgment motion as to the '601 patent, leaving for trial just the issue of induced infringement and invalidity of claims 11, 19, and 27.

C. Regeneron must be clear that it will not dispute for trial that the "visual acuity" elements in claims 1 and 16 of the '572 patent lack patentable weight.

Regeneron's visual acuity arguments wrongly accuse Mylan of construing the claims one way for induced infringement, and another for invalidity, contrary to the Court's claim construction order. (Dkt. 443, Reg. Opp. at 10, 12-15). That is both incorrect, and not even the issue. Claims 1 and 16 of the '572 patent do not use the specific "Best Corrected Visual Acuity" claim language the Court construed. They state, "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose." (Dkt. 443-1, Reg. SMF Resp. ¶ 30; *see also id.* at ¶ 34). Regeneron does not dispute that asserted claims 6-7, 12-13, 18-19, and 22-23 of the '572 patent contain this 52-week "visual acuity" language, "by virtue of dependency" on claims 1

and/or 16. (*See id.* at ¶ 34). Regeneron, not Mylan, has been unclear about treating these terms identically or differently. Regeneron's experts applied the 52-week visual acuity term of claims 1 and 16, and BCVA, interchangeably. Yet, before the PTAB, Regeneron argued the "visual acuity" language in claim 1 was an independent efficacy requirement. (Ex. 37, IPR2022-01524, Paper 7 at 18-19). In its brief, Regeneron proclaims that there is a "mountain of evidence" that Mylan encourages "the visual acuity measurements recited in the asserted claims." (Dkt. 443, Reg. Opp. at 12-13). But, Regeneron argues "under the Court's construction, Regeneron need not prove that the visual acuity language is performed …." (*Id.* at 15). It is Regeneron, not Mylan, seeking to apply a "heads we win, tails you lose" approach. (*Id.* at 10).

1. Regeneron must clearly confirm the 52-week visual acuity language of claims 1 and 16 lacks patentable weight via the Court's construction.

Mylan limited Section VI of its opening brief to the '572 patent precisely to target the language, "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose." (Dkt. 432-1 at 6, 7, 9-14). So long as everyone agrees that when Regeneron says the "visual acuity language" is non-limiting (Dkt. 443, Reg. Opp. at 15), this includes the clauses in claims 1 and 16 of the '572 patent which read, "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose," then Mylan agrees that this Court need not go further on divided infringement or inducement for the '572 patent on summary judgment.

2. <u>If</u> the 52-week visual acuity language of claims 1 and 16 has patentable weight, then Regeneron cannot meet its burden of proof.

a. Regeneron fails in its burden on divided infringement.

Mylan established that Regeneron failed to meet its burden of proof regarding infringement of the 52-week visual acuity language in claims 1 and 16 of the '572 patent. (Dkt. 432-1 at 2, 6-16). In response, Regeneron complains Mylan lacks expert testimony on the issue (Dkt. 443, Reg. Opp. at 16), an argument that improperly tries to shift its burden onto Mylan. Regeneron's string

cites that a doctor ***measures*** visual acuity (Dkt. 443, Reg. Opp. at 17) are irrelevant. What doctors must "direct or control" is the claimed patient activity—achieving visual acuity gains within 52 weeks. (*See id.*). Doctors cannot direct, control, or predict this. (Dkt. 443-1, Reg. SMF Resp. ¶ 61). Regeneron had its opportunity to provide evidence that they do, but offers none. Summary judgment on divided infringement is proper.

b. Regeneron fails in its burden on induced infringement.

The heart of Regeneron's inducement theory is that once the YESAFILI™ label stated it was interchangeable with Eylea®, Mylan then induced every doctor's aflibercept use—whether on-label or off-label; patented or unpatented; effective or ineffective; esoteric or routine. (Dkt. 443, Reg. Opp. at 17-22). That is not how inducement under 35 U.S.C. § 271(b) legally works.

"[M]ere knowledge alone of possible infringement by others is insufficient to prove inducement." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003). Inducement requires that Mylan "knowingly aided and abetted another's direct infringement." *Id.* at 1363. When "a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent." *Id.* at 1365. Inducing instructions also must specifically instruct another party to perform "every single step in the method" that the patent claims require. *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1219 (Fed. Cir. 2014). If the instructions include some, but not all, method steps claimed, or is indifferent as to which choice a user makes, the label is not inducing. *See Shire LLC v. Amneal Pharms.*, LLC, No. CIV.A. 11-3781 SRC, 2014 WL 2861430, at *5 (D.N.J. June 23, 2014) ("the statement that the medication may be taken with or without food cannot be reasonably understood to be an instruction to engage in an infringing use"; it is "indifferent to which option is selected").

A drug label cannot encourage, recommend, or promote infringement when the acts at

issue, if performed, do not obligate a doctor or patient to actually perform each and every required step of the claims. *HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019) confirmed this. The patented method in *HZNP* required three distinct steps: (1) applying diclofenac, (2) waiting for the treated area to dry and (3) applying, *e.g.*, sunscreen. *Id*. at 702. The label instructions "only require the first step of this method, nothing else," and while the label instructions stated, "[w]ait until area is completely dry before covering with clothing or applying sunscreen, insect repellent, cosmetics, … or other substances," *id*. at 700, that step was optional, not mandatory. *Id*. at 702. A label "does not encourage infringement, particularly where the label does not require" using each claimed method step. *Id*.

Regeneron argues it marshalled a "complete arsenal" of undisputed evidence that doctors regularly assess their patients, (Dkt. 443, Reg. Opp. at 17, 19); that the YESAFILI™ label instructs "administer[ing] [] YESAFILI™ to patients," (*id*. at 18); that YESAFILI™ is "highly similar" to Eylea® (Dkt. 443-1, Reg. SMF Resp. ¶ 40); that doctors using YESAFILI™ will reach similar results as with Eylea®; that YESAFILI™ is interchangeable with Eylea®; and that assessing for visual acuity is a routine, common, and desirable physician practice. (Dkt. 443, Reg. Opp. at 18-21; Dkt. 443-1, Reg. SMF Resp. ¶¶ 39-47). Regeneron insists that "physicians overwhelmingly understand" that they should measure visual acuity when they are treating patients with anti-VEGF agents. (Dkt. 443, Reg. Opp. at 19). Even if true, it is irrelevant. The claimed method step is to *achieve visual acuity gains in patients*. Regeneron argues it "does not matter" that YESAFILI™'s label instructions do not mention visual acuity gains specifically. (*Id*. at 19, n.8). But that is the ***only*** relevant fact that matters—if claims 1 and 16 require patients to achieve a gain in visual acuity, the label must instruct this step to induce. A label that lacks an instruction to the specific element in the method cannot induce. *Warner-Lambert*, 316 F.3d at 1364-65 (no inducement of

off-label uses even assuming doctors used the drug for that purpose).

Regeneron complains that "Mylan's Motion asks the Court to credit attorney argument over the sworn testimony of both sides' experts." (Dkt. 443, Reg. Opp. at 19). No. Mylan's Motion asks the Court to look for legally relevant evidence—instructions to perform ***each and every step in the claimed method***. Regeneron lacks a crucial instruction in the YESAFILI™ labeling: an instruction that patients achieve the claimed visual acuity gains.

Regeneron also complains it is not "credible" for Mylan to state it does not intend for doctors to assess visual acuity, which it calls a "callous disregard for patient care." (Dkt. 443, Reg. Opp. at 19-20). This is irrelevant hyperbole. "The pertinent question is whether the proposed label instructs users to perform the patented method." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). Moreover, Mylan has sold its BLA to another company. (Ex. 40, 11-29-22 Viatris Form 8-K at Ex. 99.1) (announcing transaction transferring biosimilar assets to Biocon); [redacted] Regeneron has yet to explain how Mylan intends to aid and abet infringement via this third party.

Regeneron's final set of specific-letter arguments fare no better.[4] Regeneron argues, without citation, that the YESAFILI™ label "expressly instructs" administering it "for patented indications." (Dkt. 443, Reg. Opp. at 21). Regeneron does not offer a label statement that specifies, "go measure" the claimed letter standards; but rather only that doctors "understand" that administering aflibercept may include "measurement of visual acuity gains." (*Id*. at 22). Again, whatever doctors do or don't understand, or are motivated to measure, label inducement requires

[4] Regeneron mischaracterizes *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1326 (Fed. Cir. 2021). (Dkt. 443, Reg. Opp. at 21). Teva had a small molecule ANDA, so the therapeutic equivalence regulatory standard is "bioequivalence"; for biological molecules, it is "interchangeable." 21 C.F.R. § 320.33; 42 U.S.C. §§ 262(i)(3), (k). The scientific conferences are also not the label; and are irrelevant now that Mylan sold its BLA to a third party.

the label must instruct to administer aflibercept ***and*** measure ***and*** achieve the results that the method steps require. Absent label instructions for *all* claim elements, inducement liability cannot attach as a matter of law. *Ericsson*, 773 F.3d at 1219.

D. Claim elements to DME, or "isotonic solution" and "nonionic surfactant" formulation, cannot salvage the claims' validity.

Regeneron now stipulates to the invalidity of claims to, *e.g.*, treating an angiogenic eye disorder by intravitreally dosing aflibercept 2 mg doses via three (3) loading doses, followed thereafter by every 8-week dosing. (Dkt. 433, Reg. Opp. at 1 (conceding, *e.g.,* invalidity of claims 5-6 and 9 of the '601 patent; and claims 1-5 of the '572 patent)). The prior art Dixon publication, among others, expressly disclosed these steps. (Dkt. 432-1 at Section VII).

Regeneron argues that claims 18, 19, 22, and 23 are different for being "directed to treating diabetic macular edema" ("DME"). (Dkt. 443, Reg. Opp. at 24). That is not a patentable distinction in the wake of Regeneron's invalidity stipulation for claim 1 of the '572 patent (Dkt. 433., Reg. Opp. at 1). Claim 1 covered a "method of treating an angiogenic eye disorder" using the dosing regimen. (Dkt. 432-21, '572 patent at col. 23 ll. 2-14). The '572 patent's specification admits that DME is an angiogenic eye disorder. (*Id.* at Abstract; col. 1, ll. 40-47; col. 5, ll. 35-42). Dixon expressly stated that aflibercept, *i.e.,* "VEGF Trap-Eye," was already in clinical trial use "for the treatment of diabetic macular edema (DME)." (Dkt. 432-29, Dixon at MYL-AFL0005012).

Regeneron also argues that elements in claims 6-7, 12-13, 18-19, 22, and 23 involving aflibercept formulated "as an isotonic solution" (claims 6, 12, 18, 22); or "with a nonionic surfactant" (claims 7, 13, 19, and 23), were not "addressed" by Mylan. (Dkt. 443, Reg. Opp. at 24-25). They too cannot render the claims patentable. The alleged "invention" of the '572 patent is dosing methods "which allow for less frequent dosing while maintaining a high level of

efficacy." (Dkt. 432-21, '572 patent at col. 2, ll. 8-9; col. 3, ll. 39-50 (invention is dosing frequency); col. 4, ll. 57-59 (invention is the dosing regimen)). Regeneron stipulates this 8-week dosing method in its claims is invalid. The '572 patent admits that the formulations that method used were those "conventionally used for injections," and hence not inventive. (*Id*. at col. 6, ll. 18-22). George Yancopoulos, the sole named inventor on the '572 patent, has no formulation expertise. (*See* Dkt. 432-27, Yancopoulos Tr. at 64:2-3). Regeneron's interrogatory responses never said that Dr. Yancopoulos invented any formulations. (*See* Dkt. 432-30, Regeneron's Responses to Mylan's Interrogatories at No. 3 ("Dr. George Yancopoulos invented the dosing regimens described in the patents," and others invented the formulation); No. 13 ("Dr. George Yancopoulos conceived of the dosing regimens")).[5]

Since Regeneron cannot validly claim what was conventional, known, inherently in use, and not invented by the named inventor, summary judgment of invalidity is proper here.

IV. CONCLUSION.

For the foregoing reasons, Mylan respectfully requests that the Court GRANT Mylan's Motion for Summary Judgment as to the remaining issues above.

Respectfully submitted,

[5] In fact, Regeneron's interrogatory responses stated that the "present formulation of aflibercept was manufactured" by other individuals, not Dr. Yancopoulos. (*See* Dkt. 432-30, Regeneron's Responses to Mylan's Interrogatories at No. 2). The VIEW 1/VIEW 2 clinical trials discussed in Dixon used that same formulation. (*See* Ex. 38, CLEAR-IT 3 Protocol at RGN-EYLEA-MYLAN-00534502, -519); *see also* Ex. 39, IPR2021-00881, Paper 93, Hearing Tr. at 35, 37 (Regeneron counsel admits Dixon used aflibercept/VEGF Trap Eye)).

Date: May 11, 2023

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IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

REGENERON PHARMACEUTICALS, INC.,

Plaintiff,

v.

MYLAN PHARMACEUTICALS INC.,

Defendant.

Case No. 1:22-cv-00061-TSK

DECLARATION OF L. SCOTT BEALL IN SUPPORT OF DEFENDANT MYLAN PHARMACEUTICALS INC.'S REPLY MEMORANDUM IN SUPPORT OF MYLAN'S MOTION FOR SUMMARY JUDGMENT

I, L. Scott Beall, hereby declare as follows:

1. I am of counsel in the law firm of RAKOCZY MOLINO MAZZOCHI SIWIK LLP, counsel for Mylan Pharmaceutical Inc. ("Mylan").

2. I am a member in good standing of the Bar of the State of Illinois (2003).

3. I submit this Declaration in support of Defendant Mylan Pharmaceuticals Inc.'s Reply Memorandum in Support of Mylan's Motion for Summary Judgment, and evidence supporting same, filed contemporaneously herewith.

4. I have personal knowledge of the facts stated in this Declaration and am competent to testify to the same.

5. I submit this Declaration to authenticate and provide to the Court certain documents cited to and referenced in Defendant Mylan Pharmaceuticals Inc.'s Reply Memorandum in Support of Mylan's Motion for Summary Judgment, submitted concurrently herewith.

6. Attached hereto as Exhibit 28 is a true and correct copy of Final Infringement Contentions of Plaintiff Regeneron Pharmaceuticals, Inc. for U.S. Patent No. 11,084,865 dated January 12, 2023.

7. Attached hereto as Exhibit 29 is a true and correct excerpt of the transcript of the Videotaped Deposition of Gregory MacMichael, Ph.D. on March 12, 2023.

8. Attached hereto as Exhibit 30 is a true and correct copy of Exhibit 18 to the transcript of the Videotaped Deposition of Gregory MacMichael, Ph.D. on March 12, 2023.

9. Attached hereto as Exhibit 31 is a true and correct excerpt of [redacted] 3.2.S.3.2 Impurities [redacted]

10. Attached hereto as Exhibit 32 is a true and correct copy of [redacted] 3.2.S.2.2 Description of Manufacturing Process and Controls [redacted]

11. Attached hereto as Exhibit 33 is a true and correct copy of Certificates of Analysis [redacted]

12. Attached hereto as Exhibit 34 is a true and correct copy of Guidance for Industry: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019).

13. Attached hereto as Exhibit 35 is a true and correct copy of Responsive Expert Report of Gregory MacMichael, Ph.D. Regarding the Non-Infringement of the Asserted Claims of U.S. Patent No. 11,084,865 dated March 2, 2023.

14. Attached hereto as Exhibit 36 is a true and correct excerpt of Quality Risk Assessment Report [redacted]

15. Attached hereto as Exhibit 37 is a true and correct excerpt of IPR2022-01524, Paper 7, Preliminary Response of Patent Owner Regeneron Pharmaceuticals, Inc. dated December 23, 2022.

16. Attached hereto as Exhibit 38 is a true and correct excerpt of A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration CLinical Evaluation of Anti-angiogenesis in the Retina - Intravitreal Trial 3 (CLEAR-IT 3) Protocol VGFT-OD-0605 (RGN-EYLEA-MYLAN-00534406-544).

17. Attached hereto as Exhibit 39 is a true and correct excerpt of the Record of IPR2021-00880 and IPR2021-00881 Oral Hearing held August 10, 2022.

18. Attached hereto as Exhibit 40 is a true and correct copy of Viatris Inc. Form 8-K dated November 28, 2022.

19. Attached hereto as Exhibit 41 is a true and correct copy of a letter from the U.S. Food & Drug Administration to Biocon Biologics Inc. dated March 17, 2023.

I, L. Scott Beall, hereby declare, under penalty of perjury under 28 U.S.C. § 1746 and the laws of the United States of America, that the foregoing Declaration is true and correct.

Dated: May 11, 2023

/s/ *L. Scott Beall*
L. Scott Beall

Exhibit 28

CONFIDENTIAL

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
CLARKSBURG DIVISION

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **JURY TRIAL DEMANDED** **CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

FINAL INFRINGEMENT CONTENTIONS OF PLAINTIFF REGENERON PHARMACEUTICALS, INC. FOR U.S. PATENT NO. 11,084,865

Plaintiff Regeneron Pharmaceuticals, Inc. ("Regeneron") discloses the following final infringement contentions regarding 11,084,865 ("Furfine '865") to Defendant Mylan Pharmaceuticals Inc. ("Mylan"). Regeneron is presently asserting claims 4, 7, 9, 11, and 14-18 from Furfine '865.

Regeneron's infringement contentions are based on the information currently available to, and known by, Regeneron. Regeneron has only received a limited set of documents from Mylan and has not yet received samples. Regeneron has also not yet obtained complete discovery from third parties that may have information relevant to this patent. Regeneron has also not yet obtained deposition testimony from a number of Mylan witnesses who may have knowledge relevant to this patent. Furthermore, the Court has not yet construed any of the asserted claims of this patent. As a result, Regeneron reserves the right to modify, amend, or otherwise supplement these infringement contentions as the pre-trial phase of the litigation proceeds and as additional information comes to light, and as provided in the case Scheduling

Order, the Federal Rules of Civil Procedure, and the Local Rules of the Northern District of West Virginia.

This claim chart is provided without prejudice to Regeneron's right to introduce expert opinions and demonstratives as expert discovery progress, and to produce and introduce at trial all evidence, whenever discovered, related to the proof of currently known and subsequently discovered facts. In addition, the division of each claim into individual limitations below is for convenience only and is without prejudice to Regeneron's right to argue for a different division at a later date.

Date: January 12, 2023

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Infringement Contentions Regarding U.S. Patent No. 11,084,865	
Claim 4	
(1pre) 1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:	To the extent the preamble is limiting, M710 comprises a vial comprising an ophthalmic formulation suitable for intravitreal administration comprising. *See, e.g.*, MYL-AFL-BLA0001414. M710 drug product (DP) is being developed as a biosimilar product to Eylea® (aflibercept) Injection. It is a sterile solution intended for intravitreal administration supplied in a single-use vial.
(1a) a vascular endothelial growth factor (VEGF) antagonist,	M710 comprises a vascular endothelial growth factor (VEGF) antagonist. *See, e.g.*, MYL-AFL-BLA0000055 at 68. Aflibercept-xxxx is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept-xxxx is produced in recombinant Chinese hamster ovary (CHO) cells.
(1b) an organic co-solvent,	M710 comprises an organic-co-solvent (e.g., polysorbate 20). *See, e.g.*, MYL-AFL-BLA0002664.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted] Furthermore, if an organic co-solvent is required to increase the solubility of the VEGF antagonist according to Mylan's claim construction, polysorbate 20 in the M710 formulation increases the solubility of aflibercept in Mylan's formulation. The POSA would have understood that polysorbate 20 functions to prevent aggregation, including the formation of insoluble aggregates, and thus increases the solubility aflibercept in Mylan's formulation. *See* B. Kerwin, *Polysorbates 20 and 80 Used in the Formulation of Protein Biotherapeutics: Structure and Degradation Pathways*, 97 J. Pharm. Sci. 2924, 2929 (2008). *See also, e.g.*, MYL-AFL-BLA0002879 at -905-912. *See also* MYL-AFL0011219 at -236-237, -262.
(1c) a buffer, and	M710 comprises a buffer (e.g., a histidine buffer). *See, e.g.*, MYL-AFL-BLA0002664.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted]
(1d) a stabilizing agent,	M710 comprises a stabilizing agent (e.g., trehalose). *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
(1e) wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and	M710 comprises a VEGF antagonist fusion protein wherein VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4. *See, e.g.*, MYL-AFL-BLA0001769, at -1773. This application is filed for M710 (aflibercept, solution for intravitreal injection) as a proposed biosimilar to the reference drug Eylea® (aflibercept, solution for intravitreal injection, Regeneron Pharmaceutical Inc.) under section 351(k) of the Public Health Service Act. *See also* MYL-AFL-BLA0000055 at 68. Aflibercept-xxxx is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept-xxxx is produced in recombinant Chinese hamster ovary (CHO) cells. *See also* MYL-AFL-BLA0001769 at -786. VEGF binds to both VEGFR-1 (Flt-1) and VEGFR-2 (KDR), thus leading to receptor dimerization and subsequent biological activities involved in angiogenesis and regulation of vascular permeability. Aflibercept consists of the binding domains of both VEGFR-1 and VEGFR-2, acting as a decoy receptor to inhibit VEGF-A binding to the associated receptors. *See also* MYL-AFL-BLA0012213 at -214. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	See also MYL-AFL-BLA0014183 at -187. **2. Introduction** WBP231 is a recombinant fusion protein, produced in CHO cells, consisting of portions of human vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR2 extracellular domains fused to the Fc portion of human IgG1, formulated for intravitreal administration. Its reference product—EYLEA® (Aflibercept) is a dimeric glycoprotein with a total molecular weight of approximately 115kDa and 5 glycosylation sites per monomer (4 sites on the VEGFR domains, and 1 site on the Fc domain). *See also* MYL-AFL-BLA0000320 at -1103. 6.5.5 Sialyation Sialylation of M710 is compared to RPP by analysis of the Site-Specific Glycopeptide method and by total sialic acid content method. Analysis assay readouts by the site specific glycopeptide show the extent of sialylation at each of the five N-glycosylation sites by calculating the mol fraction of glycan species that are sialylated at each of the five N-glycan sites; [redacted] The M710 pilot and GMP % sialylation values at each N-glycan site are shown in Table 48 and are compared to each other as well as to the ranges for both US RP and EU CP. *See also* MYL-AFL-BLA0000320 at -1148.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	
(1f) wherein at least 98% of the VEGF antagonist is present in native conformation	M710 comprises a VEGF antagonist wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography. *See, e.g.*, MYL-AFL-BLA0001462 at -70.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
following storage at 5° C. for two months as measured by size exclusion chromatography.	[redacted] *See also* MYL-AFL-BLA0001444 at -452-461. *See also* MYL-AFL-BLA0003203 at -205.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	3.2.P.5.6.5 PURITY AND IMPURITIES **3.2.P.5.6.5.1 Purity by SEC-HPLC** [redacted] Furthermore, if "native conformation" is construed to require that the VEGF antagonist not exhibit chemical or physical instability according to Mylan's proposed claim construction, then Mylan's M710 product would meet the claim limitation. In addition to size exclusion chromatography, Mylan's BLA includes drug production "parameter[s]" related to the stability attributes relevant under Mylan's claim construction, including, for example, appearance, color, clarity, particulate matter, polyacrylamide gel electrophoresis, charge heterogeneity, bacterial endotoxin, and sterility. MYL-AFL-BLA0001402, at -403-04. *See, e.g.*, MYL-AFL-BLA0001654 at -662. Additionally, the proposed formulation has been demonstrated not to impact product stability and quality under agitation, freeze-thaw and thermal stress conditions as described in M3 (Section 3.2.P.2.2). All the excipients comply with applicable pharmacopeial standards and thus are not considered to pose any impact on patient safety. *See also* MYL-AFL-BLA1080068, at -077. Conclusion: The degradation pathway of M710 was overall similar with Eylea® sourced from EU and US when compared under various stress conditions namely-temperature, pH, oxidative chemical and photo exposure stress. Major degradation pathway for both M710 and RPP was observed to be upon thermal exposure and photo-exposure. During thermal exposure, both M710 and RPP loose the monomer content impacting the potency of the molecules. Thermal degradation was observed to be faster for RPP compared to M710. During the photo-exposure, increase in methionine oxidation level is observed which leads to changes in charge profile (Group 1 in cIEF). However, this change in oxidation does not impact the functionality (i.e., potency of the molecule), but it does

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	impact the FcRn binding of the molecule. This observation is consistent with the forced oxidation study data where forceful oxidation of the molecule results in changes in charge profile and FcRn binding without affecting the potency of the molecule. Higher rate of oxidation was observed for M710 under photo-exposure condition compared to RPP. Overall, the degradation pathways were observed to be similar between M710 and RPP with minor differences in rate of degradation between M710 and RPP for thermal exposure and photo-exposure conditions. Additionally, the degradation pathways were also observed to be comparable between M710 lots manufactured using the pilot scale DS and commercial scale DS lots. *See also* MYL-AFL-BLA0002879 at -914-920. The M710 DP formulation is stable under the agitation and freeze-thaw conditions. *See also* MYL-AFL-BLA0003319 at -323-329. *See also* MYL-AFL0011219 at -261-262.
2. The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.	*See supra* claim 1. M710 comprises a vial wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate. *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted]
4. The vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.	*See supra* claim 2. M710 comprises a vial wherein said organic co-solvent comprises [redacted] *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted]
Claim 7	
5. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.	*See supra* claim 2. M710 comprises a vial wherein said organic co-solvent comprises [redacted] *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
7. The vial of claim 5, wherein said buffer comprises 5-25 mM buffer.	*See supra* claim 5. M710 comprises a vial wherein said buffer comprises 5-25 mM buffer. *See, e.g.*, MYL-AFL-BLA0002664. [redacted]
Claim 9	
9. The vial of claim 5, wherein said buffer comprises a pH about 6.2-6.3.	*See supra* claim 5. M710 comprises a glass vial wherein said buffer comprises a pH about 6.2-6.3. *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted]
Claim 11	
10. The vial of claim 5, wherein said stabilizing agent comprises a sugar.	*See supra* claim 5. M710 comprises a vial wherein said stabilizing agent comprises a sugar (e.g., [redacted]). See, e.g., MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted]
11. The vial of claim 10, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	*See supra* claim 10. M710 comprises a vial wherein said stabilizing agent comprises a sugar selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol (e.g., [redacted]). *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted]
Claim 14	
14. The vial of claim 5, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.	*See supra* claim 5. M710 comprises a vial wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4. *See, e.g.*, MYL-AFL-BLA0001769 at -773. This application is filed for M710 (aflibercept, solution for intravitreal injection) as a proposed biosimilar to the reference drug Eylea® (aflibercept, solution for intravitreal injection, Regeneron Pharmaceutical Inc.) under section 351(k) of the Public Health Service Act. *See also* MYL-AFL-BLA0000055 at 68. Aflibercept-xxxx is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept-xxxx is produced in recombinant Chinese hamster ovary (CHO) cells. *See, e.g.*, MYL-AFL-BLA0012213 at -214.

Infringement Contentions Regarding U.S. Patent No. 11,084,865

[redacted]

See also MYL-AFL-BLA0014183 at -187.

2. Introduction

WBP231 is a recombinant fusion protein, produced in CHO cells, consisting of portions of human vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR2 extracellular domains fused to the Fc portion of human IgG1, formulated for intravitreal administration. Its reference product—EYLEA® (Aflibercept) is a dimeric glycoprotein with a total molecular weight of approximately 115kDa and 5 glycosylation sites per monomer (4 sites on the VEGFR domains, and 1 site on the Fc domain).

See also MYL-AFL-BLA0000320 at -1103.

6.5.5 Sialyation

Sialylation of M710 is compared to RPP by analysis of the Site-Specific Glycopeptide method and by total sialic acid content method. Analysis assay readouts by the site specific glycopeptide show the extent of sialylation at each of the five N-glycosylation sites by calculating the mol fraction of glycan species that are sialylated at each of the five N-glycan sites; [redacted] The M710 pilot and GMP % sialylation values at each N-glycan site are shown in Table 48 and are compared to each other as well as to the ranges for both US RP and EU CP.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	See also MYL-AFL-BLA0000320 at -1148. 
Claim 15	
15. The vial of claim 5, wherein	*See supra* claim 5. M710 comprises a vial wherein the formulation is capable of providing a turbidity of 0.01 or lower at OD405 after 2 month storage at 5° C.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
said formulation is capable of providing a turbidity of 0.01 or lower at OD405 after 2 month storage at 5° C.	*See, e.g.*, MYL-AFL-BLA0001462 at -70.  *See also* MYL-AFL-BLA0001444 at -452-461. *See also* MYL-AFL-BLA0003203 at -204.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	[redacted] *See also* MYL-AFL0011219 at -253. [redacted]
Claim 16	

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
16. The vial of claim 5, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.	*See supra* claim 5. M710 comprises a vial wherein at least 99% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography. *See, e.g.*, MYL-AFL-BLA0001444 at -456.  *See also* MYL-AFL-BLA0003203 at -205.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	3.2.P.5.6.5 PURITY AND IMPURITIES **3.2.P.5.6.5.1 Purity by SEC-HPLC** [redacted]
Claim 17	
17. The vial of claim 5, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.	*See supra* claim 5. M710 comprises a vial wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography. *See, e.g.*, MYL-AFL-BLA0003269 at -283. [redacted] *See also* MYL-AFL-BLA0003203 at -205.

Infringement Contentions Regarding U.S. Patent No. 11,084,865	
	3.2.P.5.6.5 PURITY AND IMPURITIES **3.2.P.5.6.5.1 Purity by SEC-HPLC** [redacted]
Claim 18	
18. The vial of claim 5, wherein said formulation does not contain phosphate.	*See supra* claim 5. M710 comprises a glass vial wherein the formulation does not contain phosphate. *See, e.g.*, MYL-AFL-BLA0002664. [redacted]

Claims 26-50 recite a pre-filled syringe. Regeneron does not contend that these claims would be infringed by making, using, offering to sell, selling or importing into the United States the particular product that is made according to the labeling, processes, and specifications of the version of Mylan's BLA No. 761274 that Mylan has produced. It is readily apparent, however, that Mylan intends to amend its application, and that the contemplated amendments, modifications, or supplements to Mylan's BLA No. 761274 may result in infringement of those claims, and Regeneron reserves all rights to assert these claims should Mylan amend its application.

Exhibit 29

OUTSIDE ATTORNEY'S EYES ONLY

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

CLARKSBURG DIVISION

REGENERON PHARMACEUTICALS, INC.,	)	
	)	Case No.
Plaintiff,	)	1:22-cv-00061-TSK
v.	)	
MYLAN PHARMACEUTICALS INC.,	)	
Defendant.	)	

HIGHLY CONFIDENTIAL - OUTSIDE ATTORNEYS' EYES ONLY

The videotaped deposition of GREGORY MacMICHAEL, Ph.D., called by the Plaintiff for examination, reported stenographically by Cynthia J. Conforti, License No. 084-003064, at Suite 500, 6 West Hubbard Street, Chicago, Illinois, commencing at the hour of 9:05 a.m. on the 12th day of April, 2023.

DIGITAL EVIDENCE GROUP
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Washington, D.C. 20036
(202) 232-0646

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ALSO PRESENT:

Joseph Salinas, Videographer
Beth Finkelstein, In-house counsel,
Viatris Mylan (Via Zoom)

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MacMICHAEL DEPOSITION EXHIBITS

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[redacted]		
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DEPOSITION EXHIBITS (Continued)

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[redacted]		

(MacMichael Exhibit 1, Exhibit 2, Exhibit 3, Exhibit 4, Exhibit 5 marked for identification.)

THE VIDEOGRAPHER: This is File No. 1 of the videotaped deposition of Gregory MacMichael in the matter of Regeneron Pharma v Mylan Pharma in the United States District Court for the Northern District of West Virginia, Clarksburg Division, Case No. 1:22-cv-00061-TSK.

This deposition is being held at 6 West Hubbard, Chicago, Illinois, 60654, on April 12, 2023. The time on the video screen is now 9:05 a.m.

My name is Joseph Salinas. I am the legal videographer from Digital Evidence Group. The court reporter is Cynthia Conforti, also in association with Digital Evidence Group.

For the record, will counsel please introduce themselves and state whom they represent.

MR. BERL: David Berl, Williams & Connolly for Regeneron. With me are my colleagues Arthur

Argall and Andrew Trask, also with Williams & Connolly.

MR. SALMEN: Heinz Salmen of Rakoczy Molino Mazzochi Siwik LLP, on behalf of defendant Mylan. Here with me is my colleague Scott Beall, also of Rakoczy.

We have attorneys on the Zoom that should identify themselves.

MR. COPLAND: Good morning. This is Gordon Copland of Steptoe & Johnson. I'm local counsel for Mylan.

MR. POGUE: This is David Pogue of Carey Douglas Kessler & Ruby, local counsel for Regeneron.

MS. FINKELSTEIN: This is Beth Finkelstein. I'm in-house counsel for Viatris Mylan.

THE VIDEOGRAPHER: Will the court reporter please swear in the witness.

(Witness sworn.)

GREGORY MACMICHAEL,

having been duly sworn, was examined and testified

as follows:

EXAMINATION

BY MR. BERL:

Q Good morning, Dr. MacMichael.

Is there any reason you can't testify truthfully today?

A I always testify truthfully.

Q Okay. You have in front of you five exhibits that we have marked 1, 2, 3, 4 and 5.

The first exhibit is your opening invalidity expert report under Regeneron's construction, right?

A Yes.

Q The second is your opening invalidity report under Mylan's construction, right?

A Yes.

Q The third is your reply expert report on invalidity, right?

A Yes.

Q The fourth is the '865 patent that you've prepared reports about, correct?

A Correct.

correct?

A Yes.

Q And so you understood that in connection with your work on this case, you could have asked for experiments to be conducted to substantiate any opinion you wanted to provide, right?

A I didn't ask Mylan for data.

Q But you understood that you could have asked for experiments to be conducted, correct?

A I didn't ask.

Q I know you didn't ask --

A I thought we were going from the static body of evidence, not -- I didn't realize we could continue to -- I didn't -- I didn't ask the RMMS attorneys if I could get additional studies done.

If that's your question, I did not ask these gentlemen if I could have additional work done.

Q Okay. Either in support of your enablement opinions or written description opinions or indefiniteness opinions, right?

MR. SALMEN: Objection, form.

THE WITNESS: Well, I didn't ask them. So it would cover...

BY MR. BERL:

[redacted]

[redacted]

Q Is it your opinion that -- we talked about a few moments ago developing a reliable SEC method. Is it your opinion that it is undue experimentation to develop a reliable SEC method?

MR. SALMEN: Objection, form.

BY MR. BERL:

Q Is it undue experimentation --

MR. SALMEN: Objection, form.

BY MR. BERL:

Q -- to develop a reliable SEC method to measure percent native conformation of aflibercept?

MR. SALMEN: Objection, form.

THE WITNESS: Depends on the maturity of the company. Most companies already have HPL -- have size exclusion HPLC capability if they're in a biotech environment. And, therefore, they would

have to -- one to two assay aflibercept, they would have to do everything we discussed about 30 minutes ago, which is qualify the assay, understand the parameters, et cetera.

You're going to have to run that -- then generate the standard operating procedure for how to run that assay for aflibercept.

But most -- most, if not all, biotech companies that are working in proteins are going to have that capability or they're going to have an external testing company that can do that work for them.

BY MR. BERL:

Q So it wouldn't be undue experimentation to do that if you're at a biotech company?

MR. SALMEN: Objection, form, foundation, incomplete hypothetical.

THE WITNESS: I don't want to give my personal opinion on the term "undue," but you're going to have to qualify and ultimately validate that assay specifically for analyzing for aflibercept and be able to demonstrate that you're

CERTIFICATE OF COURT REPORTER - NOTARY PUBLIC

I, Cynthia J. Conforti, License No. 084-003064, CSR, CRR, and a Notary Public in and for the County of Cook, State of Illinois, the officer before whom the foregoing deposition was taken, do hereby certify that the foregoing transcript is a true and correct record of the testimony given; that said testimony was taken by me stenographically and thereafter reduced to typewriting under my direction; that reading and signing was requested; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 17th day of April, 2023. My commission expires: October 30, 2023

_____

Notary Public in and for the
State of Illinois

Gregory MacMichael, Ph.D., c/o
RAKOCZY MOLINO MAZZOCHI SIWIK
6 West Hubbard Street
Chicago, Illinois 60654

Case:Regeneron Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc.
Date of deposition: April 12, 2023
Deponent: Gregory MacMichael, Ph.D.

Please be advised that the transcript in the above referenced matter is now complete and ready for signature. The deponent may come to this office to sign the transcript, a copy may be purchased for the witness to review and sign, or the deponent and/or counsel may waive the option of signing. Please advise us of the option selected. Please forward the errata sheet and the original signed signature page to counsel noticing the deposition, noting the applicable time period allowed for such by the governing Rules of Procedure. If you have any questions, please do not hesitate to call our office at (202)-232-0646.

Sincerely,
Digital Evidence Group

Digital Evidence Group, L.L.C.
1730 M Street, NW, Suite 812
Washington, D.C. 20036
(202) 232-0646

SIGNATURE PAGE

Case:Regeneron Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc.
Witness Name: Gregory MacMichael, Ph.D.
Deposition Date: April 12, 2023

I do hereby acknowledge that I have read and examined the foregoing pages of the transcript of my deposition and that:

(Check appropriate box):
( ) The same is a true, correct and complete transcription of the answers given by me to the questions therein recorded.
( ) Except for the changes noted in the attached Errata Sheet, the same is a true, correct and complete transcription of the answers given by me to the questions therein recorded.

_____ _____
DATE WITNESS SIGNATURE

_____ _____
DATE NOTARY

Digital Evidence Group, LLC

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Washington, D.C. 20036

(202)232-0646

ERRATA SHEET

Case:Regeneron Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc.

Witness Name: Gregory MacMichael, Ph.D.

Deposition Date: April 12, 2023

Page No.	Line No.	Change

_____ _____

Signature Date

Exhibit 30

OUTSIDE ATTORNEY'S EYES ONLY

Exhibit 31

CONFIDENTIAL

EXHIBIT 31
[DKT. 466-5]

REDACTED IN FULL

Exhibit 32

CONFIDENTIAL

EXHIBIT 32
[DKT. 466-6]

REDACTED IN FULL

Exhibit 33

CONFIDENTIAL

EXHIBIT 33
[DKT. 466-7]

REDACTED IN FULL

Exhibit 34

Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sandra Benton, 301-796-1042, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Guidance for Industry

Additional copies are available from:

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and/or

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Email: ocod@fda.hhs.gov
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Biosimilars

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Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the Agency's recommendations on the design and evaluation of comparative analytical studies intended to support a demonstration that a proposed therapeutic protein product is biosimilar to a reference product licensed under section 351(a) of the Public Health Service Act (PHS Act). Additionally, this guidance is intended to provide recommendations to sponsors on the scientific and technical information for the chemistry, manufacturing, and controls (CMC) portion of a marketing application for a proposed product submitted under section 351(k) of the PHS Act.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (ACA) (Public Law 111-148). Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and provides an overview of recommendations for the comparative analytical assessment and other important scientific considerations to support a demonstration of biosimilarity between a proposed therapeutic

[1] This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

protein product (referred to as a *proposed biosimilar*[2] or *proposed biosimilar product*) and the reference product. [3]

This guidance is one in a series of guidances that FDA is developing to facilitate implementation of the BPCI Act.

Relevant final guidance documents[4] issued to date address a broad range of issues, including:

- *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015)
- *Questions and Answers on Biosimilar Development and the BPCI Act* (December 2018)
- *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016)
- *Labeling for Biosimilar Products* (July 2018)
- *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019)

In addition, FDA has published draft guidance documents related to the BPCI Act, which, when finalized, will represent FDA's current thinking. These draft guidance documents include:

- *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018)
- *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* (August 2014)
- *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (December 2018)

[2] In this guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) "biosimilar" or "biosimilar product" refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) "interchangeable biosimilar" or "interchangeable product" refers to a biosimilar product that FDA has determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act).

[3] A 351(k) application for a proposed biosimilar product must include information demonstrating biosimilarity based on data derived from, among other things, "analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components." Section 351(k)(2)(A)(i)(I)(aa) of the PHS Act.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

When applicable, references to information in these final and draft guidances are included in this guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the 1980s, FDA began to receive marketing applications for biotechnology-derived protein products, mostly for recombinant DNA-derived versions of naturally sourced products. Consequently, FDA established a regulatory approach for the approval of recombinant DNA-derived protein products, which was announced in the *Federal Register* (51 FR 23302, June 26, 1986), in conjunction with a 1985 document titled *Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology*.[5] This approach addresses the submission of an investigational new drug application (IND) to FDA for evaluation before initiation of clinical investigations in human subjects and submission and potential approval of a new drug application (NDA) or biologics license application (BLA) before marketing products made with recombinant DNA technology, even if the active ingredient in the product is thought to be identical to a naturally occurring substance or a previously approved product. The policy set forth in those documents was developed in part because of the challenges in evaluating protein products solely by physicochemical and functional testing and because the biological system in which such a protein product is produced can have a significant effect on the structure and function of the product itself.

Improvements in manufacturing processes, process controls, materials, and product testing, as well as characterization tests and studies, have led to a gradual evolution in the regulation of protein products. For example, in 1996, FDA provided recommendations in the *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products*, which explains how a sponsor may demonstrate, through a combination of analytical testing, functional assays (in vitro and/or in vivo), assessment of pharmacokinetics (PK) and/or pharmacodynamics (PD) and toxicity in animals, and clinical testing (clinical pharmacology, safety, and/or efficacy), that a manufacturing change does not adversely affect the safety, identity, purity, or potency of its FDA-approved product.

[5] For more information, this document is available on FDA's Other Recommendations for Biologics Manufacturers web page at https://www fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/other-recommendations-biologics-manufacturers.

Since 1996, FDA has approved many manufacturing process changes for licensed biological products based on a demonstration of product comparability before and after the process change, as supported by quality criteria and analytical testing and without the need for additional nonclinical data and clinical safety and/or efficacy studies. In some cases, uncertainty about the effect of the change and/or the results of the biochemical/functional comparability studies has necessitated collection and assessment of additional data, including nonclinical and/or clinical testing, to demonstrate product comparability. These concepts were further developed in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and resulted in the ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005).

Although the scope of ICH Q5E is limited to an assessment of the comparability of a biological product before and after a manufacturing process change made by the same manufacturer, certain general scientific principles described in ICH Q5E are applicable to an assessment of biosimilarity between a proposed product and its reference product. However, demonstrating that a proposed product is biosimilar to an FDA-licensed reference product manufactured by a different manufacturer typically will be more complex and will likely require more extensive and comprehensive data than assessing the comparability of a product before and after a manufacturing process change made by the product's sponsor. A manufacturer that modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. By contrast, the manufacturer of a proposed biosimilar will have no direct knowledge of the manufacturing process for the reference product and will have its own manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, acceptance criteria).

Therefore, comprehensive comparative analytical data are necessary to build the foundation for a development program for a proposed biosimilar product intended for submission under section 351(k) of the PHS Act.

The BPCI Act

The BPCI Act, enacted as part of the (ACA) on March 23, 2010, amends the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the ACA). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product or a proposed interchangeable product. An application submitted under section 351(k)

must contain, among other things, information demonstrating that "the biological product is biosimilar to a reference product" based upon data derived from:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and
- A clinical study or studies (including the assessment of immunogenicity and PK or PD) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.[6]

FDA has the discretion to determine that an element above is unnecessary in a 351(k) application.[7]

The term *biosimilar* or *biosimilarity* is defined in the PHS Act "in reference to a biological product that is the subject of an application under [section 351(k)]" to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (section 351(i)(2) of the PHS Act). The term *reference product* is defined in the PHS Act as the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act).

Section 351(k)(4) of the PHS Act provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or a supplement to such application) is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient"[8] and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[9]

The term *interchangeable* or *interchangeability* is defined in the PHS Act, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS

[6] Section 351(k)(2)(A)(i)(I) of the PHS Act.

[7] Section 351(k)(2)(A)(ii) of the PHS Act.

[8] Section 351(k)(4)(A) of the PHS Act.

[9] Section 351(k)(4)(B) of the PHS Act.

Act, to mean that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product" (section 351(i)(3) of the PHS Act).

III. SCOPE

This document provides guidance on the use of comparative analytical studies that are relevant to assessing whether the proposed product is biosimilar to a reference product for purposes of submission of a marketing application under section 351(k) of the PHS Act. This document is not intended to provide an overview of FDA's approach to determining interchangeability, which is addressed in a separate guidance document.[10] Although this guidance applies specifically to therapeutic protein products, the general scientific principles may be informative for the development of proposed biosimilars to other protein products, such as in vivo protein diagnostic products. If the reference product cannot be adequately characterized for the purpose of demonstrating that a proposed product is biosimilar to the reference product as recommended in this guidance, the application may not be appropriate for submission under section 351(k) of the PHS Act.

This guidance also describes considerations for CMC information that is relevant to assessing whether the proposed product is biosimilar to the reference product. It is critical that all product applications contain a complete and thorough CMC section that provides the necessary and appropriate information (e.g., characterization, adventitious agent safety, process controls, and specifications) to support that the manufacturing process consistently delivers a product with the intended quality characteristics. This guidance should be used as a companion to other guidances available from FDA that describe the CMC information appropriate for evaluation of protein products.[11] We encourage early interaction with FDA to discuss specific CMC issues that may arise for a sponsor's proposed product.

IV. GENERAL PRINCIPLES

Advances in analytical sciences (both physicochemical and biological) enable some protein products to be characterized extensively in terms of their physicochemical and biological properties. These analytical procedures have improved the ability to identify and characterize

[10] See FDA's guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product* (May 2019).

[11] For CMC requirements for submission of a marketing application, sponsors should consult current regulations and see the guidance for industry *Submission on Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In-vivo Use* (August 1996), as well as other applicable FDA guidance documents.

not only the desired product but also product-related substances and product- and process-related impurities.[12] Advances in manufacturing science and production methods may enhance the likelihood that a proposed product can be demonstrated to be highly similar to a reference product by better targeting the reference product's physiochemical and functional properties. In addition, advances in analytical sciences may enable detection and characterization of differences between the protein products. These differences should be further assessed to understand the impact on the biosimilar product clinical performance relative to the reference product.

Despite improvements in analytical techniques, current analytical methodology may not be able to detect or characterize all relevant structural and functional differences between the two protein products. A thorough understanding of each analytical method's limitations will be critical to a sponsor's successful identification of residual uncertainties and, in turn, to the design of subsequent testing. In addition, there may be incomplete understanding of the relationship between a product's structural attributes and its clinical performance. FDA encourages the use of available state-of-the-art technology. Sponsors should use appropriate analytical methodologies that have adequate sensitivity and specificity to detect and characterize differences between the proposed product and the reference product.

As part of a complete CMC data submission, an application submitted under section 351(k) of the PHS Act is required to include analytical studies that demonstrate that the biological product is highly similar to the reference product.[13] The rationale for the approach to the comparative analytical assessment should be clearly described, with consideration of the characteristics, known mechanism of action(s), and function of the reference product.

Comparative analytical data provide the foundation for the development of a proposed product for submission in an application under section 351(k) of the PHS Act and can influence decisions about the type and amount of animal and clinical data needed to support a demonstration of biosimilarity. Such analytical data should be available early in product development and will permit more detailed discussion with the Agency because known quality attributes can be used to shape biosimilar development and justify certain development decisions. Thus, in addition to the preliminary comparative analytical data that should be submitted to support an initial advisory meeting,[14] FDA encourages sponsors to submit comprehensive comparative analytical data early

[12] The use of the terms *product-related substances* and *product- and process-related impurities* is consistent with their use and meaning in the ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

[13] See section 351(k)(2)(A)(i)(I)(aa) of the PHS Act.

[14] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018), which provides recommendations to industry on all formal meetings between the FDA and sponsors or applicants for proposed biosimilar products or proposed interchangeable products intended to be submitted under 351(k) of the PHS Act. When final, this guidance will represent FDA's current thinking on this topic.

in the development process: at the pre-IND stage; with the original IND submission; or with the submission of data from the initial clinical studies, such as PK and PD studies. FDA will best be able to provide meaningful input on the extent and scope of animal and additional clinical studies for a proposed biosimilar development program once the Agency has considered the comparative analytical data.

Comprehensive, robust comparative physicochemical and functional studies (these may include biological assays, binding assays, and enzyme kinetics) should be performed to evaluate the proposed product and the reference product. A meaningful comparative analytical assessment depends on, among other things, the capabilities of available state-of-the-art analytical assays to assess, for example, the molecular weight of the protein, complexity of the protein (higher order structure and posttranslational modifications), degree of heterogeneity, functional properties, impurity profiles, and degradation profiles denoting stability. The capability of the methods used in these analytical assessments, as well as their limitations, should be described by the sponsor. Physicochemical and functional characterization studies should be sufficient to establish relevant quality attributes, including those that define a product's identity, quantity, safety, purity, and potency. The product-related impurities and product-related substances should be identified, characterized as appropriate, quantified, and compared using multiple lots of the proposed product and multiple lots of the reference product, to the extent feasible and relevant, as part of an assessment of the potential impact on the safety, purity, and potency of the product.

Because therapeutic proteins are made in living systems, there may be heterogeneity in certain quality attributes of these products. Heterogeneity in therapeutic proteins may arise in a number of ways and may affect the expected clinical performance of a protein product. Replication errors in the DNA encoding the protein sequence and amino acid misincorporation may occur during translation, although the level of these errors is typically low. In addition, most protein products undergo posttranslational modifications that can alter the functions of the protein by attaching other biochemical groups such as phosphate and various lipids and carbohydrates; by proteolytic cleavage following translation; by changing the chemical nature of an amino acid (e.g., formylation); or by many other mechanisms. Such modifications can result from intracellular activities during cell culture or by deliberate modification of the protein (e.g., PEGylation). Other posttranslational modifications can be a consequence of manufacturing process operations; for example, glycation may occur with exposure of the product to reducing sugars. Also, certain storage conditions may be more or less permissive for certain degradation pathways such as oxidation, deamidation, or aggregation. All of these product-related variants may alter the biological properties of the expressed recombinant protein. Therefore, identification and determination of the relative levels of these variants should be included in the comparative analytical characterization studies.

The three-dimensional conformation of a protein is an important factor in its biological function. Proteins generally exhibit complex three-dimensional conformations (tertiary structure and, in some cases, quaternary structure) because of their large size and the rotational characteristics of protein alpha carbons, among other things. The resulting flexibility enables dynamic, but subtle, changes in protein conformation over time, some of which may be required for functional

activity. These rotations are often dependent on low-energy interactions, such as hydrogen bonds and van der Waals forces, which may be very sensitive to environmental conditions. Current analytical technology is capable of evaluating the three-dimensional structure of many proteins. Using multiple, relevant, state-of-the-art methods can help define tertiary protein structure and, to varying extent, quaternary structure, and can add to the body of information supporting biosimilarity. At the same time, a protein's three-dimensional conformation can often be difficult to define precisely using current physicochemical analytical technology. Any differences in higher order structure between a proposed product and a reference product should be evaluated in terms of a potential effect on protein function and stability. Thus, functional assays are also critical tools for evaluating the integrity of the higher order structures.

A scientifically sound characterization that provides a comprehensive understanding of the chemical, physical, and biological characteristics of the proposed product is essential to the design of the manufacturing process and to the conduct of development studies for all biological products. The body of knowledge that emerges will serve to support a demonstration of product quality and the effectiveness of a suitable control system during development, and support approval of the product.

Proposed biosimilar product, manufacturers should perform in-depth chemical, physical, and bioactivity comparisons with side-by-side analyses of an appropriate number of lots of the proposed product and the reference product and, where available and appropriate, a comparison with a reference standard for suitable attributes (e.g., potency). For a discussion of reference standards, see section V.G of this guidance. Evaluation of multiple lots of a reference product and multiple lots of a proposed product enables estimation of product variability across lots. The number of lots needed to understand the lot-to-lot variability of both the reference and proposed products may differ on a case-by-case basis and should be scientifically justified by the sponsor.

FDA encourages sponsors to consult with the Agency to ensure that an appropriate number of lots are evaluated. Identification of specific lots of a reference product used in comparative analytical studies, together with expiration dates and time frames and when the lots were analyzed and used in other types of studies (nonclinical or clinical studies), should be provided. This information will be useful in justifying acceptance criteria to ensure product consistency, as well as to support the comparative analytical assessment of the proposed product and the reference product. However, acceptance criteria should be based on the totality of the analytical data and not simply on the observed range of product attributes of the reference product. This is because some product attributes act in combination to affect a product's safety, purity, and potency profile; therefore, their potential interaction should be considered when conducting the comparative analytical assessment and setting specifications. For example, for some glycoproteins, the content and distribution of tetra-antennary and N-acetyllactosamine repeats can affect in vivo potency and should not be evaluated independently of each other.

Additionally, data obtained for lots used in nonclinical and clinical studies and relevant information on the relationship between an attribute and the performance of the drug product (see ICH Q8(R2))[15] can also be used to help establish acceptance criteria.

An extensive analytical characterization may reveal differences between the reference product and the proposed product, especially when using analytical techniques capable of discriminating qualitative or quantitative differences in product attributes. Emphasis should be placed on developing orthogonal quantitative methods to definitively identify any differences in product attributes. Based on the results of analytical studies assessing functional and physicochemical characteristics, including, for example, higher order structure, posttranslational modifications, and impurity and degradation profiles, the sponsor may have an appropriate scientific basis for a selective and targeted approach to subsequent animal and/or clinical studies to support a demonstration of biosimilarity. It may be useful to compare differences in the quality attributes of the proposed product with those of the reference product using a meaningful fingerprint-like analysis algorithm[16] that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods. Enhanced approaches in manufacturing science, as discussed in ICH Q8(R2), may facilitate production processes that can better match a reference product's fingerprint.[17] Such a strategy could further quantify the overall similarity between two molecules and may lead to additional bases for a more selective and targeted approach to subsequent animal and/or clinical studies.

The type, nature, and extent of any differences between the proposed product and the reference product, introduced by design or observed from comprehensive analytical characterization of multiple manufacturing lots, should be clearly described and discussed. The discussion should include identification and comparison of relevant quality attributes from product characterization. The potential clinical effects of observed structural and functional differences between the two products should be assessed and supported by animal or clinical studies, if necessary.

V. FACTORS FOR CONSIDERATION IN PERFORMING THE COMPARATIVE ANALYTICAL ASSESSMENT

When performing the comparative analytical assessment to support a demonstration of biosimilarity, manufacturers should consider a number of factors, including the following:

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[15] See the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

[16] For more information on fingerprint-like analysis, refer to Kozlowski S, J Woodcock, K Midthun, RB Sherman, 2011, Developing the Nation's Biosimilars Program, N Engl J Med; 365:385-388.

[17] See the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009), *Q9 Quality Risk Management* (June 2006), *Q10 Pharmaceutical Quality System* (April 2009), and *Q11 Development and Manufacture of Drug Substances* (November 2012) for guidance on enhanced approaches in manufacturing science.

A. Expression System

Therapeutic protein products can be produced in microbial cells (prokaryotic or eukaryotic), cell lines (e.g., mammalian, avian, insect, plant), or tissues derived from animals or plants. It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N- or C-terminal truncations (e.g., the heterogeneity of C-terminal lysine of a monoclonal antibody) that are not expected to change the product performance, may be justified and should be explained by the sponsor. Possible differences between the chosen expression system (i.e., host cell and the expression construct) of the proposed product and that of the reference product should be carefully considered because the type of expression system will affect the types of process- and product-related substances, impurities, and contaminants (including potential adventitious agents) that may be present in the protein product. For example, the expression system can have a significant effect on the types and extent of translational and posttranslational modifications that are imparted to the proposed product, which may introduce additional uncertainty into the demonstration that the proposed product is biosimilar to the reference product.

Minimizing differences between the proposed product and reference product expression systems to the extent possible can enhance the likelihood of producing a biosimilar protein product. Use of different expression systems will be evaluated on a case-by-case basis.

B. Manufacturing Process

A comprehensive understanding of all steps in the manufacturing process for the proposed product should be established during product development. As a scientific matter, characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed product and manufacturing process. The use of enhanced approaches[18] to pharmaceutical development, along with quality risk management and effective quality systems, will facilitate the consistent manufacturing of a high-quality product. As a scientific matter, as with biological products originally licensed under section 351(a) of the PHS Act, an application for a biological product submitted for licensure under section 351(k) of the PHS Act may not incorporate by reference drug substance, drug substance intermediate, or drug product information contained in a Master File (MF) because a license holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license.[19] Other types of contract

[18] See the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009), *Q9 Quality Risk Management* (June 2006), *Q10 Pharmaceutical Quality System* (April 2009), and *Q11 Development and Manufacture of Drug Substances* (November 2012) for guidance on enhanced approaches in manufacturing science.

[19] A MF for drug substance, drug substance intermediate, or drug product information for a biological product may be referenced to support an investigational new drug application (IND) for a proposed biosimilar product. Assurance of product quality should be provided on each lot of material produced by the MF holder. Procedures

manufacturing arrangements can be considered if the sponsor does not intend to manufacture the product for licensure.[20]

A sponsor considering manufacturing changes after completing the initial comparative analytical assessment or after completing clinical studies intended to support a 351(k) application will need to demonstrate comparability between the pre- and post-change proposed product and may need to conduct additional studies. The nature and extent of the changes may determine the extent of these additional studies. The comparative analytical studies should include a sufficient number of lots of the proposed biosimilar product used in clinical studies as well as from the proposed commercial process if the process used to produce the material used in the clinical studies is different.

C. Physicochemical Properties

Physicochemical assessment of the proposed product and the reference product should consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structure; posttranslational modifications; and functional activity(ies)). The objective of this assessment is to maximize the potential for detecting differences in quality attributes between the proposed product and the reference product.

The sponsor should address the concept of the desired product (and its variants) as discussed in ICH Q6B[21] when designing and conducting the characterization studies. Thus, it will be important to understand the heterogeneity of the proposed product and the reference product (e.g., the nature, location, and levels of glycosylation) and the ranges of variability of different isoforms, including those that result from posttranslational modifications.

Particular analytical methodologies can be used to assess specific physicochemical characteristics of proteins. These methodologies are described in published documents, including scientific literature, regulatory guidelines, and pharmacopeial compendia. Some techniques provide information on multiple characteristics. It is expected that appropriate analytical test methods will be selected based on the nature of the protein being characterized and knowledge regarding the structure and heterogeneity of the reference product and the proposed product, as well as characteristics critical to product performance.

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should also be in place to ensure that the IND sponsor is notified by the MF holder of significant changes to the MF potentially affecting product quality. The sponsor is expected to provide notification to the Agency of any relevant change in the IND in order to initiate a reevaluation of the MF.

[20] See the guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics* (November 2008).

[21] See the ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

To address the full range of physicochemical properties or biological activities adequately, it is often necessary to apply more than one analytical procedure to evaluate the same quality attribute. Methods that use different physicochemical or biological principles to assess the same attribute are especially valuable because they provide independent data to support the quality of that attribute (e.g., orthogonal methods to assess aggregation). In addition, the use of complementary analytical techniques in series, such as peptide mapping or capillary electrophoresis combined with mass spectrometry of the separated molecules, should provide a meaningful and sensitive method for comparing products.

Unlike routine quality control assays, tests used to characterize the product do not necessarily need to be validated; however, the tests used to characterize the product should be scientifically sound, fit for their intended use, and provide results that are reproducible and reliable. In selecting these tests, it is important to consider the characteristics of the protein product, including known and potential impurities. Information regarding the ability of a method to discern relevant differences between a proposed product and a reference product should be submitted as part of the comparison. The methods should be demonstrated to be of appropriate sensitivity and specificity to provide meaningful information as to whether the proposed product and the reference product are highly similar.

D. Functional Activities

Functional assays serve multiple purposes in the characterization of protein products. These tests act to complement physicochemical analyses and are a quantitative measure of the function of the protein product.

Depending on the structural complexity of the protein and available analytical technology, the physicochemical analysis may be unable to confirm the integrity of the higher order structures. Instead, the integrity of such structures can usually be inferred from the product's biological activity. If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, the functional assays should reflect such mechanism(s) of action to the extent possible. Multiple functional assays should, in general, be performed as part of the comparative analytical assessments. The assessment of functional activity is also useful in providing an estimate of the specific activity of a product as an indicator of manufacturing process consistency, as well as product purity, potency, and stability.

If a reference product exhibits multiple functional activities, sponsors should perform a set of appropriate assays designed to evaluate the range of relevant activities for that product. For example, with proteins that possess multiple functional domains expressing enzymatic and receptor-mediated activities, sponsors should evaluate both activities to the extent that these activities are relevant to product performance. For products where functional activity can be measured by more than one parameter (e.g., enzyme kinetics or interactions with blood clotting factors), the comparative characterization of each parameter between products should be assessed.

The sponsor should recognize the potential limitations of some types of functional assays, such as high variability, that might preclude detection of small but significant differences between the proposed product and the reference product. Because a highly variable assay may not provide a meaningful assessment as to whether the proposed product is highly similar to the reference product, sponsors are encouraged to develop assays that are less variable and are sensitive to changes in the functional activities of the product. In addition, in vitro bioactivity assays may not fully reflect the clinical activity of the protein. For example, these assays generally do not predict the bioavailability (PK and biodistribution) of the product, which can affect PD and clinical performance. Also, bioavailability can be dramatically altered by subtle differences in glycoform distribution or other posttranslational modifications. Thus, these limitations should be taken into account when assessing the robustness of the quality of data supporting biosimilarity and the need for additional information that may address residual uncertainties. Finally, functional assays are important in assessing the occurrence of neutralizing antibodies in nonclinical and clinical studies.

E. Target Binding

When binding is part of the activity attributed to the protein product, analytical tests should be performed to characterize the proposed product in terms of its specific binding properties (e.g., if binding to a receptor is inherent to protein function, this property should be measured and used in comparative studies) (see ICH Q6B for additional details). Various methods such as surface plasmon resonance, microcalorimetry, or classical Scatchard analysis can provide information on the kinetics and thermodynamics of binding. Such information can be related to the functional activity and characterization of the proposed product's higher order structure.

F. Impurities

The sponsor should characterize**,** identify, and quantify product-related impurities in the proposed product and the reference product, to the extent feasible.[22] If a comparative physicochemical analysis reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary. However, if the manufacturing process used to produce the proposed product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary. As discussed in the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), "[i]t is

[22] The use of the terms *product-* and *process-related impurities* is consistent with their use and meaning in ICH Q6B.

preferable to rely on purification processes to remove impurities . . . rather than to establish a preclinical testing program for their qualification."[23]

Process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g., antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachables, endotoxin, bioburden) should be evaluated. The process-related impurities in the proposed product are not expected to match those observed in the reference product and are not included in the comparative analytical assessment. The chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities.[24] In particular, results of immunological methods used to detect host cell proteins depend on the assay reagents and the cell substrate used. Such assays should be validated using the product cell substrate and orthogonal methodologies to ensure accuracy and sensitivity.

As with any biological product, the safety of the proposed product with regard to adventitious agents or endogenous viral contamination, should be ensured by screening critical raw materials and confirmation of robust virus removal and inactivation achieved by the manufacturing process.[25]

G. Reference Product and Reference Standards

A thorough physicochemical and biological assessment of the reference product should provide a base of information from which to develop the proposed product and justify reliance on certain existing scientific knowledge about the reference product. Sufficient evidence that the proposed product is highly similar to the reference product must be provided to support a selective and targeted approach in early product development (e.g., selected animal studies and/or additional clinical studies).[26]

The comparative analytical assessment submitted with the marketing application to support the demonstration of biosimilarity of the proposed product to the reference product should include lots of the proposed product used in principal clinical study(ies), as well as the proposed commercial product. As stated earlier in section V.B, a sponsor considering manufacturing changes after completing the initial comparative analytical assessment or after completing clinical studies intended to support a 351(k) application may need to conduct additional

[23] See the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), page 2.

[24] See the ICH guidance for industry *Q2B Validation of Analytical Procedures: Methodology* (May 1997).

[25] See the ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin* (September 1998).

[26] See 21 CFR 312.23 for IND application content and format.

546 comparative analytical studies of the proposed product and the reference product. The nature
547 and extent of the changes may determine the extent of these additional analytical studies.
548
549 If the drug substance has been extracted from the reference product to conduct analytical studies,
550 the sponsor should describe the extraction procedure and provide support that the procedure
551 itself does not alter relevant product quality attributes. This undertaking would include
552 consideration of alteration or loss of the desired products and impurities and relevant product-
553 related substances, and it should include appropriate controls to ensure that relevant
554 characteristics of the protein are not significantly altered by the extraction procedure.
555
556 If there is a suitable, publicly available, and well-established reference standard for the protein, a
557 physicochemical and/or functional comparison of the proposed product with this standard may
558 also provide useful information.[27] For example, if an international standard for calibration of
559 potency is available, a comparison of the relative potency of the proposed product with this
560 potency standard should be performed. As recommended in ICH Q6B, an in-house reference
561 standard(s) should always be qualified and used for control of the manufacturing process and
562 product.
563
564 An in-house reference standard is typically developed from early development lots or lots used in
565 a clinical study(ies). Additional reference standards may be qualified later in development and
566 for a BLA submission. Ideally, a sponsor will have established and properly qualified primary
567 and working reference standards that are representative of proposed product lots used in clinical
568 studies that support the application.
569
570 For the development of a proposed product, a reference product lot or a lot of a non-U.S.-
571 licensed comparator product (see section VI.A.4 of this guidance) is typically qualified as an
572 initial reference standard. Once clinical lots of the proposed product have been manufactured, it
573 is expected that one of these lots will be properly qualified (including bridging to previous
574 reference standards) for use as a reference standard for release and stability, as well as
575 comparative analytical testing. If possible, once an in-house reference standard is properly
576 qualified, there should be sufficient quantities to use throughout the development of the proposed
577 product. All lots of reference standards used during the development of a proposed product
578 should be properly qualified. In addition to release testing methods, the qualification protocol
579 for reference standards should include all analytical methods that report the result relative to the
580 reference standard.
581
582 For all methods where the result is reported relative to the reference standard, the assignment of
583 a potency of 100% should include a narrow acceptable potency range and ensure control over
584 product drift. For example, a sponsor should consider the use of a pre-determined two-sided
585 confidence interval (CI) of the mean of the replicates, where the mean relative potency and the
586 95% CI are included within a sufficiently narrow range (e.g., 90-110%). There should be an

[27] Although studies with such a reference standard may be useful, they are not sufficient to satisfy the BPCI Act's requirement to demonstrate the biosimilarity of the proposed product to the U.S.-licensed reference product.

evaluation across the history of multiple reference standard qualifications to address potential drift.

A sponsor generally should not use a correction factor to account for any differences in, for example, potency or biological activity between reference standards.

Use of reference standards inadequately qualified for analytical methods that report results relative to the reference standard is likely to raise concerns regarding the comparative analytical assessment. One approach to address these concerns, if applicable, may be to store the reference product and non-U.S.-licensed comparator product lots under conditions that maintain stability long term, if feasible. Prior to submission of a 351(k) application, the prospective applicant should conduct a reevaluation of all proposed product, reference product, and non-U.S.-licensed comparator product lots using the same reference standard for those methods that report the result relative to the reference standard. Data supporting the stability of the reference product and non-U.S.-licensed comparator product beyond the expiration date under these conditions should be included in the submission.

In summary, analytical studies carried out to support the approval of a proposed product should not focus solely on the characterization of the proposed product in isolation. Rather, these studies should be part of a broad comparison that includes, but is not limited to, the proposed product, the reference product, and, where applicable, a non-U.S.-licensed comparator, applicable reference standards, and consideration of relevant publicly available information.

H. Finished Drug Product

Product characterization studies of a proposed product should be performed on the most downstream intermediate best suited for the analytical procedures used. The attributes evaluated should be stable through any further processing steps. For these reasons, characterization studies are often performed on the drug substance. However, if a drug substance is reformulated and/or exposed to new materials in the finished dosage form, the impact of these changes should be considered. Whenever possible, if the finished drug product is best suited for a particular analysis, the sponsors should analyze the finished drug product. If an analytical method more sensitively detects specific attributes in the drug substance but the attributes it measures are critical and/or may change during manufacture of the finished drug product, comparative characterization may be called for on both the extracted protein and the finished drug product.

Proteins are very sensitive to their environment. Therefore, differences in excipients or primary packaging may affect product stability and/or clinical performance. Differences in formulation and primary packaging[28] between the proposed product and the reference product are among the factors that may affect whether or how subsequent clinical studies may take a selective and

[28] See the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

targeted approach.[29] Sponsors should clearly identify excipients used in the proposed product that differ from those in the reference product. The acceptability of the type, nature, and extent of any differences between the finished proposed product and the finished reference product should be evaluated and supported by appropriate data and rationale. Additionally, different excipients in the proposed product should be supported by existing toxicology data for the excipient or by additional toxicity studies with the formulation of the proposed product**.** Excipient interactions as well as direct toxicities should be considered.

I. Stability

As part of an appropriate physicochemical and functional comparison of the stability profile of the proposed product with that of the reference product, accelerated and stress stability studies, as well as forced degradation studies, should be used to establish degradation profiles and to provide a direct stability comparison of the proposed product with the reference product. These comparative studies should be conducted under multiple stress conditions (e.g., high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period**.** Results of these studies may reveal product differences that warrant additional evaluations and also identify conditions under which additional controls should be employed in manufacturing and storage.[30] Sufficient real time, real-condition stability data from the proposed product should be provided to support the proposed shelf life.

VI. COMPARATIVE ANALYTICAL ASSESSMENT

A thorough understanding of the reference product is critical for a successful biosimilar development program. The Agency recommends that sponsors approach the comparative analytical assessment by first understanding the physicochemical and biological characteristics of the reference product. A full characterization of the reference product, in addition to consideration of publicly available information, will form the basis of product understanding. As described previously, protein products are complex molecules that generally are manufactured in living cells and purified using a variety of technologies; therefore, they have a certain degree of inherent lot-to-lot variability in terms of quality characteristics. The observed lot-to-lot variability may derive from manufacturing conditions and from analytical assay variability. Factors that contribute to lot-to-lot variability in the manufacture of a protein product include the source of certain raw materials (e.g., growth medium, resins, or separation materials) and different manufacturing sites. Therefore, the comparative analytical assessment, it is important to adequately characterize the lot-to-lot variability of the reference product and the proposed biosimilar product.

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[29] For more discussion on *selective and targeted approaches*, please refer to the guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015).

[30] See ICH guidances for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996) and *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

664
665 **A. Considerations for Reference and Biosimilar Products**
666
667 *1. Reference Product*
668
669 To ensure that the full range of product variability is accurately captured, sponsors should
670 acquire multiple reference product lots throughout the development program of a proposed
671 biosimilar in sufficient quantity to conduct multiple physiochemical and functional assays.
672 Considering the inherent heterogeneity present in protein products and the expected lot-to-lot
673 variability stemming from manufacturing processes, the Agency recommends that a sponsor
674 include at least 10 reference product lots (acquired over a time frame that spans expiration dates
675 of several years), in the analytical assessment to ensure that the variability of the reference
676 product is captured adequately. The final number of lots should be sufficient to provide adequate
677 information regarding the variability of the reference product. In cases where limited numbers of
678 reference product lots are available (e.g., for certain orphan drugs), alternate flexible comparative
679 analytical assessments plans should be proposed and discussed with the Agency.
680
681 *2. Proposed Product*
682
683 The Agency recommends that a sponsor include at least 6 to 10 lots of the proposed product in
684 the comparative analytical assessment, to ensure 1) adequate characterization of the proposed
685 product and understanding of manufacturing variability, and 2) adequate comparison to the
686 reference product. These should include lots manufactured with the investigational- and
687 commercial-scale processes, and may include validation lots, as well as product lots
688 manufactured at different scales, including engineering lots. These lots should be representative
689 of the intended commercial manufacturing process. If there is a manufacturing process change
690 during development, it may be possible, with adequate scientific justification, to use data
691 generated from lots manufactured with a different process. However, data should be provided in
692 the 351(k) BLA to support comparability of drug substance and drug product manufactured with
693 the different processes and/or scales. The extent of process development design (as described in
694 guidelines *ICH Q8 (R2) Pharmaceutical Development* and *ICH Q11 Development and*
695 *Manufacture of Drug Substances*) and process understanding should be used in support of the
696 number of proposed biosimilar product lots proposed for inclusion in the comparative analytical
697 assessment in the 351(k) application.
698
699 To the extent possible, proposed biosimilar lots included in the comparative analytical
700 assessment described in section VI.B, Considerations for Data Analysis, should be derived from
701 different drug substance batches to adequately represent the variability of attributes inherent to
702 the drug substance manufacturing process. Drug product lots derived from the same drug
703 substance batch(es) are not considered sufficiently representative of such variability, except for
704 use in testing certain drug product attributes for which variability is mostly dependent on the
705 drug product manufacturing process (e.g., protein concentration). Although it may be preferable
706 to compare the proposed product lots to the reference product lots, it may be acceptable to also

include independent drug substance batches (if the drug substance was not used to make drug product), if needed, to attain a sufficient number of lots for the comparative analytical assessment.

3. Accounting for Reference Product and Proposed Product Lots

Sponsors should account for all the reference product lots acquired and characterized. The 351(k) BLA should include data and information from all reference product and proposed product lots that were evaluated in any manner, including the specific physicochemical, functional, animal, and clinical studies for which a lot was used. When a lot is specifically selected to be included in or excluded from certain analytical studies, a justification should be provided. The date of the analytical testing as well as the product expiration date should be provided in the application. In general, expired reference product lots should not be included in the comparative analytical assessment because lots analyzed beyond their expiration date could lead to results outside the range that would normally be observed in unexpired lots, which may result in overestimated reference product variability. Testing of lots past expiry may be acceptable if samples are stored under long term conditions (e.g., frozen at -80°C) provided that sponsors submit data and information demonstrating that storage does not impact the quality of the product (see section V.G).

The same type of information and data described above to be collected for reference product lots should also be provided on every manufactured drug substance and drug product lot of the proposed product.

Reference product and proposed product lots used in the clinical studies (e.g., PK and PD, if applicable, similarity, and comparative clinical study) should be included in the comparative analytical assessment.

4. Reference Product and Non-U.S.-Licensed Comparator Products

As described in other guidances, a sponsor that intends to use a non-U.S.-licensed comparator in certain studies should provide comparative analytical data and analysis for all pairwise comparisons (i.e., U.S.-licensed product versus proposed biosimilar product, non-U.S.-licensed comparator product versus proposed biosimilar product, and U.S.-licensed product versus non-U.S.-licensed comparator product).

The acceptance criteria used to support a demonstration that a proposed biosimilar product is highly similar to the reference product should be derived from data generated from a sponsor's analysis of the reference product. The comparative analytical assessment should be based on a direct comparison of the proposed product to the reference product. As a scientific matter, combining data from the reference product and non-U.S.-licensed comparator product to determine the acceptance criteria or to perform the comparative analytical assessment to the proposed product would not be acceptable to support a demonstration that the proposed product

is biosimilar to the reference product. For example, combining data from the reference product and non-U.S.-licensed products may result in a larger range and broader similarity acceptance criteria than would be obtained by relying solely on data from reference product lots. Sponsors are encouraged to discuss with FDA, during product development, any plans to submit data derived from products approved outside of the U.S. in support of a 351(k) application.

B. Considerations for Data Analysis

Sponsors should develop a comparative analytical assessment plan and discuss the approach with the Agency as early as practicable. A final comparative analytical assessment report should be available at the time a 351(k) BLA is submitted.

The Agency recommends development of a comparative analytical assessment plan using a stepwise approach. The first step is a determination of the quality attributes that characterize the reference product in terms of its structural/physicochemical and functional properties. These quality attributes are then ranked according to their risk to potentially impact activity, PK/PD, safety, efficacy, and immunogenicity. Finally, the attributes are evaluated using quantitative analysis, considering the risk ranking of the quality attributes, as well as other factors. It should be noted, however, that some attributes may be highly critical (e.g., primary sequence) but not amenable to quantitative analysis.

1. Risk Assessment

FDA recommends that sponsors develop a risk assessment tool to evaluate and rank the reference product quality attributes in terms of potential impact on the mechanism(s) of action and function of the product. Certain quality evaluations of the reference product (e.g., its degradation rates, which are determined from stability or forced degradation studies) generally should not be included in the risk ranking. However, these evaluations should still factor into the comparative analytical assessment of the proposed biosimilar and reference product.

Development of the risk assessment tool should be informed by relevant factors, including:

- Potential impact of an attribute on clinical performance: Specifically, FDA recommends that sponsors consider the potential impact of an attribute on activity, PK/PD, safety, efficacy, and immunogenicity. Sponsors should consider publicly available information, as well as the sponsor's own characterization of the reference product, in determining the potential impact of an attribute on clinical performance.

- The degree of uncertainty surrounding a certain quality attribute: For example, when there is limited understanding of the relationship between the degree of change in an attribute and the resulting clinical impact, FDA recommends that that attribute be ranked as having higher risk because of the uncertainty raised.

FDA recommends that an attribute that is a high risk for any one of the performance categories (i.e., activity, PK/PD, safety, efficacy, and immunogenicity) be classified as high risk. Ideally, the risk assessment tool should result in a list of attributes ordered by the risk to the patient. The risk scores for attributes should, therefore, be proportional to patient risk. The scoring criteria used in the risk assessment should be clearly defined and justified, and the risk ranking for each attribute should be justified with appropriate citations to the literature and data provided.

2. Quantitative and Qualitative Data Analysis

Appropriate analyses of the comparative analytical data are necessary to support a demonstration that the proposed product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. One approach to data analysis would be the use of descriptive quality ranges for assessing quantitative quality attributes of high and moderate risk, and the use of raw data/graphical comparisons for quality attributes with the lowest risk ranking or for those quality attributes that cannot be quantitatively measured (e.g., primary sequence). The acceptance criteria for the quality ranges (QR) method in the comparative analytical assessment should be based on the results of the sponsor's own analysis of the reference product for a specific quality attribute. The QR should be defined as $(\hat{\mu}_R - X\hat{\sigma}_R, \hat{\mu}_R + X\hat{\sigma}_R)$, where $\hat{\mu}_R$ is the sample mean, and $\hat{\sigma}_R$ is the sample standard deviation based on the reference product lots. The multiplier (X) should be scientifically justified for that attribute and discussed with the Agency. Based on our experience to date, methods such as tolerance intervals are not recommended for establishing the similarity acceptance criteria because a very large number of lots would be required to establish meaningful intervals. The sponsor can propose other methods of data analysis, including equivalence testing.

The objective of the comparative analytical assessment is to verify that each attribute, as observed in the proposed biosimilar and the reference product, has a similar population mean and similar population standard deviation. Comparative analysis of a quality attribute would generally support a finding that the proposed product is highly similar to the reference product when a sufficient percentage of biosimilar lot values (e.g., 90%) fall within the QR defined for that attribute. The Agency recommends that narrower acceptance criteria of the QR method in the comparative analytical assessment (e.g., a lower X value) be applied to higher risk quality attributes.

In addition to risk ranking, other factors should be considered in determining which type of quantitative data analysis should be applied to a particular attribute or assay. Some additional factors that should be considered when determining the appropriate type of data evaluation and analysis of results include:

- Nature of the attribute: Attributes that are known to be of high risk should be prioritized over attributes with unknown but potentially high risk (i.e., attributes with a high-risk ranking due to uncertainty).

- Distribution of the attribute: In general, the Agency recommends that sponsors develop the manufacturing process to target the centers of distribution of the quality attributes of the reference product as closely as possible. Therefore, the QR, which assumes that the population mean and standard deviation are similar, is an appropriate approach to demonstrate that the proposed product is highly similar to the reference product. If there are concerns with the distribution, additional information or analyses may be needed to support the QR method or to support a different analysis approach. For example, the distribution of an attribute in the proposed biosimilar product that is biased towards one side of the reference product distribution may raise concerns depending on the nature of the attribute and the role the attribute plays in, for example, the mechanism of action of the product. If such a distribution is observed, appropriate justification may be needed, as a scientific matter, to support the comparative analytical assessment of the products. In cases where an attribute in the reference product is not normally distributed, sponsors should consult with the Agency.

- Abundance of the attribute: Because of the inherent heterogeneity present in protein products, an attribute of the reference product that may pose a high risk when the attribute is present in high abundance (e.g., percent aggregation or percent oxidation) may pose a significantly lower risk (or negligible risk) if the attribute is low-abundance. The abundance of the attribute should be confirmed in both the reference product (as determined by the proposed product sponsor's analysis of the reference product) and the proposed product. Limit assays do not necessarily need to be evaluated using QR; however, the selected limits regarding the amount of an attribute should be defined and justified. The justification should also include consideration of how the amount of the attribute changes over time.

- Sensitivity of assay used for assessing an attribute: Although multiple, orthogonal assays are encouraged for assessing an attribute, not all assays assessing the attribute need to be evaluated in the same manner. While the most sensitive assay for detecting product differences should be evaluated using QR, it may be appropriate to evaluate the results of other assays for the same attribute using a graphical comparison. A justification should be provided for the method of evaluation used for each type of assay.

- Types of attributes/assays: Quantitative analyses may not be applicable to some attributes, (e.g., protein sequence or certain assays used for higher order structure evaluation, or to assays that are only qualitative). The comparative analytical assessment plan should clearly define specific assays where quantitative data analyses would not be applied, and the rationale for that decision.

- Publicly available information: Publicly available information may be relevant to the appropriate type of data analysis and acceptance criteria in the comparative analytical assessment. A sponsor should seek additional advice from the Agency on the inclusion of any publicly available information in the comparative analytical assessment.

For qualitative analyses of lower risk attributes, FDA recommends side-by-side data presentation (e.g., spectra, thermograms, graphical representation of data), to allow for a visual comparison of the proposed product to the reference product.

The final comparative analytical assessment plan should include the risk ranking of attributes, the type of data evaluation to be used for each attribute/assay, and the final data analysis plan. The plan should specify the anticipated availability of both proposed biosimilar and reference product lots for evaluation of each attribute/assay and should include a rationale for why the proposed number of lots should be considered sufficient for the evaluation. The comparative analytical assessment plan should be discussed with the Agency as early in the biosimilar development program as possible so that agreement can be reached on which attributes/assays should be evaluated. The final comparative analytical assessment plan should be submitted to the Agency prior to initiating the final analytical assessments; typically, this occurs in a meeting with the Agency.

C. Comparative Analytical Assessment Conclusions

In the comparative analytical assessment, risk ranking and data analysis are used to evaluate a large number of attributes, often using multiple orthogonal assays. FDA evaluates the totality of the analytical data; if the results of a particular assay do not meet pre-specified criteria, this alone does not preclude a demonstration of high similarity. For example, if differences between products are observed as part of the comparative analytical assessment (including the components of the assessment that were not included in the risk ranking), the sponsor may provide additional scientific information (risk assessment and additional data) and a justification for why these differences do not preclude a demonstration that the products are highly similar.

In certain situations, changes to the manufacturing process of the biosimilar product may be needed to resolve differences observed in the comparative analytical assessment. Data should be provided demonstrating that the observed differences were resolved by any manufacturing changes, and that other quality attributes were not substantially affected. If other attributes were affected by the manufacturing change, data should be provided to demonstrate that the impact of the change has been evaluated and addressed.

VII. CONCLUSION

The foundation for an assessment and a demonstration of biosimilarity between a proposed product and its reference product includes analytical studies that demonstrate that the proposed product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. The demonstration that the proposed product is biosimilar to the reference product thus involves robust characterization of the proposed product, including comparative physicochemical and functional studies with the reference product. The information gained from these studies is necessary for the development of a proposed product as a biosimilar. In addition,

a 351(k) application for a proposed product must contain, among other things, information demonstrating biosimilarity based on data derived from animal studies (including the assessment of toxicity) and a clinical study or studies (including the assessment of immunogenicity and PK or PD), unless the Agency determines that an element is unnecessary in a particular 351(k) application.[31] A sponsor's ability to discern and understand the impact of relevant analytical differences between the proposed product and its reference product is critical to determine whether the statutory standard for biosimilarity can be met.

VIII. RELEVANT GUIDANCES

The following draft and final guidance documents may be relevant to sponsors developing or considering development of a proposed biosimilar product. All Agency guidance documents are available on FDA's web page (https://www.fda.gov/regulatory-information/search-fda-guidance-documents).

1. Guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015)

2. Guidance for industry *Questions and Answers on Biosimilar Development and the BPCI Act* (December 2018)

3. Draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (December 2018)

4. Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (June 2018)

5. Guidance for industry *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016)

6. *Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* (April 1996)

7. *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (February 1997)

8. Guidance for industry for the *Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use* (August 1996)

[31] Section 351(k)(2)(A)(i)(I) of the PHS Act.

9. Guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics* (November 2008)

10. ICH guidance for industry *M4: The CTD —Quality* (ICH M4Q) (August 2001)

11. ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (ICH Q1A(R2)) (November 2003)

12. ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (ICH Q2(R1) (November 2005)

13. ICH guidance for industry *Q2B Validation of Analytical Procedures: Methodology* (ICH Q2B) (May 1997)

14. ICH guidance for industry *Q3A(R) Impurities in New Drug Substances* (ICH Q3A(R)) (June 2008)

15. ICH guidance for industry *Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* (ICH Q5A) (September 1998)

16. ICH guidance for industry *Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products* (ICH Q5B) (February 1996)

17. ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (ICH Q5C) (July 1996)

18. ICH guidance for industry *Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* (ICH Q5D) (September 1998)

19. ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (ICH Q5E) (June 2005)

20. ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (ICH Q6B) (August 1999)

21. ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7) (September 2016)

22. ICH guidance for industry *Q8(R2) Pharmaceutical Development* (ICH Q8(R2)) (November 2009)

23. ICH guidance for industry *Q9 Quality Risk Management* (ICH Q9) (June 2006)

24. ICH guidance for industry *Q10 Pharmaceutical Quality System* (ICH Q10) (April 2009)

25. ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (ICH Q11) (November 2012)

26. ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (ICH S6(R1)) (May 2012)

GLOSSARY[32]

For the purpose of this document, the following definitions apply:

Biosimilar or biosimilarity means "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[33]

Chemically synthesized polypeptide means any alpha amino acid polymer that (a) is made entirely by chemical synthesis and (b) is less than 100 amino acids in size.

Product, when used without modifiers, is intended to refer to the intermediates, drug substance, and/or drug product, as appropriate. The use of the term *product* is consistent with the use of the term in ICH Q5E.

Protein means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

Reference product means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application.[34]

[32] For additional information on the Agency's interpretation of certain terms relevant to implementation of the BPCI Act, see the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* (December 2018). When final, this guidance will represent FDA's current thinking on this topic.

[33] Section 351(i)(2) of the PHS Act.

[34] Section 351(i)(4) of the PHS Act.

Exhibit 35

OUTSIDE ATTORNEY'S EYES ONLY

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **CONFIDENTIAL: CONTAINS ATTORNEY'S EYES ONLY INFORMATION**

RESPONSIVE EXPERT REPORT OF GREGORY MACMICHAEL, PH.D. REGARDING THE NON-INFRINGEMENT OF THE ASSERTED CLAIMS OF U.S. PATENT NO. 11,084,865

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TABLE OF REFERENCES

REFERENCE	BATES RANGE	ABBREVIATION
Opening Expert Report of Gregory MacMichael, Ph.D. Regarding the Invalidity of The Asserted Claims of U.S. Patent No. 11,084,865 Under 35 U.S.C. § 112 Assuming Mylan's Construction of the Claim Terms "Organic Cosolvent" and "Native Conformation" and Regarding the Invalidity of Claims 6, 7, 12, 13, 18, 19, 22, and 23, of U.S. Patent No. 11,253,572 Under 35 U.S.C. § 112		"MacMichael Opening Reports"
Opening Expert Report of Gregory MacMichael, Ph.D. Regarding the Invalidity of The Asserted Claims of U.S. Patent No. 11,084,865 Under 35 U.S.C. § 112 Assuming Regeneron's Claim Construction Proposal of the Claim Terms "Organic Co-Solvent" and "Native Conformation" and Regarding the Invalidity of Claims 6, 7, 12, 13, 18, 19, 22, and 23, of U.S. Patent No. 11,253,572 Under 35 U.S.C. § 112		
Declaration of Gregory MacMichael, Ph.D. in Support of Defendant's Claim Construction Brief	MYL-AFL0092518-47	"MacMichael Declaration"
U.S. Patent No. 11,084,865	RGN-EYLEA-MYLAN-00028406-19	"the '865 patent"
U.S. Patent No. 11,253,572	RGN-EYLEA-MYLAN00036361-87	"the '572 patent"
Opening Expert Report of Bernhardt L. Trout, Ph.D., dated February 2, 2023		"Trout Report"

REFERENCE	BATES RANGE	ABBREVIATION
Curriculum vitae of Gregory MacMichael, Ph.D.		"MacMichael CV"
Jacques Gaudreault, et al., *Preclinical Pharmacokinetics of Ranibizumab(rhuFabV2) after a Single Intravitreal Administration* 46 Investigative Ophthalmology & Visual Science 726 (2005)	MYL-AFL0092357-64 (*see also* RGN-EYLEA-MYLAN-00540294-302)	DX.714 or "Gaudreault 2005"
European Medicines Agency Scientific Discussion of Avastin (2006)	MYL-AFL0096087-147 (*see also* RGN-EYLEA-MYLAN-00610208-69)	DX.716 or "EMA Avastin Scientific Discussion"
PCT Patent Publication No. WO 2006/047325	MYL-AFL0093289-334 (*see also* RGN-EYLEA-MYLAN-00007248-93)	DX.726 or "Shams"
CDER, BLA Application Number: 125156, Medical Review	MYL-AFL0007087-257	"Lucentis Medical Review"
LUCENTIS® Prescribing Information (2006)	MYL-AFL0092511-17 (*see also* RGN-EYLEA-MYLAN-00573025-32)	DX.727 or "Lucentis PI 2006"
European Medicines Agency Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006: Lucentis (2016).	MYL-AFL0095484-92	"EMA Lucentis Assessment Report"
2006-03-21 Email and attachment from K. DeWald re FW: Sucrose VGT formulation help	RGN-EYLEA-MYLAN-00559098-100	DX.722 or "Eylea Product Composition (March 21, 2006)"
2006-04-21 Email and attachment from K. Graham re Placebo and 40 mg/mL VEGF Trap ITV Formulations	RGN-EYLEA-MYLAN-00580791-94	DX.736 or "Placebo and 40 mg/mL VEGF Trap ITV Formulations"
BLA 125387, 2.3.P Drug Product	RGN-EYLEA-MYLAN-00295196-229	"BLA 125387, 2.3.P Drug Product"

REFERENCE	BATES RANGE	ABBREVIATION
BLA 125387, 2.3.P Drug Product, JHP	RGN-EYLEA-MYLAN-00077042-82	"BLA 125387, 2.3.P Drug Product, JHP"
BLA 125387, 2.3.P Drug Product, Vetter	RGN-EYLEA-MYLAN-00076825-78	"BLA 125387, 2.3.P Drug Product, Vetter"
2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods	RGN-EYLEA-MYLAN-00057253-81	"2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods"
M710 BLA, 2.6 Nonclinical Summaries	[redacted]	"M710 BLA, 2.6 Nonclinical Summaries"
M710 BLA, 2.4 Nonclinical Overview	[redacted]	"M710 BLA, 2.4 Nonclinical Overview"
M710 BLA, 1.6.3 - Correspondence Regarding Meetings	[redacted]	"M710 BLA, 1.6.3 - Correspondence Regarding Meetings"
M710 BLA, 2.3 Drug Product - Description and Composition of Drug Product - Quality Overall Summary	[redacted]	"M710 BLA, 2.3.P.1.2 Drug Product Composition"
M710 BLA, 3.2.P.1 Description and Composition of the Drug Product	[redacted]	"M710 BLA, 3.2.P.1 Drug Product Composition"
M710 BLA, Extractable/Leachables Risk Assessment for Viatris M710 Drug Product, Fill Finish and Shelf-life	[redacted]	"M710 BLA, Extractable/Leachables Risk Assessment Report"
M710 BLA, 3.2.P.2.2 Drug Product	[redacted]	"M710 BLA, 3.2.P.2.2 Drug Product"
IPR2021-00881 (U.S. Patent No. 9,254,338), Ex.2051	MYL-AFL0096241-307	"IPR2021-00881 (U.S. Patent No. 9,254,338), Ex.2051"

REFERENCE	BATES RANGE	ABBREVIATION
IPR2021-00881 (U.S. Patent No. 9,254,338), Paper 21	MYL-AFL0096308-48	"IPR2021-00881 (U.S. Patent No. 9,254,338), Paper 21"
IPR2022-01225 (U.S. Patent No. 10,130,681), Paper 14	MYL-AFL0096413-94	"IPR2022-01225 (U.S. Patent No. 10,130,681), Paper 14"
IPR2022-01226 (U.S. Patent No. 10,888,601), Paper 13	MYL-AFL0096495-556	"IPR2022-01226 (U.S. Patent No. 10,888,601), Paper 13"
601 Institution Decision: Dkt. No. 254-2		"601 Institution Decision: Dkt. No. 254-2"
681 Institution Decision: Dkt. No. 254-1		"681 Institution Decision: Dkt. No. 254-1"
Joint Claim Construction Chart: Dkt. No. 102		"Joint Claim Construction Chart: Dkt. No. 102"
Opening Expert Report of Karl G. Csaky, M.D., Ph.D.		"Csaky Report"
Deposition Transcript of Gregory MacMichael dated December 29, 2022		"MacMichael Tr."
Deposition Transcript of Eric Furfine dated January 12, 2023		"Furfine Tr."
Deposition Transcript of Kenneth Graham dated January 19, 2023		"Graham Tr."
Deposition Transcript of Hana Chang dated January 18, 2023		"Chang Tr."
Markman Hearing Transcript, January 24, 2023		"Markman Tr."

REFERENCE	BATES RANGE	ABBREVIATION
DI 173-1 – Mylan Responsive Claim Construction Brief, served December 15, 2022		"Dkt. No. 173-1 (Mylan Response)"
Michael J. Akers, *Drug Delivery—Parenteral Route*, Encyclopedia Of Pharmaceutical Technology 910 (James Swarbrick & James Boylan eds., 2002)	MYL-AFL0095454-69	"Akers"
Theodore W. Randolph & LaToya S. Jones, *Surfactant-Protein Interactions*, *in* Rational Design Of Stable Protein Formulations 159 (John F. Carpenter & Mark C. Manning eds., 2002)	MYL-AFL0090383-99 (*see also* RGN-EYLEA-MYLAN-00015798-814)	"Randolph"
Material Safety Data Sheet: Aflibercept (Sept. 7, 2007)	MYL-AFL0095449-53	"Aflibercept MSDS"
Liquid Formulation Development for Momenta's M710	MYL-AFL0011219-95	"IntegrityBio Report"
File History of U.S. Patent Application No. 16/159,269, 7/22/2019 Response	RGN-EYLEA-MYLAN-00015158-00015164	"Dkt. 146, Mylan's Exhibits to Opening Claim Construction Brief, Ex. 16"
File History of U.S. Patent Application No. 16/159.,269, 8/21/2019 Notice of Allowance	RGN-EYLEA-MYLAN-00015173-00015180	"Dkt. 146, Mylan's Exhibits to Opening Claim Construction Brief, Ex. 15"
M710 BLA, 3.2.S.2.2 Description of Manufacturing Process and Controls	[redacted]	"M710 BLA, 3.2.S.2.2 Description of Manufacturing Process and Controls"
[redacted] Quality Risk Assessment Report	[redacted]	[redacted] Quality Risk Assessment Report"
2005-08-15 Email from K. Frye re Avastin & Macugen formulations	RGN-EYLEA-MYLAN-00555138-39	"Avastin & Macugen formulations"

REFERENCE	BATES RANGE	ABBREVIATION
Loyd V. Allen, Jr. et al., *Dosage Form Design: Pharmaceutical and Formulation Considerations*, ANSEL'S PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS 92 (8th ed. 2005)	MYL-AFL0095470-83	"Ansel"

I. INTRODUCTION.

1. I, Dr. Gregory MacMichael, having been retained to testify as an expert in this case on behalf of Mylan Pharmaceuticals Inc. ("Mylan") in the above-captioned action submit this Responsive Expert Report in the above identified proceeding.

2. I am the same Gregory MacMichael that submitted Opening Expert Reports in this case dated February 2, 2023 ("MacMichael Opening Reports").[1] I am also the same Gregory MacMichael that submitted a declaration entitled "Declaration of Gregory MacMichael, Ph.D. in Support of Defendant's Claim Construction Brief" dated November 28, 2022 ("MacMichael Declaration"). I incorporate by reference the MacMichael Opening Reports and the MacMichael Declaration and all Exhibits to the extent relevant and necessary, and reserve the right to provide testimony on any issues or subject matter contained therein.

3. This Report discloses my opinions, and the bases and reasons supporting my opinions, regarding, among other things, issues that I understand relate to Regeneron Pharmaceuticals, Inc.'s, ("Plaintiff" or "Regeneron") claims for alleged infringement of U.S. Patent No. 11,084,865 ("the '865 patent") including in response to the Opening Expert Report of Bernhardt L. Trout, Ph.D., dated February 2, 2023 ("Trout Report").

4. This Report sets forth the additional opinions I have formed based on information available as of the date below. In the event Regeneron submits any expert report or other response

[1] My opening reports are entitled: "Opening Expert Report of Gregory MacMichael, Ph.D. Regarding the Invalidity of The Asserted Claims of U.S. Patent No. 11,084,865 Under 35 U.S.C. § 112 Assuming Mylan's Construction of the Claim Terms "Organic Co-solvent" and "Native Conformation" and Regarding the Invalidity of Claims 6, 7, 12, 13, 18, 19, 22, and 23, of U.S. Patent No. 11,253,572 Under 35 U.S.C. § 112" and "Opening Expert Report of Gregory MacMichael, Ph.D. Regarding the Invalidity of The Asserted Claims of U.S. Patent No. 11,084,865 Under 35 U.S.C. § 112 Assuming Regeneron's Claim Construction Proposal of the Claim Terms "Organic Co-Solvent" and "Native Conformation" and Regarding the Invalidity of Claims 6, 7, 12, 13, 18, 19, 22, and 23, of U.S. Patent No. 11,253,572 Under 35 U.S.C. § 112."

to the subject matter addressed in this Report, I reserve the right to respond to such submission. I expect to be called to testify at trial in the above-captioned action.

II. PROFESSIONAL QUALIFICATIONS AND BACKGROUND.

5. Details regarding my background, education and experience are summarized in paragraphs 2-14 of the MacMichael Opening Reports and are incorporated by reference herein. (*See also* MacMichael Declaration ¶¶ 3-14).

6. A copy of my current *curriculum vitae* is attached to this Report as Exhibit A.

III. SUMMARY OF MY OPINIONS.

7. As set forth in more detail below, I disagree with Dr. Trout's infringement analysis. In my opinion, Dr. Trout's opinions do not prove that Mylan's M710 BLA Product infringes the Asserted Claims of the '865 patent under either Mylan's Proposed Constructions or Regeneron's Claim Construction Proposals.

8. In forming my opinions in this Report, the materials I have considered, in addition to my experience, education, and training, are identified herein, in the MacMichael Opening Reports, the MacMichael Declaration, and/or in Exhibit B.

IV. REQUIRED DISCLOSURES.

9. The terms of my retention, compensation, or the matters in which I have given testimony over the last four years, have not changed since the MacMichael Opening Reports.

V. TECHNOLOGY BACKGROUND AND TUTORIAL.

10. The '865 patent is directed to stable formulations of VEGF-specific fusion proteins. As such, in order to frame my analysis and provide proper context for my opinions, I provided an overview of some of the relevant technology at issue in paragraphs 42-70 of my opening expert reports. (*See* MacMichael Opening Reports at ¶¶ 42-70; *see also* MacMichael Declaration ¶¶ 40-44). I incorporate by reference as fully set forth herein my prior technology background and

tutorial opinions. I also reserve the right to expand on my prior technology background and tutorial opinions as needed to address any Regeneron expert opinions submitted in response to my Opening Expert Reports and/or this responsive expert report.

11. If I testify at trial in this case, I may rely on exhibits and/or visual aids to demonstrate the basis for my opinions. I have not yet prepared any such exhibits or visual aids. I also reserve the right to provide a tutorial relating to the general topics contained in this report and incorporated herein by reference, including a discussion of the references discussed.

VI. LUCENTIS® AND AVASTIN®.

12. **February 2005.** Ranibizumab is a humanized monoclonal Fab fragment capable of blocking the activity of VEGF-A, and is marketed by Genentech under the name LUCENTIS®. LUCENTIS® was originally indicated for the treatment of wet AMD via monthly intravitreal (ITV) administration. (Shams at MYL-AFL0093320; Lucentis PI 2006 at MYL-AFL0092511). ITV treatment involves administering an injection directly into the vitreous of the eye. Genentech, in a publication dated February 2005, demonstrated that polysorbate-containing formulations were safe for intravitreal administration. In this publication, Genentech was reporting a study designed to investigate the systemic, vitreous, aqueous humor, and retinal pharmacokinetics of ranibizumab, when administered as a single ITV injection to monkeys. (Gaudreault 2005 at MYL-AFL0092357; *see also* DX.714, RGN-EYLEA-MYLAN-00540295). The ranibizumab formulation is shown below and contained 0.05% Tween-20, which is another name for polysorbate 20.

> through the sclera and pars plana, 4 mm posterior to the limbus, with the needle directed posterior to the lens into the midvitreous. Group-3 and -4 monkeys received a single IV bolus (1 mL) of drug at 1000 or 4000 μg/animal, respectively. Ranibizumab was formulated as 10 mM sodium succinate, 10% trehalose, and 0.05% Tween-20 (pH 5.0).

(Gaudreault 2005 at MYL-AFL0092357-58 (emphasis added); *see also* DX.714, RGN-EYLEA-MYLAN-00540295-96). Genentech determined that "[r]anibizumab was well tolerated."

(Gaudreault 2005 at MYL-AFL0092357-58; *see also* DX.714, RGN-EYLEA-MYLAN-00540295-96).

13. **April 2005.** Another anti-VEGF treatment was bevacizumab, marketed by Genentech as AVASTIN®. Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting VEGF-A. In April 2005, during the approval process in front of the European Medicines Agency ("EMA"), the bevacizumab formulation was disclosed to contain 0.04% polysorbate 20.

Composition

Avastin is provided as a concentrate for solution for infusion in a single-use vial, which contains a nominal amount of either 100 mg of bevacizumab in 4 ml or 400 mg of bevacizumab in 16 ml (concentration of 25 mg/ml). Bevacizumab is formulated with 51 mM sodium phosphate pH 6.2, 60 mg/ml , -trehalose dihydrate and 0.04% polysorbate 20. The drug product is a clear to slightly opalescent, colourless to pale brown sterile liquid solution that has to be diluted in 0.9 % sodium chloride solution prior to administration.

(EMA Avastin Scientific Discussion at MYL-AFL0096089 (emphasis added); *see also* DX.716, RGN-EYLEA-MYLAN-00610211); and

Drug Product

∞ Pharmaceutical Development

The goal was to develop a stable liquid intravenous formulation. Early pharmacokinetic and toxicological phase I and early phase II clinical studies were conducted with a liquid formulation containing 10mg/ml bevacizumab, 10 mM histidine, 100 mg/ml trehalose dihydrate and 0.02% polysorbate 20. Late phase II and phase III trials used a formulation containing 51 mM sodium phosphate, 60 mg/ml trehalose dihydrate and 0.04% polysorbate 20 (as the formulation to-be-marketed). The bevacizumab concentration was increased from 10 mg/ml to 25 mg/ml in the sodium phosphate formulation for use in the phase III trials.

Selection of excipients was based on stability screening studies using different buffer systems.. A histidine buffer system at pH 5.5 was selected.

Trehalose dihydrate was selected to adjust osmolality.

Due to physical instability of the liquid formulation used in phase I and phase II clinical studies the formulation was changed by increasing the pH to 6.2, changing the histidine buffer for sodium phosphate, increasing the ionic strength by increasing the concentration of the buffering species, decreasing the trehalose concentration to modify the osmolality, and increasing the polysorbate 20 concentration. These changes resulted in a formulation that had acceptable stability at room temperature for shipping and handling of the product. This formulation was used in phase II and phase III clinical trials.

(EMA Avastin Scientific Discussion at MYL-AFL0096094 (emphasis added); *see also* DX.716,

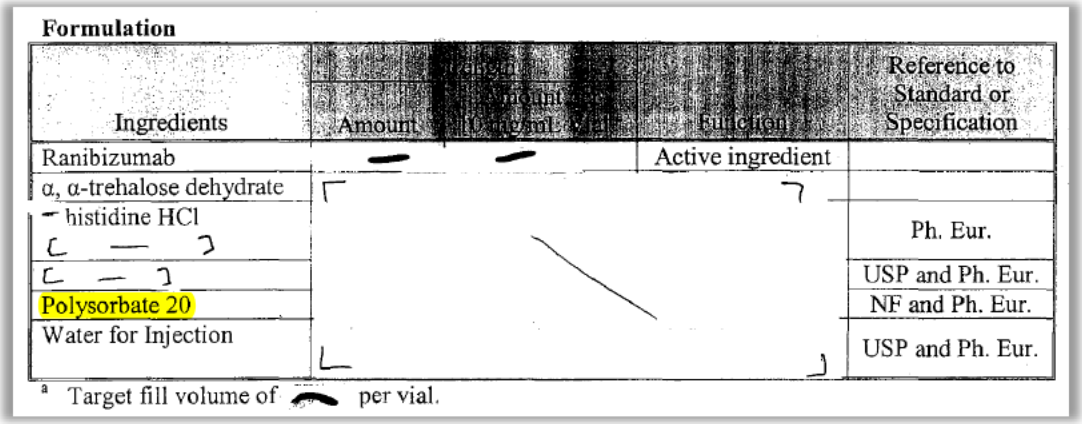
RGN-EYLEA-MYLAN-00610216; RGN-EYLEA-MYLAN-00555138 (August 2005) (disclosing iso-osmolar Avastin formulation as 10 mM Phosphate, 6% trehalose and 0.04% polysorbate 20)). I understand that AVASTIN® is used by retina specialists for the off-label ITV treatment of neovascular (wet) age-related macular degeneration ("AMD"), retinal vein occlusion ("RVO"), diabetic macular edema ("DME"), and diabetic retinopathy ("DR"). Further, as shown above, the polysorbate 20 containing formulation "was used in phase II and phase III clinical trials." (EMA Avastin Scientific Discussion at MYL-AFL0096094; *see also* DX.716, RGN-EYLEA-MYLAN-00610216).

14. **May 2006.** International Application WO 2006/047325 ("the '325 publication") was published. The '325 publication was directed to a method for ITV administration of a VEGF antagonist. One of the example VEGF antagonists disclosed in the '325 publication was ranibizumab (LUCENTIS®). The formulation for ITV administration contained 0.01% polysorbate 20, shown below:

> *Ranibizumab Injection*: For intravitreal administration, the study drug, ranibizumab, is supplied in a liquid-filled vial of ranibizumab. Each vial contains 0.7 mL of either 6 mg/mL (0.3 mg dose level) or 10 mg/mL (0.5-mg dose level) of ranibizumab aqueous solution (pH 5.5) with 10 mM of histidine, 100 mg/mL of trehalose, and 0.01% polysorbate 20. All study drug is stored at 2°C–8°C (36°F–46°F), and should not be frozen. Drug should be protected vials from direct sunlight.

(Shams at MYL-AFL0093320 (emphasis added); *see also* DX.726, RGN-EYLEA-MYLAN-00007279).

15. **June 30, 2006.** In the Drug Approval Package for LUCENTIS®, approved on June 30, 2006, the Medical Review listed the formulation as containing polysorbate 20, as shown below:



Formulation

Ingredients	Amount	Function	Reference to Standard or Specification
Ranibizumab	[redacted]	Active ingredient	
α, α-trehalose dehydrate	[redacted]		
histidine HCl	[redacted]		Ph. Eur.
[redacted]	[redacted]		USP and Ph. Eur.
Polysorbate 20			NF and Ph. Eur.
Water for Injection	[redacted]		USP and Ph. Eur.

[a] Target fill volume of [redacted] per vial.

(Lucentis Medical Review at MYL-AFL0007091 (emphasis added)).

16. **June 30, 2006.** Also, in the Drug Approval Package and accompanying the product sold as of June 30, 2006, is the package insert for LUCENTIS®. The approved label includes a disclosure of the formulation showing that LUCENTIS® contains 0.01% polysorbate 20.

> LUCENTIS is a sterile, colorless to pale yellow solution in a single-use glass vial. LUCENTIS is supplied as a preservative-free, sterile solution in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL LUCENTIS aqueous solution with 10 mM histidine HCl, 10% α, α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5.

(Lucentis PI 2006 at MYL-AFL0092514 (emphasis added); *see also* DX.727, RGN-EYLEA-MYLAN-00573029).

17. **May 2016.** The EMA released an assessment report based on a completed study that included using LUCENTIS® in paediatric patients with visual impairment due to VEGF driven macular edema (ME). The pharmaceutical formulation was described as including polysorbate 20 at 0.01% w/v and stated that the function of the polysorbate 20 was a "surfactant to minimize the risk of aggregation."

1.2. Information on the pharmaceutical formulation used in the study

Lucentis 10 mg/ml ranibizumab solution for injection as the currently marketed formulation in the EU has been used. The formulation contains:

- Trehalose 10% (w/v) (provides an isotonic solution) for the intravitreal injection of ranibizumab.
- Histidine HCl 10 mM (buffer)
- Polysorbate 20, 0.01% w/v (surfactant to minimize the risk of aggregation).

During review of PIP [EMEA-000527-PIP03-13], the formulation working group concluded that "the formulation is already optimized so there is no concern for its intravitreal injection to the pediatric population."

(EMA Lucentis Assessment Report at MYL-AFL0095486 (emphasis added)).

VII. EYLEA®.

18. In the development history of the EYLEA® product, Regeneron consistently identifies the function of the polysorbate 20 in the formulation as a "stabilizer."

Formulation: 10 mM Phosphate
40 mM NaCl
0.03% Polysorbate 20
5% Sucrose
40 mg/mL VEGF Trap
pH 6.25

****Insert material names in the chart in the appropriate order of addition.****

Order of Addition	Material Name	Grade	Formula Weight	Vendor	Mixing Duration	Composition in g/l	Function
1	WFI	-	-	-	-	-	Solvent
2	Phosphate, monobasic, monohydrate	USP	137.99	JT Baker	TBD	0.800	Buffer (See note #1 below)
3	Phosphate, dibasic, 7-hydrate	USP	268.07	JT Baker	TBD	1.126	Buffer (See note #1 below)
4	NaCl	USP	58.44	JT Baker	TBD	2.338	Salt
5	Sucrose	NF/EP	342.30	Ferro Pfanstiehl	TBD	50	Stabilizer
6	10% Polysorbate 20	NF			TBD	3.0	Stabilizer
7	VEGF Trap	-	-	-	TBD	40	Drug
8	WFI	-	-	-	-	-	Solvent

(DX.722, Eylea Product Composition (March 21, 2006) at RGN-EYLEA-MYLAN-00559099

(emphasis added)).

19. More examples are shown below:

Formulation: 10 mM Phosphate
135 mM NaCl
0.03% Polysorbate 20
pH 6.3

Order of Addition	Material Name	Grade	Formula Weight	Vendor	Mixing Duration	Composition in g/L	Function
1	WFI	-	-	-	-	-	Solvent
2	Phosphate, monobasic, monohydrate	USP	137.99	JT Baker	TBD	1.007	Buffer (See note #1 below)
3	Phosphate, dibasic, 7-hydrate	USP	268.07	JT Baker	TBD	0.724	Buffer (See note #1 below)
4	NaCl	USP	58.44	JT Baker	TBD	7.889	Salt (See note #1 below)
5	10% Polysorbate 20	NF			TBD	3.0	Stabilizer
6	WFI	-	-	-	-	-	Solvent

(DX.736, Placebo and 40 mg/mL VEGF Trap ITV Formulations at RGN-EYLEA-MYLAN-00580794 (emphasis added)); and

Formulation: 10 mM Phosphate
135 mM NaCl
0.03% Polysorbate 20
40 mg/mL VEGF Trap
pH 6.3

Order of Addition	Material Name	Grade	Formula Weight	Vendor	Mixing Duration	Composition in g/L	Function
1	WFI	-	-	-	-	-	Solvent
2	Phosphate, monobasic, monohydrate	USP	137.99	JT Baker	TBD	0.552	Buffer (See note #1 below)
3	Phosphate, dibasic, 7-hydrate	USP	268.07	JT Baker	TBD	1.608	Buffer (See note #1 below)
4	NaCl	USP	58.44	JT Baker	TBD	7.889	Salt (See note #1 below)
5	10% Polysorbate 20	NF			TBD	3.0	Stabilizer
6	VEGF Trap	-	-	-	TBD	40	Drug
7	WFI	-	-	-	-	-	Solvent

(*Id.* at RGN-EYLEA-MYLAN-00580792 (emphasis added)).

20. Further, in Regeneron's filings with the United States Food and Drug Administration ("FDA") during the approval process for EYLEA®, Regeneron describes the function of the polysorbate 20 as a "stabilizing agent."

Table 1: Nominal Composition of VEGF Trap-Eye DP, 40 mg/mL Formulation

Ingredient	Function	Reference to Quality Standard	40 mg/mL DP	
			DP Concentration	Quantity per Unit (0.278 mL)
VEGF Trap-Eye	Active ingredient	Regeneron	40 mg/mL	11.1 mg
Sodium Phosphate, Monobasic, Monohydrate	Buffering agent	USP, BP	1.104 mg/mL[a]	0.307 mg
Sodium Phosphate, Dibasic, Heptahydrate	Buffering agent	USP	0.537 mg/mL	0.149 mg
Sodium Chloride	Tonicity agent	USP, Ph. Eur., JP	2.338 mg/mL	0.650 mg
Sucrose	Stabilizing agent	NF, Ph. Eur., JP	50 mg/mL	13.900 mg
Polysorbate 20	Stabilizing agent	NF, Ph. Eur., JPE	0.3 mg/mL	0.083 mg
Water for Injection	Solvent	USP, Ph. Eur.	Quantity sufficient	Quantity sufficient

BP, British Pharmacopeia; JP, Japanese Pharmacopeia; JPE, Japanese Pharmaceutical Excipients; NF, National Formulary; Ph. Eur., European Pharmacopeia; USP, United States Pharmacopeia

(BLA No. 125387, 3.2.P Drug Product at RGN-EYLEA-MYLAN-00295199 (emphasis added); BLA No. 125387, 3.2.P Drug Product, JHP at RGN-EYLEA-MYLAN-00077045 (same); BLA No. 125387, 3.2.P Drug Product, Vetter at RGN-EYLEA-MYLAN-00076829 (same)).

21. Regeneron further described the function of the "stabilizing agent" polysorbate 20 in the EYLEA® formulation as "reduc[ing] the rate of aggregation and precipitation when the protein is handled, and agitated as a liquid." (BLA No. 125387, 3.2.P Drug Product at RGN-EYLEA-MYLAN-00295200; BLA No. 125387, 3.2.P Drug Product, JHP at RGN-EYLEA-MYLAN-00077046 (same); BLA No. 125387, 3.2.P Drug Product, Vetter at RGN-EYLEA-MYLAN-00076830 (same); *see also* M710 BLA, 3.2.P.2.2 Drug Product at MYL-AFL-BLA0002905 ("[F]ormulation that did not contain polysorbate 20 showed an extra peak by DLS,

which indicated possible aggregation in the M710 formulation without polysorbate 20.")).

22. For the early clinical studies, Regeneron used an aflibercept formulation that did not contain polysorbate 20. Referred to as ITV-1, the formulations used in phase I and phase II contained 135 mM sodium chloride, 0.1% polyethylene glycol (PEG) 3350, and lacked sucrose.

> **2.2.1. Formulation Development**
>
> VEGF Trap-Eye, examined in initial pre-clinical safety studies that assessed effects of intravitreal (IVT) administration on local and systemic toxicities in non-human primates (Module 2.6.6 Toxicology Written Summary), utilized a liquid formulation consisting of an aqueous vehicle of 10 mM sodium phosphate, 135 mM sodium chloride, and 0.1% polyethylene glycol (PEG) 3350 (pH 6.3) containing 5, 10, 20, or 40 mg/mL concentrations of VEGF Trap-Eye. This formulation, designated as ITV-1, was also used in Phase 1 and Phase 2 clinical studies performed during early clinical development (Module 2.7.1 and Module 2.7.2).

(BLA No. 125387, 3.2.P Drug Product at RGN-EYLEA-MYLAN-00295201 (emphasis added)). According to Regeneron, an "improved formulation" ("ITV-2") was developed where the polysorbate 20 was added to improve "the resistance to agitation-induced particle formation of VEGF Trap-Eye."

> An improved formulation of VEGF Trap-Eye (ITV-2) was subsequently developed to increase thermal stability and enhance stability to agitation stress. This formulation consisted of an aqueous vehicle of 10 mM sodium phosphate, 5% sucrose, 40 mM sodium chloride, and 0.03% polysorbate 20 (pH 6.2). The addition of sucrose and polysorbate 20 in this formulation improved both the thermal stability and the resistance to agitation-induced particle formation of VEGF Trap-Eye, respectively. To maintain iso-tonicity the sodium chloride concentration in the ITV-2 formulation was reduced relative to that of the ITV-1 formulation. The role of each excipient in the ITV-2 formulation is summarized in Table 2.

(*Id.* (emphasis added)). A comparison of the ITV-1 and ITV-2 formulations is shown below:

Table 3: Summary of DP Formulations used in Clinical Trials

Component	DP Formulation Composition	
	ITV-1	ITV-2
Aflibercept	5, 10, 20, 40 mg/mL	10 and 40 mg/mL
Sodium Phosphate, Monobasic, Monohydrate	10 mM Sodium phosphate	10 mM Sodium phosphate
Sodium Phosphate, Dibasic, Heptahydrate		
Sodium Chloride	135 mM	40 mM
Sucrose	None	5 % (w/v)
Polyethylene Glycol 3350	0.1 % (w/v)	None
Polysorbate 20	None	0.03% (w/v)
Water for Injection	Quantity sufficient	Quantity sufficient

(*Id.* (emphasis added)).

23. A detailed breakdown of the ITV-1, ITV-2, intravenous ("IV"), and subcutaneous ("SC") formulations is shown below.

Table 3: Comparison of Formulations by Ingredients

Ingredients	ITV-1	ITV-2	IV	SC
Sodium phosphate	10 mM	10 mM	5 mM	NA[a]
Sodium chloride	135 mM	40 mM	100 mM	NA
Citrate	NA	NA	5 mM	NA
PEG 3350	1% (w/v)	NA	NA	3% (w/v)
Polysorbate 20	NA	0.03% (w/v)	0.1% (w/v)	NA
Sucrose	NA	5% (w/v)	20% (w/v)	5% (w/v)
Histidine	NA	NA	NA	20 mM
Glycine	NA	NA	NA	1.5% (w/v)
pH	6.3	6.2	6.0	6.3

[a] NA: Not applicable, not part of formulation

(2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods at RGN-EYLEA-MYLAN-00057262). The development of the ITV-2 formulation was described as improving "stability to heat and shear compared to the previous ITV-1 formulation."

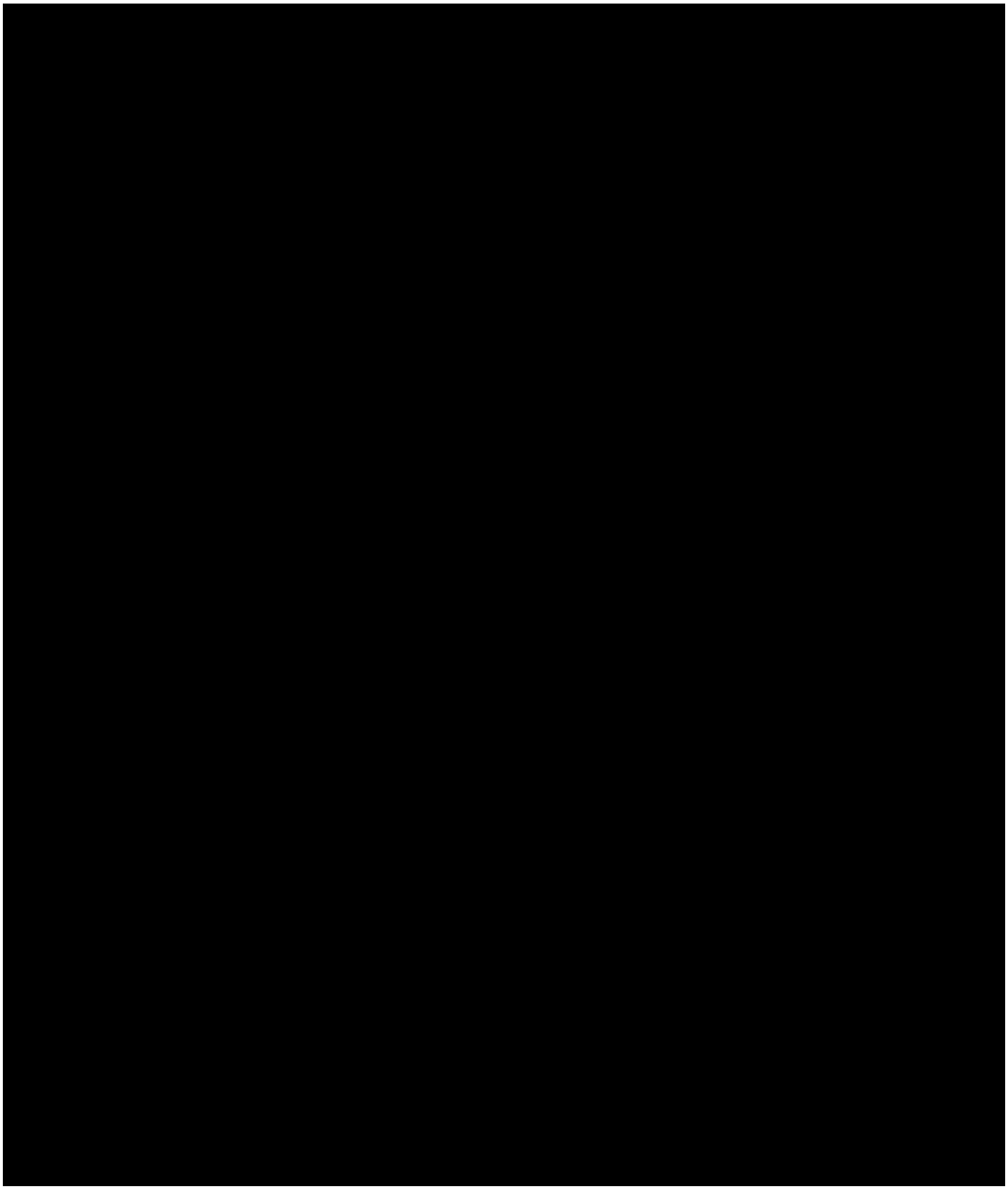
> The initial development formulation for IVT administration (ITV-1) contained 5, 10, 20 or 40 mg/mL VEGF Trap in an aqueous solution of 10 mM sodium phosphate, 135 mM sodium chloride, 0.1% (w/v) polyethylene glycol 3350, adjusted to pH 6.3 (Table 3). Subsequently, an improved ITV-2 commercial formulation was developed which had improved stability to heat and shear compared to the previous ITV-1 formulation (Module 3.2.P.5.4). The ITV-2 formulation contains 10, 40 or 80 mg/mL VEGF Trap concentrations in an aqueous, buffered iso-osmotic solution of 5% (w/v) sucrose, 10 mM sodium phosphate, 0.03% (w/v) polysorbate 20 and 40 mM NaCl (pH 6.2). In a stressed stability study conducted in glass vials stored for 28 days at 37°C, the ITV-2 formulation showed only a 7.5 % decrease in purity, as measured by size exclusion HPLC, compared with a 20.6% decrease in purity of the ITV-1 formulation stored under the same conditions (Module 3.2.P.2.2). VEGF Trap-Eye in both the ITV-1 and ITV-2 formulations have both been shown to be stable after storage for up to 6 hours in a tuberculin syringe and delivery through a 30-guage needle (Module 3.2.P.5.4).

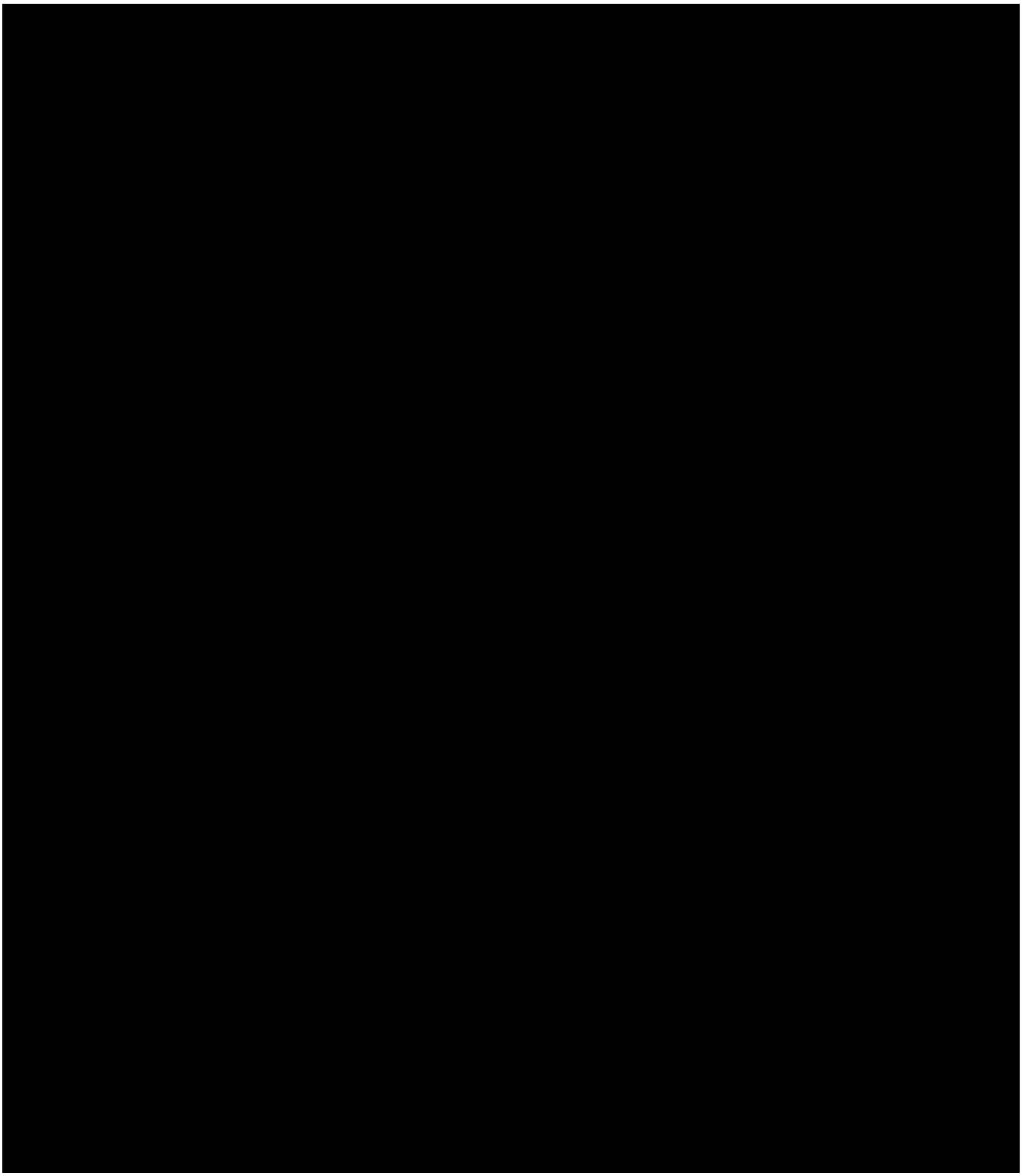
(*Id.* (emphasis added)).

[redacted]

[redacted]

[redacted]





IX. PERSON OF ORDINARY SKILL IN THE ART

A. U.S. Patent No. 11,084,865 ("The '865 patent").

29. My definition of a person of ordinary skill in the art has not changed since my declaration and opening reports. (*See* MacMichael Declaration ¶¶ 34-38; MacMichael Opening Reports ¶¶ 37-41).

30. I understand that Dr. Trout provided the following definition for a person of

ordinary skill in the art for the Asserted Claims of the '865 patent:

> In my opinion, based on my review of the '865 patent, its prosecution history, and my research experience, the POSA would have held an advanced degree, such as a Master's in a biopharmaceutical science, or a related discipline, such as chemical engineering, and several years of experience in the development of biologics products. Alternatively, the POSA could have a Ph.D. in such discipline and less experience. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases.

(Trout Report at ¶ 32).

31. In my opinion, there are no appreciable differences between the definition that I offered in my opening reports and Dr. Trout's definition, though, in my opinion, it is easier for someone to meet Dr. Trout's definitional standards as compared to mine in the context of education status and level of experience. Nevertheless, I qualify as at least a person of ordinary skill in the art under either definition and I am qualified to testify from the perspective of a person of ordinary skill in the art under either definition. Further, my opinions regarding the '865 patent would not change even if one were to apply Dr. Trout's definition.

B. U.S. Patent No. 11,253,572 ("The '572 patent").

32. I understand that Dr. Trout provided his opinions "from the perspective of" the following, purported "[person of ordinary skill in the art]" of the '572 patent:

> [T]he POSA would have an advanced degree, such as a Master's in a biopharmaceutical science, or a related discipline, such as chemical engineering, and several years of experience in the development of biologics products. Alternatively, the POSA could have a Ph.D. in such discipline and less experience. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases.

(Trout Report at ¶ 33).

33. It is also my understanding that Regeneron has offered several other definitions for a person or ordinary skill in the art of the '572 patent. Specifically, I have been informed of the

following, which I have listed in the chronological order that they were presented:

- **2022-Feb-10:** Regeneron and its expert witness, Dr. Diana Do, offered the following definition for a person of ordinary skill in the art of the '338 patent, which I understand is a parent of the '572 patent, and shares the same specification:

> [T]he skilled artisan is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists. In the event that Mylan argues that the skilled artisan need not be a licensed physician (ophthalmologist), whatever other qualification they must possess, I disagree because ***only an ophthalmologist*** would have the firsthand experience of diagnosing and treating angiogenic eye disorders to which the patent is plainly directed.

(IPR2021-00881 (U.S. Patent No. 9,254,338), Ex.2051 at ¶ 28 (emphasis added));

- **2022-Oct-13:** Regeneron did not dispute the following Mylan definition for a person of ordinary skill in the art of U.S. Patent No. 10,888,601 ("the '601 patent") and U.S. Patent No. 10,130,681 ("the '681 patent"), which I understand are parents of the '572 patent, and share the same specification:

> A [person of ordinary skill in the art] would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

(*See* IPR2022-01226 (U.S. Patent No. 10,888,601), Paper 13; IPR2022-01225 (U.S. Patent No. 10,130,681), Paper 14) (definition in IPR2022-01226 (U.S. Patent No. 10,888,601), Paper 2 at 25-26; IPR2022-01225 (U.S. Patent No. 10,130,681), Paper 2 at 28-29); and

- **2023-Feb-2:** Regeneron and its expert witness, Dr. Karl Csaky, offered the following

definition for a person of ordinary skill in the art of the '572 patent:

> [T]he POSA relevant to the Yancopoulos patents [which includes the 572 patent] is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists, and would have access to individuals with experience with intravitreal injection formulations.

(Csaky Report at ¶ 60).

34. It is also my understanding that the Patent Trial and Appeal Board ("PTAB") for the United States Patent and Trademark Office ("PTO") adopted Mylan's definition of the person for ordinary skill in the art as "reasonable and consistent with the '338 patent and the prior art." (IPR2021-00881 (U.S. Patent No. 9,254,338), Paper 21 at 15-16). That definition reads as follows:

> A [person of ordinary skill in the art] would have [:] (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

(*Id*. at 15). I understand that the PTAB also adopted this definition in IPR2022-01226 and IPR2022-01225 regarding the '601 and '681 patents, respectively. (*See* 601 Institution Decision: Dkt. No. 254-2 at 15-16; 681 Institution Decision: Dkt. No. 254-1 at 20-21).

35. In my opinion, the "perspective" Dr. Trout applied to forming his opinions regarding the '572 patent is not consistent with the education and experience for the person of ordinary skill in the art that Regeneron and the PTAB have respectively applied to the parent patents of the '572 patent. Dr. Trout's perspective is also inconsistent with Dr. Csaky's definition of a person of ordinary skill in the art for the '572 patent. Nevertheless, I qualify as at least a

person of ordinary skill in the art under Dr. Trout's definition. Further, my opinions regarding the '572 patent would not change even if one were to apply Dr. Trout's definition.

X. ANALYSIS.

36. The Asserted Claims of the '865 patent recite as follows (along with certain unasserted claims from which an asserted claim depends):[2]

Claim 1 [UNASSERTED]	A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises: a vascular endothelial growth factor (VEGF) antagonist an organic co-solvent, a buffer, and a stabilizing agent, wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.
Claim 2 [UNASSERTED]	The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.
Claim 4	The vial of **claim 2**, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.
Claim 5 [UNASSERTED]	The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.
Claim 7	The vial of **claim 5**, wherein said buffer comprises 5-25 mM buffer.
Claim 9	The vial of **claim 5**, wherein said buffer comprises a pH about 6.2-6.3.
Claim 10 [UNASSERTED]	The vial of claim 5, wherein said stabilizing agent comprises a sugar.
Claim 11	The vial of **claim 10**, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.
Claim 14	The vial of **claim 5**, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine

[2] As stated in the MacMichael Opening Reports, I understand that Regeneron is currently asserting claims 4, 7, 9, 11, and 14-18 (i.e., the "Asserted Claims").

	residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.
Claim 15	The vial of **claim 5**, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.
Claim 16	The vial of **claim 5**, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.
Claim 17	The vial of **claim 5**, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.
Claim 18	The vial of **claim 5**, wherein said formulation does not contain phosphate.

('865 patent at claims 1-2, 4-5, 7, 9-11, 14-18).

37. I understand the parties' respective claim construction proposals for the claim terms "organic co-solvent" and "[present in] native conformation" are as follows:

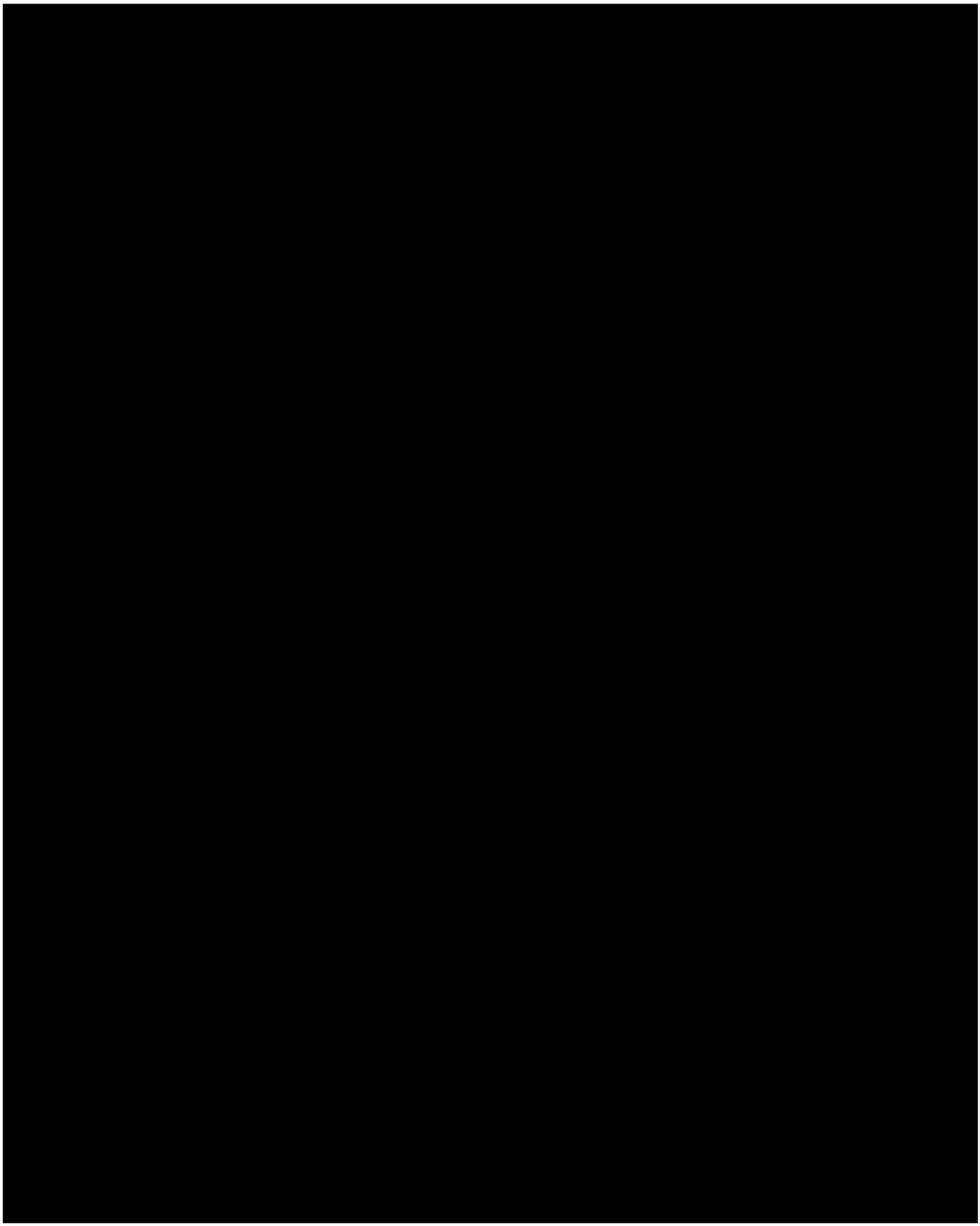
Claim Term	Regeneron's Claim Construction Proposal	Mylan's Proposed Construction
"organic co-solvent"	Plain and ordinary meaning in view of the claims and specification; to the extent there is a dispute as to claim scope, "organic co-solvent" includes polysorbate 20, polysorbate 80, polyethylene glycol, or propylene glycol, or a combination thereof	Plain and ordinary meaning: *an organic substance added to a primary solvent to increase the solubility of said VEGF antagonist*
"[present in] native conformation"	This term does not need to be construed outside of the context of the limitations in which it appears (e.g., "wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography."). Within that context, it should be given its plain and ordinary meaning in view of the claims and the specification	Plain and ordinary meaning: *[present in] a form that does not exhibit chemical or physical instability*

(Joint Claim Construction Chart: Dkt. No. 102 at 9-10).

A. ORGANIC CO-SOLVENT.

1. Mylan's Proposed Construction: Dr. Trout's opinions (¶¶ 76-83) do not prove that Mylan's M710 BLA Product comprises an "organic co-solvent."

[redacted]



[redacted]

b. *The terms surfactants and "co-solvents" are not interchangeable.*

42. The function that an ingredient plays in a formulation is important. Accordingly, as I previously explained, polysorbates may, *in some circumstances*, qualify as a co-solvent. (*See, e.g.*, MacMichael Tr. at 129:11 – 130:1 ("[Polys]orbate would have to be added at a sufficiently high concentration to be able to behave as a co-solvent.")).[5] The POSA would understand that the terms surfactants and "co-solvents" are not interchangeable. A co-solvent is a pharmaceutical excipient used in conjunction with a primary solvent to dissolve a drug substance in preparing a solution. (*See* MacMichael Declaration at ¶ 53). This solvent/co-solvent definition is repeated

[4] As I testified at deposition, "[a] co-solvent, by definition, changes the overall behavior of the [] combined mixtures of the two solvents." (MacMichael Tr. at 56:3-5; ; *see also id.* at 108:10-13 ("[I]n the case of an organic co-solvent, it's a substance added at sufficient volume to change the overall physical chemistry of the primary solvent."); *id.* at 81:2-4, 105:20-106:2).

[5] I understand Mylan asserted the same in its claim construction briefing. (*See* Dkt. No. 173-1 (Mylan Response) at 7 ("Mylan does not dispute that in some circumstances, polysorbates 'may be' (and conversely, may *not* be) co-solvents—which is *exactly* how the claims and specification describe the use of polysorbates.")).

throughout the scientific literature.[6] Surfactants (e.g., polysorbate 20), however, are "[s]ubstances that absorb to surfaces or interfaces to reduce surface or interfacial tension." (Ansel at MYL-AFL0095481).[7]

43. Furthermore, the POSA would recognize that the '865 patent specification repeatedly qualifies its polysorbate descriptions. For example, in column 2, the specification states that "the organic co-solvent ***may be*** polysorbate … polyethylene glycol … or a combination thereof," not "is" or "must include" one or more of these ingredients. ('865 patent at 2:39-42) (emphasis added). Similarly, when column 2 states that the "organic co-solvent is polysorbate and/or PEG," and gives examples of preferred formulations, the immediately preceding text qualifies all of them as reflective of "various ***embodiments***." (*Id*. 2:49-50 (emphasis added)). This is also true for the formulations described as "specific preferred embodiment[s]" or "examples." (*Id*. at 3:1-10; *see also id*. at 3:28-31 ("In another ***embodiment***, the organic co-solvent is selected from one or more of polysorbate…) (emphasis added); *see generally* cols. 3-4, describing formulations with polysorbate as embodiments); 7:2-5 ("An ***example*** of a pharmaceutically acceptable liquid formulation comprises … an organic co-solvent ***such as*** polysorbate …") (emphasis added)).

44. The '865 patent claims also avoid any absolute definitions. For example, the claims also state "wherein said organic co-solvent ***comprises*** polysorbate." (*Id*. 19:41-43 (Claim 2); *see also id*. 19:44-50 (Claims 3-5)). Regeneron's consistently qualified use of the terms "co-solvent"

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[6] *See, e.g.*, Akers at MYL-AFL0095456 ("Water-miscible cosolvents operate on the principle of lowering the dielectric constant property of water, thereby increasing the aqueous solubility.").

[7] *See also* Akers at MYL-AFL0095456 ("Surface active agents increase the dispersability and ***water solubility of poorly soluble drugs*** owing to their unique chemical properties of possessing both hydrophilic and hydrophobic functional groups in the same molecule.") (emphasis added)).

and "polysorbate" informs the POSA that the named inventors of the '865 patent do not consider the terms interchangeable.

c. *Dr. Trout's infringement opinion relies on a flawed assumption.*

45. Dr. Trout's opinion that "[p]olysorbate 20 also 'increase[s] the solubility of said VEGF antagonist' according to Mylan's proposed construction," assumes that "inhibiting the formation of insoluble aggregates" equates to "increasing the solubility of aflibercept." (Trout Report at ¶ 79). I disagree with Dr. Trout's opinion and underlying assumption.

46. Dr. Trout sidesteps what a POSA understands to be a "co-solvent"—i.e., the term's actual plain and ordinary meaning. As I explained in my Declaration (¶¶ 52-55), an "organic co-solvent" (in the claims of the '865 patent) is an organic substance that is added to increase the solubility of the VEGF antagonist, i.e., aflibercept. (*See also* MacMichael Tr. at 56:3-5; *id*. at 81:2-4, 105:20-106:2, 108:10-13). A POSA would understand that the term "organic co-solvent" in the Asserted Claims conveys that the substance in question is indeed acting as a ***solvent*** and (as a co-solvent) working in conjunction with a primary solvent (e.g., water) to increase the solubility of the VEGF antagonist drug substance (i.e., aflibercept). (*See, e.g.*, MacMichael Tr. at 127:5-13 ("An organic co-solvent is something added at sufficient quantity to change the overall physiochemistry of the aqueous environment [i.e., primary solvent]. By changing the overall environment, one could improve solubility of proteins.")). Dr. Trout does not establish this.

47. Dr. Trout instead cites to Randolph to get around the plain and ordinary meaning of "organic co-solvent" (as set forth in Mylan's Proposed Construction). In place of evidence from Mylan's M710 BLA, Dr. Trout relies on Randolph's statement that the formation of a protein-surfactant complex "***effectively*** increases the solubility of the complex." (Trout Report at ¶ 79 (emphasis added)). I disagree with Dr. Trout's reliance on Randolph. An "***effective[]*** increase" in solubility is not the function of a co-solvent. A co-solvent actually increases the solubility of a

drug substance by (as I previously testified) changing the physiochemistry of the primary solvent. (*See* MacMichael Tr. at 108:16-20, 55:9 – 56:8, 80:19 – 81:10, 95:6-22, 105:16 – 106:14, 107:13 – 108:13, 115:9-14, 125:11 – 126:6; *see also* Akers at MYL-AFL0095461 (explaining that liquid cosolvents "act by reducing the dielectric constant properties of the solvent system")).

48. Dr. Trout asserts that "[s]urfactants like polysorbate accomplish an increase in solubility through what is known as a 'hydrophobicity reversal.'" (Trout Report at ¶ 79). Dr. Trout relies on Randolph for this premise: "As Randolph and Jones explained, '[t]he hydrophobic portion of non-ionic surfactants can bind to ***hydrophobic patches on proteins***. This naturally causes the surfactant to order itself so that more hydrophilic groups are solvent exposed, resulting in a 'hydrophobicity reversal'." (*Id.* (emphasis added)). Dr. Trout then concludes that "[t]he consequence of this interaction is that 'the protein-surfactant complex is more hydrophilic tha[n] either the surfactant or protein alone, and effectively increases the solubility of the complex' and 'reduce[s] the propensity of the protein to form higher-order aggregates.'" (*Id*. (quoting Randolph at 168)). While Dr. Trout correctly quotes Randolph, his application of Randolph's teachings to the '865 patent suffers from a fatal flaw: *aflibercept is highly soluble in water alone*. (*See* Aflibercept MSDS at MYL-AFL0095452 ("Solubility in water at 25 °C: > 100 mg/mL"); *see also* Graham Tr. at 195:19-196:15 ("[W]e start off with a liquid drug substance or a drug substance in a liquid form, and we add the excipients, which includes the polysorbate in a liquid form.")). Accordingly, there is no evidence (and Dr. Trout provides no relevant opinion) that aflibercept (i.e., the VEGF antagonist *required* under the Asserted Claims) actually has "hydrophobic patches" that would render it prone to hydrophobic aggregation or that such protein-surfactant complexes are even present much less have increased solubility.

[redacted]

[redacted]

50. For the reasons provided above, it is my opinion that Dr. Trout has failed to show that Mylan's M710 BLA Product infringes either claim 1 or any of the Asserted Claims of the '865 patent under Mylan's Proposed Construction of the claim term "organic co-solvent." [redacted]

[redacted]

[redacted]

2. Regeneron's Claim Construction Proposal: Dr. Trout's opinions (¶¶ 71-75) do not prove that Mylan's M710 BLA Product comprises an "organic co-solvent."

a. *Regeneron's proposal is neither a "construction" nor the term's "plain and ordinary meaning."*

51. Dr. Trout argues that "[u]nder Regeneron's construction, the term 'organic co-solvent' is given its plain and ordinary meaning in view of the claims and specification." (Trout Report at ¶ 71). I strongly disagree with this statement. As an initial matter, it is my understanding that neither Dr. Trout nor any other Regeneron expert offered any opinions to rebut my testimony regarding the proper plain and ordinary meaning of "organic co-solvent" (in view of the intrinsic evidence to the '865 patent) during the claim construction phase of this matter. Dr. Trout, therefore, has provided no basis for his apparent conclusion that Regeneron's proposal captures the claim term's plain and ordinary meaning. Moreover, Dr. Trout does not state *what* "plain and ordinary meaning" he used to reach his conclusions. For this reason alone, I disagree that Dr. Trout's analysis demonstrates that Mylan's M710 BLA Product comprises an "organic co-solvent."

52. As I set forth in my expert declaration provided in support of Mylan's opening claim construction brief (MacMichael Declaration at ¶¶ 62-64), I do not interpret Regeneron's proposal as either a "construction" or a "plain and ordinary meaning" of the claim term "organic co-solvent." Instead, Regeneron's proposal—which reads as follows—only provides a limited list of materials that "organic co-solvent" purportedly "includes": *"Plain and ordinary meaning in view of the claims and specification; to the extent there is a dispute as to claim scope, 'organic co-*

solvent' includes polysorbate 20, polysorbate 80, polyethylene glycol, or propylene glycol, or a combination thereof." (*See id.* at ¶ 62 (emphasis added)). This is not a construction (or definition) of the claim term.

b. *Dr. Trout tethers his infringement opinions to Regeneron's flawed interpretation of the '865 patent specification.*

53. Dr. Trout states that *Regeneron's counsel told him* that "polysorbate 20 ***is*** an organic co-solvent ***because*** the specification and the claims of the '865 patent ***confirm repeatedly*** that polysorbate 20 is an organic co-solvent." (Trout Report at ¶ 71 (emphasis added)).[9] I disagree with Regeneron's interpretation of the '865 patent specification. The '865 patent does not "confirm" (much less "repeatedly" confirm) that polysorbate 20—i.e., in all instances, at any amount or concentration—"is" an "organic co-solvent." Instead, the '865 patent specification repeatedly confirms that polysorbate ***may be*** (and thus also may not be) an organic co-solvent. This is evidenced by the qualifiers consistently used throughout the '865 patent specification and claims when describing polysorbate-containing embodiments, for example:

- "In one or more specific embodiments, the organic co-solvent ***may be*** polysorbate, for example, polysorbate 20 …" ('865 patent at 2:39-42 (emphasis added)); and
- "In ***various embodiments***, the organic co-solvent is polysorbate and/or PEG …" (*id.* at 2:49-50 (emphasis added)).

[9] I find it important to point out an additional contradiction in Dr. Trout's opinions. Specifically, to reach his conclusions regarding infringement of the '865 patent Asserted Claims, Dr. Trout accepted Regeneron's representation to him that "polysorbate 20 is an organic co-solvent." However, in evaluating claims 7, 13, 19, and 23 of the '572 patent, Dr. Trout concludes that the exact same [redacted] is a "nonionic surfactant." (Trout Report ¶¶ 147-50). As I explain above, the terms "co-solvent" and "surfactant" are not interchangeable. (*See* ¶¶ 42-44 above). Dr. Trout makes no effort to explain why or how the [redacted] satisfies being *both* a co-solvent and a nonionic surfactant.

54. Likewise, and contrary to Regeneron's representation to Dr. Trout, the '865 patent claims do **not** state that polysorbate 20 ***is*** the organic co-solvent in the claimed formulation:

- "[Claim 2]: The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent ***comprises*** polysorbate." (*Id.* at 19:41-43 (emphasis added)); and
- "[Claim 4]: The vial of claim 2, wherein said organic co-solvent ***comprises*** about 0.03% to about 0.1% polysorbate 20." (*Id.* at 19:46-47 (emphasis added)).

55. Conversely, the Examples provide formulations using polysorbate but make zero mention of the disclosed formulations comprising an "organic co-solvent"; for example:

Example 1	Example 3
An ophthalmic liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 5% sucrose, and pH 6.25, was stored at 5° C. in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months.	A liquid formulation containing 40 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5° C. in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months.

(*Id.* at 8:32-41, 9:12-28).

56. In sum, the '865 patent does not confirm that polysorbate 20 is an organic co-solvent but only that polysorbate 20 may be the organic co-solvent in a particular formulation. In my opinion, Dr. Trout's reliance on Regeneron's flawed, unsupported interpretation of the '865 patent specification undermines the credibility of his opinions.

c. *Dr. Trout has not demonstrated that Mylan's M710 BLA Product comprises an "organic co-solvent."*

57. Setting aside Regeneron's flawed and unsupported interpretation of the '865 patent specification (and Dr. Trout's reliance thereon to form his opinions), I also disagree with Dr. Trout's conclusions and opinions. Specifically, in my opinion, Dr. Trout never actually applies Regeneron's Claim Construction Proposal (i.e., a so-called "plain and ordinary meaning") against the information provided in Mylan's M710 BLA. This is not surprising to me because, as I explain above, neither Regeneron nor Dr. Trout actually identify *what* their "plain and ordinary meaning" of "organic co-solvent" actually is. Instead, I read Dr. Trout's opinions as (1) Regeneron telling Dr. Trout to assume that "polysorbate 20 ***is*** an organic co-solvent," followed by (2) Dr. Trout identifying [redacted] and, based on Regeneron's instruction (Trout Report at ¶ 71), Dr. Trout jumping to the conclusion that Mylan's M710 BLA Product therefore meets the "organic co-solvent" element of the claims. I disagree that Dr. Trout's approach—which openly relies on Regeneron's interpretation of the '865 patent specification—confirms that Mylan's M710 BLA Product comprises an "organic co-solvent."

58. Specifically, the Asserted Claims require, among other things, "[a] vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises: [i] a vascular endothelial growth factor (VEGF) antagonist" and "[ii] an organic co-solvent." (*See* '865 patent at claim 1). Dr. Trout makes no effort to demonstrate that the [redacted] is "an organic co-solvent." Instead, Dr. Trout bases his entire opinion here on a BLA document where Mylan describes [redacted] (Trout Report at ¶ 73 [redacted]

59. In fact, Mylan *never* describes polysorbate 20 as an "organic co-solvent" in Mylan's

BLA Product, and Dr. Trout does not cite a single Mylan document supporting his re-characterization of Mylan's [redacted] as a "co-solvent." Regeneron's Claim Construction Proposal requires that the term "organic co-solvent" "[includes] polysorbate 20," but, more importantly, that the term ***retains*** its "plain and ordinary meaning in view of the claims and specification." (*See* Trout Report at ¶ 71). As I previously testified, polysorbate 20 may, in certain circumstances, act as a co-solvent. (*See, e.g.*, MacMichael Tr. at 129:11 – 130:1 ("[Polys]orbate would have to be added at a sufficiently high concentration to be able to behave as a co-solvent.")).[10]

60. However, under Regeneron's proposal—which invokes the plain and ordinary meaning of "organic co-solvent," a POSA would understand that the substance in question (e.g., polysorbate 20) ***must still function as a co-solvent***. Dr. Trout does not show that [redacted] is present in Mylan's formulation in the role of a co-solvent. Dr. Trout's only "support" for this opinion is [redacted] Nothing in that chart or in Mylan's BLA demonstrates that the [redacted] is present in the role of co-solvent. Instead, the document Dr. Trout relies upon expressly describes [redacted] (Trout Report at ¶ 73 [redacted].

61. In my opinion, Dr. Trout failed in paragraphs 71-75 of his report to show that Mylan's M710 BLA Product infringes either claim 1 or any of the Asserted Claims of the '865

[10] I understand Mylan asserted the same in its claim construction briefing. (*See* Dkt. No. 173-1 (Mylan Response) at 7 ("Mylan does not dispute that in some circumstances, polysorbates 'may be' (and conversely, may *not* be) co-solvents—which is *exactly* how the claims and specification describe the use of polysorbates.")).

patent under Regeneron's Claim Construction Proposal for the claim term "organic co-solvent."

3. Claim 2: "wherein said organic co-solvent comprises polysorbate."

62. Mylan's Construction. Claim 2 recites that "said organic co-solvent comprises polysorbate." As I explain above (¶¶ 38-50), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claim 1, from which claim 2 depends. Therefore, for the same reasons as described above for claim 1 (¶¶ 38-50), Mylan's M710 BLA Product does not meet the limitations of claim 2 (which also requires an "organic co-solvent") as well.

63. Regeneron's Claim Construction Proposal. Claim 2 recites that "said organic co-solvent comprises polysorbate." As I explain above (¶¶ 51-61), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claim 1, from which claim 2 depends. Therefore, for the same reasons as described above for claim 1 (¶¶ 51-61), Mylan's M710 BLA Product does not meet the limitations of claim 2 (which also requires an "organic co-solvent") as well.

4. Claim 4: "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20."

64. Mylan's Construction. Claim 4 recites that "said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." As explained above (¶¶ 38-50, 62), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claims 1 or 2, from which claim 4 depends. Therefore, for the same reasons as described above for claim 1 (¶¶ 38-50), Mylan's M710 BLA Product does not meet the limitations of claim 4 (which also requires an "organic co-solvent") as well.

65. Regeneron's Claim Construction Proposal. Claim 4 recites that "said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." As I explained above (¶¶ 51-61, 63), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claims 1 or 2, from which claim 4 depends. Therefore, for the same reasons as described above for claim 1

(¶¶ 51-61), Mylan's M710 BLA Product does not meet the limitations of claim 4 (which also requires an "organic co-solvent") as well.

5. Claims 5, 7, 9, 11, and 14-18: "wherein said organic cosolvent comprises 0.01% to 3% polysorbate 20."

66. Mylan's Construction. Claim 5 recites that "said organic co-solvent comprises 0.01% to 3% polysorbate 20." As I explained above (¶¶ 38-50, 62), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claims 1 or 2, from which claim 5 depends. Therefore, for the same reasons as described above for claim 1 (¶¶ 38-50), Mylan's M710 BLA Product does not meet the limitations of claim 5 (which also requires an "organic co-solvent") as well.

67. Regeneron's Claim Construction Proposal. Claim 5 recites that "said organic co-solvent comprises 0.01% to 3% polysorbate 20." As I explained above (¶¶ 51-61, 63), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claim 1 or 2, from which claim 5 depends. Therefore, for the same reasons as described above for claim 1 (¶¶ 51-61), Mylan's M710 BLA Product does not meet the limitations of claim 5 (which also requires an "organic co-solvent") as well.

68. Claims 7, 9, 11, and 14-18 all depend from claim 5. I have been informed that claims 7, 9, 11, and 14-18, therefore require the same "wherein said organic cosolvent comprises 0.01% to 3% polysorbate 20" element of claim 5. As I explained above (¶¶ 66-67), Mylan's M710 BLA Product does not meet the "organic co-solvent" limitation of claim 5 under either Mylan's Construction or Regeneron's Claim Construction Proposal, and therefore does not infringe claim 5. For the same reasons, it is my opinion that Mylan's M710 BLA Product does not meet the "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20" element of claims 7, 9, 11, and 14-18, and therefore, does not infringe claims 7, 9, 11, and 14-18.

B. NATIVE CONFORMATION.

1. <u>Mylan's Proposed Construction:</u> Dr. Trout's opinions (¶¶ 95-108) do not prove that "at least 98% of the VEGF antagonist" in Mylan's M710 BLA Product "is present in native conformation following storage at 5° C. for two months."

69. Dr. Trout argues that "native conformation" under Mylan's construction is somehow unclear. (Trout Report at ¶¶ 95-96). I disagree. As I explained in my Declaration (¶¶ 65-73), Mylan's Construction provides the full scope of the term's well-known, plain and ordinary meaning: "[present in] a form that does not exhibit chemical or physical instability." (*Id.*). In my opinion, a POSA is very familiar with this definition and there is nothing unclear about it.

70. Mylan's plain and ordinary meaning construction is also confirmed by the '865 patent, as well as Regeneron's counsel and expert, wherein the "native" protein is the original, intact, aflibercept fusion protein, standing alone as a single molecule. (*See* Markman Tr. at 29:13-18 ("So one of the things that you want this formulation to do is keep all of the single aflibercept molecules alone, separated from each other, not aggregated to each other. And that's what's going on in this part of the claim, that you have something present in the native conformation. That's the aflibercept by itself."); Graham Tr. at 46:11-14 ("The native form as determined by size exclusion chromatography is the intact molecule as an individual species."); *see also id.* at 46:18-25 ("VEGF Trap or aflibercept is comprised of two arms that come together. So the molecule is a dimer. So if you mean by a monomer or a native monomer, that dimer, then, yes."); 50:22-25 ("[I]f I have an aflibercept molecule, a native aflibercept molecule, and I take it through the purification process, the intent is not to change that molecule.…"); 55:17-18 ("if I'm missing a piece of the molecule, I don't have the native molecule")). Indeed, the '865 patent specification expressly states that proteins can degrade (i) **<u>chemically</u>**, through "deamination" reactions, "aggregation," by "clipping

of the peptide backbone," and by "oxidation of methionine residues" ('865 patent at 5:56-58); and (ii) **physically**, though "many phenomena, including, for example, aggregation and/or precipitation" (*id*. at 5:58:60). The POSA would understand that if aflibercept is chemically changed, it is no longer aflibercept, and, if it is aggregated or precipitated, it also will no longer be a single aflibercept molecule. Accordingly, a POSA understands that "native conformation" refers to more than just aggregation as Regeneron and Dr. Trout attempt. This is confirmed in the '865 patent specification.

71. The '865 patent specification discusses aggregation properties. For example, it describes and defines "substantially free of aggregates" to mean that "at least 90% of the weight of fusion protein is not present in an aggregate" at the time of formulation:

> most preferably at least 99%. The fusion protein is preferably substantially free of aggregates. "Substantially free of aggregates" means that at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation. Unless stated otherwise, the phosphates

('865 patent at 6:45-55 (also defining "substantially free of contaminants")). The Asserted Claims do not use the term "aggregate." Accordingly, the POSA would understand that the claim term "native conformation" must mean something broader and include more than just aggregation.

72. As I previously testified, a POSA also knows that aflibercept may be able to comply with the SEC test found in the claims without independently satisfying the "native conformation" standard. (MacMichael Dep. Tr. at 203:8 – 205:14; *see also* MacMichael Declaration at ¶¶ 67-71). For example, there may be oxidation or the loss of a sulfur or an amino group – these degradation products would not be evident in the SEC test. (*See* MacMichael Tr. at 203:8 – 205:14). Dr. Trout's analysis does not account for this scenario, further undermining the credibility of his opinions. Accordingly, I disagree that Dr. Trout has proven Mylan's M710 BLA

Product meets the "native conformation" limitation of the Asserted Claims.

73. Further, Regeneron never told the PTO that the term "native conformation" only includes one type of purity/stability when it added this term to the claim to secure allowance even though a POSA would know that size exclusion chromatography ("SEC") cannot show whether the aflibercept molecule is stable with respect to all of the chemical and physical degradation pathways discussed in the '865 patent specification. (*See*, *e.g.*, MacMichael Dep. Tr. at 203:8 – 205:14; *see also* MacMichael Declaration ¶¶ 66-70). Instead, Regeneron expressly told the PTO that the "native conformation" related to "stability," generally. (*See* Dkt. 146, Mylan's Exhibits to Opening Claim Construction Brief, Ex. 16 at RGN-EYLEA-MYLAN-00015158-63 (wherein Regeneron represented to the PTO Examiner that "native confirmation" "relat[es] to the ***stability*** of the protein conformation in storage over a period of time" and represented that this element was "not contained within any of the [prior art patent] claims") (emphasis added)). Accordingly, the PTO Examiner relied on Regeneron's representation, withdrawing the rejection and granting the patent based on the added stability limitation. (Dkt. 146, Mylan's Exhibits to Opening Claim Construction Brief, Ex. 15 at RGN-EYLEA-MYLAN-00015179). Dr. Trout nonetheless only cites to Mylan's SEC data to show that Mylan's M710 BLA Product infringes the Asserted Claims. (Trout Report at ¶¶ 91-93).

74. Dr. Trout also cites to other testing performed in Mylan's BLA to show that Mylan's M710 BLA Product infringes the claims. (Trout Report at ¶¶ 98-106). However, none of these tests is SEC and thus, in my opinion, Dr. Trout cannot show infringement according to the Asserted Claims, all of which require "measure by size exclusion chromatography."

75. As such, Dr. Trout, in his opening report (¶¶ 95-108), has failed to show that Mylan's M710 BLA Product infringes either claim 1 or any of the Asserted Claims of the '865

patent under Mylan's construction of the claim term "native conformation."

2. Regeneron's Claim Construction Proposal[11]: Dr. Trout's opinions (¶¶ 87-94) do not prove that "at least 98% of the VEGF antagonist" in Mylan's M710 BLA Product "is present in native conformation following storage at 5° C. for two months."

76. Dr. Trout argues that "native conformation" under Regeneron's Claim Construction Proposal does not consider all aspects of physical and chemical stability, but only the aspects of stability that are described in the specification and that may be measured by the specific technique required by the claims, i.e., size exclusion chromatography, a measure only of aggregation. (*See* Trout Report at ¶ 87). Although I agree with Dr. Trout's inherent concession that the full scope of "native conformation" encompasses aggregation, I disagree that his opinions prove Mylan's M710 BLA Product meets the "native conformation" element even under Regeneron's inappropriately narrow interpretation of that term.

77. In my opinion, the '865 patent considers all aspects of physical and chemical stability and therefore a POSA would afford "native conformation" the full scope of its plain and ordinary meaning (as I discuss above). As outlined above (¶¶ 10, 70), the POSA would understand that if aflibercept is chemically changed, it is no longer aflibercept, and, if it is aggregated or precipitated, it is no longer a single aflibercept molecule. Dr. Trout's sole focus on the state of protein aggregation, as his opinions show, goes against what the POSA would understand the more general "native conformation" term includes, i.e., it is tied to multiple stability considerations.

78. Dr. Trout's "stability" argument also conflicts with the prosecution history. Regeneron had claims that lacked the "native conformation" term, which the PTO rejected. (*See*

[11] As I explain in my Declaration at paragraph 72, Regeneron's Claim Construction Proposal is not a construction (or definition), and therefore, in my opinion, cannot "assign[] the proper scope and meaning to the patent claims asserted." (*See* Trout Report at ¶ 30). Accordingly, I disagree that Dr. Trout can form a credible opinion regarding infringement of the Asserted Claims.

Dkt. 146, Mylan's Exhibits to Opening Claim Construction Brief, Ex. 16 at RGN-EYLEA-MYLAN-00015158-63). To overcome the rejection, Regeneron added the language "and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C for two months as measured by size exclusion chromatography." (*Id*. at RGN-EYLEA-MYLAN-00015159). Regeneron represented this element as "relating to the ***stability*** of the protein conformation in storage over a period of time" and represented that this element was "not contained within any of the claims" of the prior art patent that served as the basis for the double-patenting rejection. (*Id*. at RGN-EYLEA-MYLAN-00015162). The PTO relied on this amendment to withdraw the rejection. (Dkt. 146, Mylan's Exhibits to Opening Claim Construction Brief, Ex. 15 at RGN-EYLEA-MYLAN-00015179). During prosecution, Regeneron also characterized the "present in native conformation" clause as relating to the general stability of the required protein, but now Dr. Trout says that the term does not involve general stability, rather only "purity"—more specifically, "purity" as measured by SEC. (Trout Report at ¶ 87-88). In my opinion, which is supported by the prosecution history, "native conformation" relates to the more generalized stability concepts.

79. Dr. Trout anchors his opinion that Mylan's M710 BLA Product meets the "native conformation" element of claim 1 (and the dependent Asserted Claims) of the '865 patent solely on Mylan's SEC testing. (Trout Report at ¶ 88). I disagree with Dr. Trout. As I previously testified (and as I discuss above), a POSA knows that SEC testing is only sufficient for differentiating between aggregated and non-aggregated protein. (*See*, *e.g.*, MacMichael Dep. Tr. at 203:8 – 205:14; *see also* MacMichael Declaration at ¶¶ 67-71). *The Asserted Claims however require the VEGF antagonist be in native conformation*, not merely non-aggregated.

80. As such, Dr. Trout (¶¶ 87-94) has failed to show that Mylan's M710 BLA Product

infringes the Asserted Claims of the '865 patent under Regeneron's Claim Construction Proposal for the claim term "native conformation."

3. Native Conformation – Claim 16.

81. Claim 16 depends from claim 5, which recites that "said organic co-solvent comprises 0.01% to 3% polysorbate 20." As I explained above (¶¶ 38-68), Dr. Trout's opinions do not prove that Mylan's M710 BLA Product meets this "organic co-solvent" limitation under either Mylan's Proposed Construction or Regeneron's Claim Construction Proposal. Claim 5 depends from claim 2, which depends from claim 1, and as described above for claim 1 (¶¶ 38-61), Mylan's M710 BLA Product does not meet the limitations of this claim either.

82. Claim 16 of the '865 patent further limits the formulation of claim 5 to "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." As I explained above (¶¶ 69-80), it is my opinion that Dr. Trout has failed to show that Mylan's M710 BLA Product is "[present in] native conformation" under either Mylan's Proposed Construction or Regeneron's Claim Construction Proposal. Accordingly, I disagree that Dr. Trout's opinions prove that Mylan's M710 BLA Product meets the "[present in] native conformation."

4. Native Conformation – Claim 17.

83. Claim 17 also depends from claim 5, which recites that "said organic co-solvent comprises 0.01% to 3% polysorbate 20." As I explained above (¶¶ 38-68), Dr. Trout's opinions do not prove that Mylan's M710 BLA Product meets this "organic co-solvent" limitation under either Mylan's Proposed Construction or Regeneron's Claim Construction Proposal. Claim 5 depends from claim 2, which depends from claim 1, and as described above for claim 1 (¶¶ 38-61), Mylan's M710 BLA Product does not meet the limitations of this claim either.

84. Claim 17 of the '865 patent further limits the formulation of claim 5 to "wherein at

least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." As I explained above (¶¶ 69-80), it is my opinion that Dr. Trout has failed to show that Mylan's M710 BLA Product is "[present in] native conformation" under either Mylan's Proposed Construction or Regeneron's Claim Construction Proposal. Accordingly, I disagree that Dr. Trout's opinions prove that Mylan's M710 BLA Product meets the "[present in] native conformation" limitation.

85. For the reasons explained above, it is my opinion that Dr. Trout has failed to show that Mylan's M710 BLA Product is "[present in] native conformation" under either Mylan's Proposed Construction or Regeneron's Claim Construction Proposal.

C. CLAIM 18: FORMULATION DOES NOT CONTAIN PHOSPHATE.

1. Dr. Trout's opinions (¶¶ 141-42) do not prove that Mylan's M710 BLA Product formulation "does not contain phosphate."

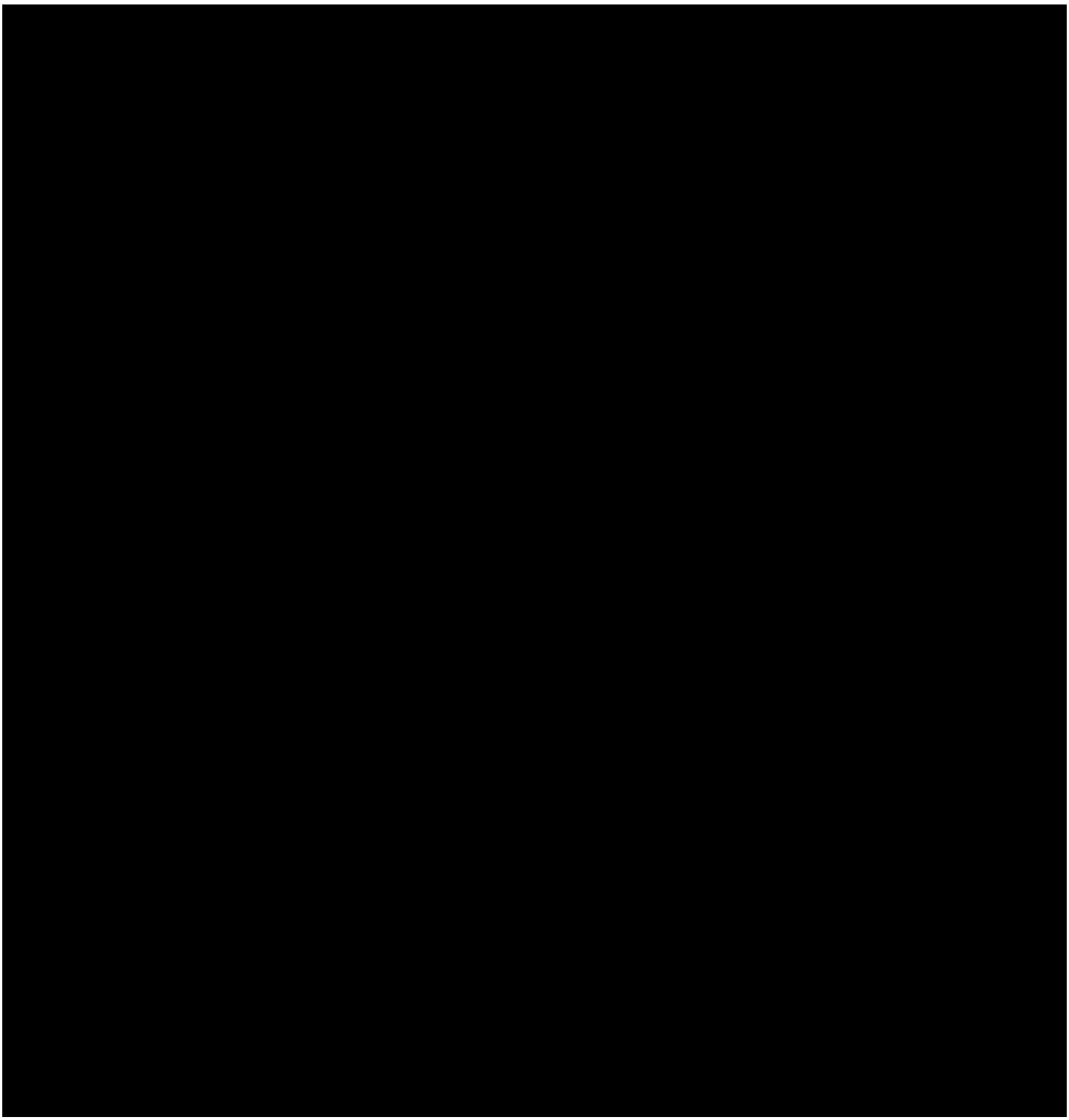
86. Dr. Trout's entire opinion regarding claim 18 is presented in only two short sentences of his 51-page expert report [redacted] (Trout Report at ¶ 142 (emphasis added)). Dr. Trout's abbreviated analysis ignores the full scope of claim 18's negative limitation, and therefore, I disagree that Dr. Trout's opinion proves Mylan's M710 BLA Product infringes Asserted Claim 18.

87. The '865 patent does not define the term "phosphate" and it is my understanding that Regeneron never asked the Court to construe the claim term "phosphate." Dr. Trout also does not provide a definition or proposed construction. In my opinion, a POSA would understand that "phosphate" in a pharmaceutical formulation is not limited to "***phosphate buffer***" as Dr. Trout suggests with his infringement opinion. Consistent with my opinion, "phosphate" and "phosphate buffer" are both separately used in the claims and the specification, which would further inform a

POSA that "phosphate" in claim 18 is broader than just a "phosphate buffer." For example, claim 6 (which depends from claim 5) requires that "***said buffer*** comprises a ***phosphate buffer***." ('865 patent at claim 6 (emphasis added)). Claim 31 uses the same language—specifically, "wherein ***said buffer*** comprises a ***phosphate buffer***." ('865 patent at claims 31 (emphasis added)). Claims 51 and 56 also use similar language—specifically referencing a "sodium ***phosphate buffer***." ('865 patent at claims 51 and 56 (emphasis added)).

88. Whereas, claim 18 (which also depends from claim 5) requires that "***said formulation*** does not contain phosphate." The "formulation" of claim 18 (which depends on claim 5, which depends on claim 2, which depends on claim 1) refers to the entirety of the "vial comprising an ophthalmic formulation suitable for intravitreal administration." ('865 patent at claim 1). Accordingly, Dr. Trout's focus on Mylan's M710 BLA Product formulation [redacted] is insufficient to determine whether Mylan's ***formulation*** contains phosphate. Likewise, Dr. Trout's blanket statement—without any supporting data or testing—that none of the other excipients in Mylan's M710 BLA Product include phosphate is also not sufficient to establish that Mylan's ***formulation*** does not contain phosphate, as required by claim 18.

89. Separately, Mylan's M710 BLA contradicts Dr. Trout's opinion. [redacted]



92. In my opinion, a POSA would not assume without testing (as Dr. Trout does) that Mylan's M710 BLA Product "does not contain phosphate" [redacted]

93. Further, Mylan's M710 BLA expressly identifies another acceptable source of phosphate [redacted]

[redacted]

94. In my opinion, a POSA would understand that there are many sources of phosphate in the manufacturing and purification process and without any data or testing of Mylan's M710 BLA Product for phosphate, there cannot be a credible determination that Mylan's M710 BLA Product "does not contain phosphate."

95. Claim 18 definitively requires that "said formulation does not contain phosphate." ('865 patent at claim 18). In my opinion, Dr. Trout's citation to Mylan's BLA [redacted] is

not sufficient to show that Mylan's M710 BLA Product "does not contain phosphate." (Trout Report at ¶ 84 [redacted] However, Dr. Trout has not shown (i.e., via testing) that Mylan's M710 BLA Product "does not contain phosphate."

96. As such, Dr. Trout has failed in paragraphs 141-42 of his opening report to show that Mylan's M710 BLA Product infringes claim 18 of the '865 patent.

XI. FUTURE OPINIONS.

97. This Report sets forth the opinions I have formed based on information available as of the date of this Report. Because other as yet unknown and unidentified material may be introduced during this litigation, which may fall within my area of expertise, I may have relevant and important opinions regarding such as yet unknown and unidentified material. I reserve the right to be able to offer such opinions if they may become relevant or important as such material becomes known. I further reserve the right and intend to testify and offer additional opinions in response to any opinions offered by Regeneron or its purported experts.

98. I further reserve the right to supplement or amend this Report based on additional information made available to me, including in light of ongoing fact discovery (including third party discovery) and any expert reports submitted on behalf of Regeneron, or in order to clarify the information provided herein. I also reserve the right to supplement or amend this Report in

light of any claim interpretations (or changes or supplements thereto) made by the Court.

Dated: March 2, 2023

Gregory MacMichael, Ph.D.

Exhibit 36

CONFIDENTIAL

EXHIBIT 36
[DKT. 466-10]

REDACTED IN FULL

Exhibit 37

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

U.S. Patent No. 11,253,572

IPR Trial No. IPR2022-01524

PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.

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its validity will be a focus of the litigation.

III. CLAIM CONSTRUCTION

For purposes of this preliminary response only, Regeneron does not propose a construction of "initial dose," "secondary dose," or "tertiary dose" that is different than that proposed by Petitioner. Regeneron does not concede that Petitioner's proposed constructions are correct, and for the sake of completeness, Regeneron notes that it is maintaining its position, in related proceedings, that Petitioner's proposed construction is not correct, *see, e.g.*, Ex.2019, but the Board need not address that issue here, as the absence of other claim limitations in the asserted prior art demonstrates that Petitioner has not met its burden.

Also, for purposes of this preliminary response only, Regeneron does not contest Petitioner's proposed constructions of "4 weeks" or "8 weeks," or its proposed definition of a person of ordinary skill in the art.

A. "Wherein the patient achieves/gains…"

Each of the Challenged Claims contains a distinct limitation requiring that "the patient" or "the method" achieve certain visual acuity endpoints as assessed

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Regeneron, 1:22-cv-00061-TSK (Oct. 28, 2022), ECF No. 87. Regardless of Regeneron's selection of patents for the June 2023 trial, the '572 patent and its validity will remain live issues in the litigation, as neither Regeneron nor Mylan has indicated it will drop the '572 patent from its pleadings.

by the physician. Petitioner assumes that these Visual Acuity limitations should be ignored, but there is no such legal rule, and Petitioner fails to show that the Visual Acuity limitations in the Challenged Claims are properly construed as not having patentable weight under the applicable law. First, Petitioner has not shown that the Visual Acuity limitations lack patentable weight. Second, numerous claims differ only in the specific Visual Acuity recited, such that rendering those limitations a nullity as Petitioner urges would violate principles of claim differentiation. Third, both the specification and prosecution history show that the Visual Acuity limitations "state[] a condition material to patentability," and therefore "cannot be ignored." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

1. The Visual Acuity limitations have patentable weight because they do not duplicate the other method steps

In what amounts to a concession that the Visual Acuity limitations cannot be found in the prior art, Petitioner urges reading them out of the claims entirely. That makes no sense as a matter of construction, as it is a basic "claim-construction principle that meaning should be given to all of a claim's terms." *Dell Inc. v. Acceleron, LLC*, 818 F.3d 1293, 1300 (Fed. Cir. 2016). Petitioner's argument for abandoning that principle here appears to be based on its unargued assumption that claim limitations involving efficacy "do not alter the steps of the method" and therefore are non-limiting. Pet. 17. That is wrong, and the law is the opposite. "[T]here is no general rule that efficacy language in a claim is non-limiting."

Gilead Scis., Inc. v. United States, No. IPR2019-01456, 2020 WL 582217, at *11 (P.T.A.B. Feb. 5, 2020). "Whether such language should be given patentable weight turns on facts unique to each patent." *Id.*; *see also Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1374 (Fed. Cir. 2019). "Wherein" clauses must be given effect when they "relate back to and clarify what is required by the count," giving "meaning and purpose to the manipulative steps." *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). They should be given effect where they narrow the claims and do not merely "duplicate" other limitations. *LA BioMed*, 849 F.3d at 1061; *Allergan*, 935 F.3d at 1378–80 (Prost, C.J., concurring).

That is true of the method claims challenged here. The Visual Acuity limitations in the Challenged Claims add additional requirements that may be—but are not necessarily—met upon performance of the dosing steps recited earlier in the claim. Claim 1, for example, recites a method that requires not just administering doses of aflibercept in certain amounts and at certain intervals to "a patient," but further requires that "the patient achieves a gain in visual acuity within 52 weeks following the initial dose." Ex.1001, 23:1–15. This is a requirement that is not met unless the patient receiving the doses does, in fact, experience the required gain in visual acuity within the timeframe specified. *Id.* Instead of duplicating the method steps, the Visual Acuity limitation gives them "meaning and purpose" by adding an additional condition for success. *Griffin*, 285

F.3d at 1033. Petitioner's assertion that these limitations do not "alter or change the steps of the method" is thus at odds with the language of the claims. Pet. 18. As detailed below in Section IV.B, results vary widely between patients who receive the claimed dosing regimen, and there is no guarantee that the recited Visual Acuity limitations are met just because the other steps are.

The Visual Acuity limitations parallel the efficacy limitations in *Allergan*, which were found to have patentable weight. *Allergan*, 935 F.3d at 1374 ("[W]herein the method is as effective as the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day."). There the challenger contended that these clauses merely state "intended results," but the court found that "the language of the claims, followed by the language of the specification and prosecution history," which conveyed that efficacy was a critical part of the invention that distinguished it over the prior art, compelled a different result. *Id.* So too here. Petitioner has not attempted to show that the Visual Acuity limitations "merely state[] the result of the limitations in the claim," as required for them to lack patentable weight. *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1319 (Fed. Cir. 2003); *see also Allergan*, 935 F.3d at 1379 (Prost, C.J., concurring) ("Sandoz provides no basis for us to conclude with any certainty that the safety and efficacy requirements of the 'wherein' clauses would always result from two doses of (1) any formulation of the combination at (2) any interval

in a 24-hour period."); *Gilead*, 2020 WL 582217, at *12 (finding efficacy limitations had patentable weight because they were not "necessarily inherent in administering" claimed drugs).

Petitioner's cited cases are inapplicable for several reasons, including that they involved claim preambles or other non-standalone limitations,[8] in contrast to the Visual Acuity limitations in the Challenged Claims, which are freestanding.

[8] *Bristol*, 246 F.3d at 1371–72 ("A method *for treating* a patient suffering from a taxol-sensitive tumor," "A method for treating a cancer patient *to effect regression* of a taxol-sensitive tumor" (emphases added)); *Syntex*, 407 F.3d at 1374 ("an ethoxylated alkyl phenol that conforms generally to the formula C_8H_{17} $C_6H_4(OCH_2CH_2)_nOH^2$ where n has an average value of 40 *in a stabilizing amount* between 0.001% and 1.0% wt/vol" (emphasis added)); *Endo Pharms. Inc. v. Watson Lab'ys, Inc.*, No. 2:13-CV-192-JRG, 2014 WL 2859349, at *1 (E.D. Tex. June 23, 2014) ("A method for administering a topically or systemically active agent *with increased penetration*," "A method *for reducing inflammation* associated with topical application of a topically or systemically active agent" (emphases added)); *In re Copaxone 40 Mg*, No. CV 14-1171-GMS, 2016 WL 873062, at *2 (D. Del. Mar. 7, 2016) (noting that the court was construing "the preamble terms [as] nonlimiting").

LA BioMed, 849 F.3d at 1061 ("While not dispositive, it is significant that the phrase 'arresting or regressing the [penile] fibrosis' is drafted as part of a separate step of the method, not as the preamble or introduction to a process carried out by the administration of the drug." (alteration in original)). In addition, in the cases Petitioner cites, "the court made a claim-specific judgment of the intended effect of the language; and in each case, the language at issue identified a property in only very general terms and appeared in the very same claim that stated the other more concrete requirements," in contrast to the Challenged Claims, which state precise visual acuity changes, including in separate dependent claims. *L'Oréal USA, Inc. v. Olaplex, Inc.*, 844 F. App'x 308, 324 (Fed. Cir. 2021); *see also Allergan*, 935 F.3d at 1379 (Prost, J., concurring) (efficacy limitation entitled to patentable weight where it "d[id] not simply require some general level of therapeutic effectiveness").

Petitioner's cited cases finding that claim language lacks patentable weight turn on facts that are not applicable here. Petitioner has failed to show here, for example, that the Visual Acuity limitations (found in the body of the Challenged Claims, not the preamble) are duplicative of the dosing steps of the claim. Indeed, *Bristol*, a case Petitioner asserts is "strikingly similar," turned on the court's finding that the efficacy limitations "essentially duplicate[] the dosage amounts recited in the claims." *Bristol-Myers Squibb v. Ben Venue Lab'ys, Inc.*, 246 F.3d

1368, 1375 (Fed. Cir. 2001). Petitioner's remaining cases are similarly inapplicable. *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1376 (Fed. Cir. 2005) (limitation lacked patentable weight where "[t]he claim term makes clear that combining the recited ingredients in the claimed weight to volume ratio *will* stabilize the compound" (emphasis added)); *In re Copaxone 40 Mg*, No. CV 14-1171-GMS, 2016 WL 873062, at *1 n.2 (D. Del. Mar. 7, 2016) (noting without analysis that claim terms either "duplicate the dosage requirements" or "list the intended outcome from following the claimed steps").

Petitioner's attempt to read out limitations of the claims also conflicts with the principle of claim differentiation, which holds that there is a presumption that differences between claims are significant. *Comark Comm'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998); *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984) (claim differentiation provides that "each claim of a patent constitutes a separate invention and gives rise to separate rights"). As Petitioner acknowledges, dependent claims 2–4, 8–10, 28, and 30 "further specify the particular amount of gain and the timing for achieving those gains," over and above the Visual Acuity limitations recited in the independent claims. Pet. 18. For example, claim 3 specifies that the "patient gains at least 7 letters," while claim 8 requires the patient to gain "at least 8 letters." Ex.1001, 24. The sole difference between these claims is their respective Visual Acuity limitations, and by giving no

claim-limiting effect to those words, Petitioner has eliminated any distinction between these claims, rendering them identical in scope. In addition, it makes no sense to treat these limitations as merely statements of intended results, as doing so would suggest that the same method steps have different intended results. Petitioner's construction should be rejected as violating the doctrine of claim differentiation and as failing to give effect to the words of the claim. *L'Oréal*, 844 F. App'x at 324 (treating efficacy limitations "as of no legal effect would be to interpret each of these dependent claims as entirely a nullity").

2. The specification and prosecution history show the Visual Acuity limitations have patentable weight

Even if the salience of an efficacy limitation were not apparent from the text of the claim itself (contrary to the situation here), "the language of the specification and prosecution history" may suggest that an efficacy limitation is entitled to patentable weight. *Allergan*, 935 F.3d at 1374 (concluding that efficacy limitations had patentable weight because specification and prosecution history showed they were "material to patentability").

Here, each Visual Acuity limitation is satisfied when a patient achieves the recited degree of success in treating angiogenic eye disorders. As in *Allergan*, the importance of efficacy to the claimed dosing regimen appears throughout the specification. The inventors note that they "have surprisingly discovered that beneficial therapeutic effects can be achieved in patients suffering from angiogenic

eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks." Ex.1001, 2:22–28. The specification is replete with references to the materiality of achieving efficacy, especially visual acuity gains, in treating angiogenic eye disorders. Ex.1001, 7:1–8, 7:36–52, 8:33–36, 8:58–65, 9:38–43, 9:49–53, 9:54–56, 12:23–29, 13:28–38, Table 1; *see also Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) (holding that a specification "replete with references" to preamble language may show the inventor regarded the language as "an important characteristic of the claimed invention" and limit the claims); *Allergan*, 935 F.3d at 1375 ("[T]he specification demonstrates that [patent owner] believed the increased efficacy and safety of the claimed methods to be material to patentability.").

The prosecution history also shows that efficacy coupled with a less frequent dosing regimen was used to distinguish the invention from the prior art. *Allergan*, 935 F.3d at 1374, 1375–76, *Javelin Pharms., Inc. v. Mylan Lab'ys Ltd.*, No. CV 16-224-LPS, 2017 WL 4511352, at *3 (D. Del. Oct. 10, 2017) (efficacy limitation was limiting where efficacy was unexpected and the limitation was "used to define the claimed invention and distinguish it from the prior art"); *Wi-LAN Inc. v. Sharp Elecs. Corp.*, No. CV 15-379-LPS, 2018 WL 1997982, at *6 (D. Del. Apr. 27,

2018) (where claim limitation was an important aspect of the invention and material to patentability, it was therefore limiting). In response to rejections made by the Examiner during prosecution of parent applications, the applicant noted that results from the administration of the claimed dosing regimen "clearly show that by administering the VEGF antagonist in accordance with a dosage regimen as claimed in [the pending claims], it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis than previously thought possible." Ex.1013, 289; Ex.2006, 137; Ex.2012, 175; Ex.2005, 149. The applicant further argued that "the results show that the treatment groups which were compared with the monthly treatment groups surprisingly did not obtain an inferior result," Ex.1013 at 290, such that "the claimed treatment protocol provides enormous advantages to patients," *id.* at 291. The applicant's reliance on the efficacy of the claimed dosing regimen demonstrates that the Visual Acuity limitations are material to the invention. *Allergan*, 935 F.3d at 1376–77 ("The prosecution history thus demonstrates that the formulation's efficacy and safety … were expressly relied on to define the claimed methods and distinguish them from the prior art."); *Gilead*, 2020 WL 582217, at *12 (finding efficacy limitation had patentable weight because it was "key in the patent's prosecution").

Thus, Petitioner is incorrect that the Visual Acuity limitations merely express intended results. The claims, specification, and prosecution history

demonstrate that they are independent limitations that should be given patentable weight separate and apart from the dosing steps.

B. "Wherein the exclusion criteria for the patient include both of…"

With respect to Claim 14, Petitioner again proposes a construction that eviscerates a clear, express limitation, reading out every element that claim 14 adds to claim 1, from which it depends: "wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection." (the "Exclusion Criteria limitation"). Petitioner argues that the Exclusion Criteria "are entitled no patentable weight under the printed matter doctrine," relying on *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018). Pet. 20. Petitioner is wrong.

The printed matter doctrine does not apply here, and the Exclusion Criteria limitation is entitled to patentable weight. The court in *Praxair* held that a claim limitation is not entitled to patentable weight if (1) it is directed to printed matter, and (2) the printed matter is not functionally related to its substrate. *Praxair*, 890 F.3d at 1032. The Exclusion Criteria limitation is not directed to the content of information. And far from supporting Petitioner's printed matter argument, *Praxair* establishes that the Exclusion Criteria limitation ***is*** entitled to patentable weight, defining and limiting the scope of the claimed method and "the patient[s]" to be treated in claim 1, and requiring the treating clinician to take action based on

assessment of the patient.

The Exclusion Criteria limitation does not constitute "merely adding an instruction sheet or other informational content to a drug product," "providing information," or a "recommendation," which are "not sufficient to create a functional relationship." *Id.* at 1032–33. Instead, it is "interrelated with the rest of the claim," like the dependent claim at issue in *Praxair* that was found *not* to comprise unpatentable subject matter. *Id.* at 1032. Even though that claim incorporated a "recommendation" limitation, it further required a medical provider to take a specific action—discontinuing treatment—based on the recommendation. *Id.* at 1029, 1035. As a result, it was functionally related to the body of the claim and had patentable weight. *Id.* at 1035. Like claim 9 in *Praxair*, the Exclusion Criteria limitation requires the clinician to take action based on an assessment of the patient by proceeding to administer the drug only if the patient has neither active inflammation nor infection. *See* Ex.1001, 4:52–55 ("The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination"), 17:41–44 ("[T]he amount of VEGFT and/or volume of formulation administered to a patient may be varied based on patient characteristics, severity of disease, and other diagnostic assessments by a physician or other qualified medical professional."). The Exclusion Criteria limitation thus bear a functional

reasonable likelihood of prevailing on any challenged claim. Each discrete, express limitation of the claims carries patentable weight, and Petitioner's inherent disclosure arguments are legally and factually deficient. In addition, because the Examiner already considered the asserted art and Petitioner presented no evidence of material error, and because trial on the validity of the '572 patent is imminent, the Board should exercise its discretion to deny institution.

Dated: December 23, 2022

Respectfully submitted,

By: /Adam R. Brausa/
Adam R. Brausa (Reg. No. 60,287)
Lead Counsel for Patent Owner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for the Patent Owner declares that the argument section of this Preliminary Response has a total of 12,741 words, according to the word count tool in Microsoft Word™.

/Adam R. Brausa/
ADAM R. BRAUSA

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned hereby certifies that true and correct copies of the foregoing Preliminary Response of Patent Owner of U.S. Patent No. 11,253,572 and accompanying Exhibits 2001-2032 were served on December 23, 2022 via electronic mail on the following counsel of record for Patent Owner:

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Exhibit 38

OUTSIDE ATTORNEY'S EYES ONLY

A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration

CLinical Evaluation of Anti-angiogenesis in the Retina - Intravitreal Trial 3 (CLEAR-IT 3)

Protocol VGFT-OD-0605

BB-IND 12462

Investigator(s):	Multi-Investigator Study
Institution(s):	Multi-Center Study
Trial Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Director:	Avner Ingerman, MD
Medical Monitor:	Avner Ingerman, MD
Study Monitor:	Johanna Mendoza
Study Statistician:	Imogene Grimes, PhD
Date of Issue:	January 15, 2007
Amendment 1 Date	May 17, 2007
Version:	VGFT-OD-0605.01

Protocol Synopsis

Title	A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration
Indication	Neovascular Age-Related Macular Degeneration (AMD) of all subtypes
Primary Objective	To assess the efficacy of intravitreal (ITV) administered VEGF Trap compared to ranibizumab in a non-inferiority paradigm in preventing moderate vision loss in subjects with all subtypes of neovascular AMD.
Secondary Objective(s)	• To assess the safety and tolerability of repeated ITV administration of VEGF Trap in subjects with all sub-types of neovascular AMD for periods up to 2 years. • To assess the effect of repeated ITV administration of VEGF Trap on Vision-Related Quality of Life (QOL) in subjects with all sub-types of neovascular AMD, as assessed using the NEI VFQ-25 questionnaire.
Study Design	VGFT-OD-0605 is a double-masked, randomized, Phase III study. Subjects will be randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) 2 mg VEGF Trap administered every 4 weeks (2Q4), 2) 0.5 mg VEGF Trap administered every 4 weeks (0.5Q4), 3) 2 mg VEGF Trap administered every 8 weeks (2Q8), and 4) 0.5 mg ranibizumab administered every 4 weeks (RQ4); subjects assigned to (2Q8) will receive the 2 mg injection every 4 weeks to week 8 and then a sham injection at interim monthly (i.e. every 8 weeks) visits during the first 12 months of the study. Each subject is scheduled to be on study for 24 months (one study month equals 4 weeks or 28 days). Thus, the study duration will be 24 months plus the recruitment period. For the first 12 months, subjects will receive an ITV or sham injection in the study eye every 4 weeks. During the second 12 months of study, subjects will be evaluated every 4 weeks and will receive an ITV injection at least every 12 weeks. During this period, injections may be given as frequently as every 4 weeks, but no less frequently than every 12 weeks, according to the following criteria: • Increase from any previous visit, i.e. difference compared to the lowest previous OCT-value to avoid a gradual increase in retinal thickness from visit to visit in central

retinal thickness of ≥ 100 μm as measured by OCT, or

- A loss from any previous visit, i.e. loss compared to optimal visual function achievable of ≥ 5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT, or
- New or persistent fluid as indicated by OCT, or
- New onset classic neovascularization, or
- New or persistent leak on FA, or
- New macular hemorrhage, or
- 12 weeks have elapsed since the previous injection.

During the second 12 months of the study, sham injections will not be given.

Subjects will be evaluated every 4 weeks for safety and best corrected visual acuity (BCVA) using the 4 meter Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Quality of Life (QOL) will be evaluated using the NEI VFQ-25 questionnaire. Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA) examinations will be conducted periodically.

Only one eye per subject may be enrolled in the study. If a subject's fellow (non-study) eye requires treatment for AMD at study entry, or during the subject's participation in the study, the fellow eye can receive any FDA approved treatment for wet AMD. Although the fellow eye can receive treatment, it will not be considered an additional study eye. Subjects who receive treatment for the fellow eye should remain in the study. Safety for the fellow eye will be monitored, and systemic adverse events will be collected.

Sample Size	Approximately 1200 subjects will be enrolled with a target enrollment of 300 subjects per treatment arm. Assuming 90% of subjects treated with 0.5 mg ranibizumab will maintain vision (defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline), 90% of subjects treated with VEGF Trap will maintain vision, and defining the non-inferiority margin to be 10%, 191 subjects per group provides 90% power to demonstrate non-inferiority assuming an alpha level of 0.049 (which includes an adjustment of 0.001 for the IDMC safety assessments, 0.0001 for each of the 10 assessments), thus preserving an overall alpha of 0.05 for the study). Assuming a dropout rate of 30%, (a high dropout rate is being assumed because of the availability of competing, approved therapies),enrollment of 300 subjects per group will provide adequate power for this study to achieve its objectives.
Study Site	Multi-Center
Location	USA and Canada
Key Subject Eligibility Criteria	All ophthalmic eligibility criteria apply only to the study eye unless otherwise specified. The reading center will confirm subject eligibility based on angiographic criteria prior to randomization. *Key Inclusion Criteria:* • Signed Informed Consent • Men and women ≥ 50 years of age. • Active primary or recurrent subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye • ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye. • Willing, committed, and able to return for ALL clinic visits and complete all study-related procedures. • Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member. See Appendix J.4) understand and willing to sign the informed consent form.

Key Exclusion Criteria:

- Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins.
- Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins.
- Any prior treatment with anti-VEGF agents.
- Total lesion size > 12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye.
- Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
- Scar or fibrosis, making up > 50% of total lesion in the study eye.
- Scar, fibrosis, or atrophy involving the center of the fovea.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
- History of any vitreous hemorrhage within 4 weeks prior to Visit 1 in the study eye.
- Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis in the study eye.
- History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye.
- Prior vitrectomy in the study eye.
- History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
- Any history of macular hole of stage 2 and above in the study eye.
- Any intraocular or periocular surgery within 3 months of

Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection.

- Prior trabeculectomy or other filtration surgery in the study eye.
- Uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye.
- Prior laser treatment for glaucoma in the study eye.
- Active intraocular inflammation in either eye.
- Active ocular or periocular infection in either eye.
- Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.
- Any history of uveitis in either eye.
- Active scleritis or episcleritis in either eye.
- Presence or history of scleromalacia in either eye.
- Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye.
- Previous therapeutic radiation in the region of the study eye.
- History of corneal transplant or corneal dystrophy in the study eye.
- Significant media opacities, including cataract, in the study eye that might interfere with visual acuity, assessment of safety, or fundus photography.
- Any concurrent intraocular condition in the study eye (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 24 month study period.
- Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that

	might affect interpretation of the results of the study or render the subject at high risk for treatment complications. • Participation as a subject in any clinical study within the 12 weeks prior to Day 1. • Any systemic or ocular treatment with an investigational agent in the past 12 weeks prior to Day 1. • The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. • Any history of allergy to povidone iodine. • Known serious allergy to the fluorescein sodium for injection in angiography. • Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®). • Females who are pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening); IUD; Depo-Provera®; Norplant® System implants; bilateral tubal ligation; vasectomy; condom or diaphragm plus either contraceptive sponge, foam or jelly.
Drug Dosage, Formulation, and Route of Administration	VEGF Trap will be supplied by Regeneron Pharmaceuticals, Inc. and will be administered by ITV injection using standard ophthalmic techniques. VEGF Trap will be supplied in sealed 3 mL single use vials each with a "withdrawable" volume of approximately 0.5 mL at a concentration of 10 mg/mL or 40 mg/mL. The VEGF Trap will be withdrawn using aseptic technique through an 18 "gauge" needle attached to a 1 mL syringe. The syringe needle will then be removed and replaced with a 30 gauge needle to be used for the ITV injection. The injection volume will be 50 µL (0.05 mL) for the 0.5 mg and 2 mg doses of VEGF Trap and 0.5 mg ranibizumab. Commercially available ranibizumab (Lucentis®) 0.5 mg will be acquired independently by the sites and reimbursed by Regeneron Pharmaceuticals, Inc. Sham injection will be performed with no active drug and without intraocular penetration.

Masking	An unmasked physician will perform the study drug or sham injection. This individual, who will be unmasked to treatment assignment, must not have any role in the study beyond the receipt, tracking, preparation, destruction and administration of study drug, as well as assessing safety at 30-60 minutes post ITV injection. A separate masked physician must be assigned to 1) assess AEs 2) supervise the masked assessment of efficacy. All other study site personnel must remain masked to treatment assignment in order to allow for an unbiased assessment of visual acuity, safety, and ancillary study measures. Second Year Masking During the second year of the study, a study report will be issued that will indicate the efficacy outcomes of the first year data. All subjects and study personnel who were masked in year 1 will remain masked to the individual subject treatment assignments even after the issuance of the study report.
Safety Parameters	Safety and tolerability will be assessed by clinical laboratory testing, adverse event (AE) reporting, and ophthalmic examinations. Anti-VEGF Trap antibody titers will be measured quarterly in the first year and semi annually in the second year on all subjects.
Primary Endpoint (Efficacy)	The primary endpoint will be prevention of vision loss of greater than or equal to 15 letters on the ETDRS chart, compared to baseline, at 12 months.
Secondary Endpoint(s) (Efficacy)	• Change from baseline to Month 12 in letter score on the ETDRS chart compared to baseline • Gain from baseline to month 12 of 15 letters or more on the ETDRS chart. • Change from baseline in total NEI VFQ-25 score. • Change from baseline in CNV area.
Statistical Analysis	*Populations of analysis:* The full analysis set (FAS) includes all randomized subjects who receive any study medication and have at least one post-baseline assessment. The per protocol set (PPS) includes all subjects in the FAS who receive at least 9 injections of study drug or sham and attend at

least 9 scheduled visits during the first year, except for those who are excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results (e.g. missing two consecutive visits). The PPS also includes subjects who are treatment failures at anytime during the first 12 months.

The safety set (SAF) includes all subjects who receive any study medication.

Variables of analysis:

Primary: The primary variable of analysis is the proportion of subjects who do not have a loss of 15 letters or more on the ETDRS chart at month 12.

Secondary: Secondary variables of analysis are as follows:

- Mean change from baseline in visual acuity.
- The proportion of subjects who gain at least 15 letters of vision.
- Mean change from baseline in total NEI VFQ-25 score.
- Mean change from baseline in CNV area.

Statistical Methodology:

Primary: The primary analysis will be conducted in the PPS analysis population and is a conditional sequence of statistical evaluations of non-inferiority of VEGF Trap to 0.5 mg ranibizumab. The non-inferiority margin is set at 10%. The methodological approach includes a conditional sequence of calculations of the 95.1% confidence intervals (reflecting an alpha adjustment of 0.1% for the IDMC safety assessments) of the difference between the proportions of subjects with maintained vision for the group treated with 0.5 mg ranibizumab and the proportion of subjects with maintained vision for each of the groups treated with VEGF Trap. The conditional sequence will be: 2Q4, 0.5Q4, then 2Q8. VEGF Trap is considered to be non-inferior to ranibizumab if the confidence interval of the difference lies entirely below 10%, where a positive difference favors ranibizumab. These analyses will be performed using the PPS.

Secondary: If all three VEGF Trap groups are shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons of those non-inferior VEGF Trap groups to ranibizumab will be made with respect to secondary endpoints. Each secondary analysis will be for superiority of VEGF Trap over ranibizumab. The secondary analyses are ordered into a

	conditional sequence of hypothesis tests to control for multiplicity. These secondary analyses will be performed on the FAS following the intent-to-treat (ITT) principle. Analysis of proportions will be done using Fisher's Exact test for the pairwise comparisons of 2Q4, 0.5Q4, and 2Q8 to RQ4. Analyses of continuous variables use analysis of covariance with a main-effects model with baseline measure as a covariate and treatment as a factor; interaction terms will be examined for pairwise comparisons. **Interim Analysis** There is no interim analysis in this study. However, an external, independent data monitoring committee (IDMC) will be engaged to monitor this study.
Sponsor	Regeneron Pharmaceuticals, Inc.

Table of Contents

List of Abbreviations

AE	Adverse Event
ALT (SGOT)	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
ANC	Absolute Neutrophil Count
AST (SGPT)	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
βHCG	Beta Human Chorionic Gonadotropin
BRB	Blood Retinal Barrier
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CLIA	Clinical Laboratory Improvement Amendments
cm	Centimeter
CMSO	Chief Medical Safety Officer
CNV	Choroidal Neovascularization
CRF	Case Report Form
CR/LT	Central retinal/lesion thickness
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DA	Disc Areas
DLT	Dose-Limiting Toxicity
DME	Diabetic Macular Edema
DMS	Director, Medical Safety
E-CRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
DR	Diabetic Retinopathy
ECR/LT	Excess Central retinal/lesion thickness
EFT	Excess Foveal Thickness
ERT	Excess retinal thickness

ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Fundus Photography
GCP	Good Clinical Practice
GLD	Guidelines for Laboratory Design
IB	Investigator's Brochure
IC	Informed Consent
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
ITV	Intravitreal
IOP	Intraocular Pressure
KD	Dissociation Rate Constant
kDa	Kilodalton
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
mmHg	Millimeters Of Mercury
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NME	New Molecular Entity
NOAEL	No Observed Adverse Event Level
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OIR	Oxygen-Induced Retinopathy

PDT	Photodynamic Therapy
PLGF	Placental Growth Factor
PPI	Patient Prescribing Information
PPS	Per Protocol Set
PRN	As needed
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SDF	Study Data File
SMT	Safety Monitoring Team
TBD	To Be Determined
TEAE	Treatment-emergent Adverse Event
TEAV	Treatment-emergent Abnormal Value
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VPF	Vascular Permeability Formula
WBC	White Blood Cell
YAG	Yttrium Aluminum Garnet

11 Study Drug

Study drug may not be used outside the scope of this clinical trial.

11.1 Description

VEGF Trap will be supplied by Regeneron Pharmaceuticals, Inc.in sterile vials for ITV injection. All drug supplies are to be kept under recommended storage conditions. Commercially available Ranibizumab (Lucentis®) 0.5 mg will be will be acquired independently by the sites and reimbursed by Regeneron Pharmaceuticals, Inc. The method for administering ranibizumab is described in the approved label (Appendix E).

11.2 Packaging, Labeling and Storage

11.2.1 VEGF Trap

VEGF Trap is formulated as a sterile liquid to a final concentration of either 10 mg/mL or 40 mg/mL VEGF Trap in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. VEGF Trap study drug will be supplied by Regeneron Pharmaceuticals Inc. in sealed, sterile 3 mL vials each with a "withdrawable" volume of approximately 0.5 mL. The volume of injection will be 50 µl (0.05 mL) for the 0.5 mg dose of VEGF Trap and the 2 mg dose of VEGF Trap. The study drug will be withdrawn using aseptic technique through an 18 gauge needle attached to a 1 mL syringe. The needle is to be aseptically removed from the syringe and replaced with a 30 gauge needle for the ITV injection.

Study drug will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2˚ to 8˚ C. The investigator, or an approved representative (e.g. pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2˚ to 8˚ C.

When vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may

result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

11.2.2 Ranibizumab

Ranibizumab (Lucentis®) 0.5 mg will be acquired independently by the sites and reimbursed by Regeneron Pharmaceuticals, Inc. Appropriate storage conditions are described in the approved label (Appendix E).

11.3 Supply and Disposition of Drug

Study drug will be shipped to the Investigator or designee at regular intervals or as needed during the study. Ranibizumab (Lucentis®) 0.5 mg will be acquired independently by the sites and reimbursed by Regeneron Pharmaceuticals, Inc. At specified time points during the study (i.e., interim site monitoring visits) and at the end of the study (i.e., site close-out visit), and following reconciliation and documentation by the site monitor, all used and unused vials will either be destroyed at the site with a Regeneron-designee present or returned to Regeneron Pharmaceuticals, Inc., or a specified designee for disposal.

11.4 Drug Accountability

The Investigator is responsible for the accountability of all used and unused study drug, and drug accountability records must be kept current. These records should contain the dates, quantities and identification numbers (or lot numbers) of study drug received by the Investigator, dispensed or administered to specified subjects, returned from subjects (if applicable), disposed of at the site (with a Regeneron designee present), or returned to Regeneron Pharmaceuticals, Inc. or a specified designee for disposal. These inventories, along with shipment receipts, shipment temperature recordings (if applicable) and storage temperature logs, pharmacy dose preparation logs, and IVRS confirmation reports (if applicable), must be made available for inspection by Regeneron's monitoring and QA auditing staff or designees and all regulatory agency inspectors. At the conclusion of the study, photocopies of all drug accountability records must be provided by each site to Regeneron.

12 Study Documentation

12.1 Case Report Forms

12.1.1 Case Report Form Documents

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (e-CRFs) provided for each subject by Regeneron Pharmaceuticals, Inc. The e-CRFs will be on a web-based system that will bear information identifying the protocol number study site and subject identification number.

12.1.2 Recording Data on e-CRFs

E-CRFs are used to record clinical study data and as such are a key component of the study and are the basis from which the study results are tabulated and final reports are written. Data recorded on e-CRFs must therefore be complete and accurate. Subjects are to be identified on the e-CRFs only by their Subject Identification Number and initials; full names or other identifying information should not appear.

E-CRFs demand the same attention to accuracy and completeness as paper CRFs. E-CRFs should be completed according to procedures outlined in the Investigator's Procedures Manual as soon as possible following each subject visit.

Missing data should be handled according to e-CRF completion guidelines and other instruction provided by Regeneron or its designees at the beginning of the study.

12.1.3 Source Documents and the Study Data File (SDF)

US FDA regulations contained in 21 CFR 312.62(b) require "an investigator to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, progress notes of the physician, the individual's hospital charts, and nurses' notes. The case history for each individual shall document that IC was obtained prior to participation in the study." Source documents will include the following: subject case histories; original copies of laboratory data, test reports, instrument- or computer-generated data; working copies (if used) of the CRFs; narrative reports or progress notes of subject study visits; subject correspondence and

records of interim (unscheduled) subject contacts.

Source documents must be kept on file by the Investigator. Availability of source documentation is required by regulatory agencies to confirm the integrity of the study data. The file containing the e-CRFs and source documents for a given subject is referred to as that subject's Study Data File (SDF). Review of source documentation is an integral part of study monitoring visits by Regeneron clinical trials monitoring and quality assurance (QA) personnel, or their designee. E-CRFs and source documents must be available at all times for inspection by authorized representatives of Regeneron and the FDA, and other regulatory agencies.

12.1.4 Record Keeping Using Electronic Systems

When using remote electronic trial data systems or a local electronic trial data handling system, the Investigator must maintain SOPs for using the system, adequate security to limit access to the electronic system and the electronic records, a list of authorized users, and documentation that authorized users have been trained to the SOPs. If the sponsor provides an Electronic Data Capture (EDC) system (in lieu of data collection using paper CRFs) to the Investigator, the EDC system Completion Guidelines will serve as the SOP above.

If study data are captured via a remotely administered EDC, the Investigator will be provided with a viewable copy of the electronic records including the audit trail for each subject. These records must be retained and handled as described in Section 12.1.7 "Retention of Records."

If electronic data systems other than those provided by and supported by the sponsor are used for primary or source documentation or for data handling, the Investigator must ensure that the systems are validated and maintain adequate back-up of the data. Electronic records and documentation related to electronic data systems should be retained as described in Section 12.1.7 "Retention of Records."

If an electronic medical records system (that is not provided and supported by the sponsor) is replaced or decommissioned, the Investigator must maintain a way to retrieve

the records electronically or arrange for records to be converted into an alternate electronic or paper-based format that can be easily retrieved

12.1.5 Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded in the e-CRFs must be signed by the Investigator. This certification form accompanies each set of e-CRFs. The signed form will be returned to the Sponsor with the final set of e-CRFs for each subject.

12.1.6 Monitoring of Study Sites

The Regeneron Study Monitor and/or Study Director, Medical Monitor and/or their designee (e.g. monitor(s) from a contract CRO) will visit each site prior to enrollment of the first subject, and periodically during the study. The Study Monitor or designee will also visit each site at other appropriate dates for the purposes of 1) reviewing e-CRFs for accuracy 2) reviewing source documents to verify the accuracy of transcription of original data, and 3) reviewing the status of study drug and CRF inventories. Drug dispensing records will also be reviewed, and a copy of the appropriate drug dispensing log forms will also be collected for return to Regeneron.

12.1.7 Retention of Records

The Investigator must retain all records, including source documents and Investigator copies of CRFs (paper or electronic) for 2 years following FDA approval, or until two years after the last planned regulatory approval. In the event that the drug is not approved for sale, or the clinical research program is terminated by Regeneron, records must be retained for 2 years beyond the completion of the entire research program or its termination. Investigator should consult with Regeneron before discarding or destroying records. Records must be destroyed in a manner to ensure confidentiality.

12.2 Clinical Laboratory Data

12.2.1 Laboratory Certification

Clinical laboratory (ies) will be selected before initiation of the trial. The curriculum vita of the relevant laboratory director, and current certification for the laboratory (e.g. College of American Pathologists [AP], Clinical Laboratory Improvement Amendments

[CLIA]) must be provided by the Investigator and/or central laboratory, if applicable, to Regeneron. In addition, the ranges of values considered normal for the determinations each laboratory is performing for the trial must be provided to the Sponsor.

12.2.2 Shipment of Laboratory Samples

The local or central laboratory will provide procedures for shipment of all laboratory samples prior to the initiation of the study.

Laboratory samples, required by the protocol to be shipped to Regeneron or designee, should be packed in the cushioned, leak-proof containers provided. Samples for determination of levels of antibodies to VEGF Trap in serum should be kept frozen until shipment and then shipped on dry ice. A log of the date of sample acquisition, storage conditions, date of shipment and names of the individuals sending the material (and accepting responsibility for its receipt), should accompany any samples. See the Study Manual for detailed instructions.

12.2.3 Reporting of Laboratory Data

The Investigator or his/her designee will receive reports of laboratory values. In the case of analog data, elements of the report or the interpretation of the findings will be transcribed into the e-CRF. Copies of original laboratory data reports and related source documentation are to be retained as part of the Study Data File as described above. (See Study Manual)

12.2.4 Abnormal Laboratory Values and Adverse Laboratory Events

All abnormal laboratory values will require a comment from the Investigator as to their significance. Clinically significant abnormal laboratory values must be designated as AEs and so reported. Significantly abnormal tests should be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to be resolved or cannot be explained by events or conditions unrelated to the study medication or its administration, the Study Director at Regeneron, or their designee, should be consulted. If it is decided that the patient's participation in the clinical trial should be terminated or the dosage regimen modified due to the laboratory abnormality, the appropriate test(s) should be

repeated until normalization is confirmed or an alternative diagnosis explaining the abnormality is reached. (See Study Reference Manual)

13 Ethical and Regulatory Considerations

13.1 GCP Statement

This clinical study is being conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and the applicable regulatory requirements.

13.2 Institutional Review Board

This clinical study will be reviewed and approved by the Institutional Review Board (IRB)/Ethics Committee (EC) representing each participating institution prior to enrolling subjects and must be reviewed again on an annual basis. Such IRBs must be appropriately constituted and meet all requirements as described in Part 56, Title 21 of the Code of Federal Regulations. The review must include the protocol, the IC document for the trial and any other materials that will be provided to the prospective subjects (e.g. advertisements). A copy of the Letter or Notice of Approval from the IRB must be received by Regeneron, or their designee, prior to shipment of drug supplies to the Investigator. The composition of the IRB membership must be described and submitted to Regeneron, or their designee, with the written IRB approval and updated lists, if applicable.

13.2.1 IRB Record Keeping

The records of the IRB review and approval of all study documents (including annual IRB approval of ongoing studies) must be kept on file by the Investigator. These records may be open to inspection by representatives of the Food and Drug Administration (FDA) at any time during and after the study. As detailed in 21 CFR Part 56, the Investigator must submit IND safety reports, annual reports and a final report to the IRB according to the guidelines of the IRB or more often if unanticipated AEs occur. The Investigator must keep an accurate and complete record of all submissions to the IRB and IRB approvals to facilitate their retrieval.

13.2.2 Protocol Amendments

Changes in the design or operation of the protocol, whether initiated at the study site or by Regeneron, must be incorporated into a Protocol Amendment. All protocol amendments must be reviewed and approved by the IRB at each applicable study site. Notice of such review and approval must be provided to the Study Director at Regeneron, or their designee

13.3 Informed Consent

The principles of informed consent are described in 21CFR Part 50. A copy of the Informed Consent document to be used for the study, together with documentation of its review and approval by the appropriate IRB, must be provided to and approved by Regeneron, or their designee, before study medication can be shipped to the study site. Each subject's Study Data File must include documentation that informed consent was obtained prior to participation in the study. See Appendix J, for additional information regarding the informed consent document.

13.4 Subject's Rights

In accordance with the current revision of the Declaration of Helsinki and FDA, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator and Sponsor also have the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Should a subject (or a subject's legally authorized representative) decide to withdraw consent, all efforts will be made to complete and report the observations as thoroughly as possible on the appropriate case report form.

13.5 Subject Confidentiality

The Investigator must ensure that the subject's anonymity is maintained. Subjects will be identified by their initials and a subject identification number only on the e-CRFs or other documents submitted to Regeneron Pharmaceuticals, Inc. Documents that will not be submitted to Regeneron Pharmaceuticals, Inc. (e.g. signed informed consent form) should be kept in strict confidence by the Investigator.

The Investigator shall permit representatives of the Sponsor, US FDA, or representatives from other regulatory agencies providing the same function to inspect the subject's medical records, however, the confidentiality of the records must be maintained.

14 Audits

All documentation pertaining to this clinical study may be subject to a quality assurance audit by personnel designated by Regeneron, US FDA, or other regulatory agencies with similar responsibilities. The auditor will have access upon request, for inspection, copying, review, and audit of all source documentation, e-CRFs, medical records, correspondence, and informed consent documents pertaining to the participants in the study. The Investigator agrees to promptly take any reasonable steps that are required by the Sponsor as a result of an audit to cure deficiencies in the study documentation and e-CRFs. Other documentation subject to quality assurance audit includes the Investigator's IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of storage of study materials are also subject to inspection. Representatives of Regeneron Pharmaceuticals, Inc. may observe conduct of any aspect of the clinical trial or its supporting activities both within and outside of the Investigator's institution.

15 Language

All written information and other material to be used by subjects and paraclinical staff must use a vocabulary and language that are both appropriate and clearly understandable to the study participant.

16 References

Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasqauale LR, Thieme H, Iwamoto MA, Park JE. Vascular endothelial growth factor in ocular fluid of subjects with diabetic retinopathy and other retinal disorders. N Eng J Med 1994; 331:1480-1487.

Aiello, Lloyd P. Md; Brucker, Alexander J. Md; Chang, Stanley Md; Cunningham, Emmett T. Jr Md, Phd, Mph; D'amico, Donald J. Md; Flynn, Harry W. Jr Md; Grillone, Lisa R. Phd; Hutcherson, Steve; Liebmann, Jeffrey M. Md; O'brien, Terrence P. Md; Scott, Ingrid U. Md, Mph; Spaide, Richard F. Md; Ta, Christopher Md; Trese, Michael T. Md. Evolving Guidelines For Intravitreous Injections. Retina 2004; 24:S3-S19.

Anderson DC, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw PM, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, Cohen N, Lister CE. Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group. The Pharmacogenomics Journal 2002;2:284-292.

Basic and Clinical Science Course Section 9: Intraocular Inflammation and Uveitis. American Academy of Ophthalmology. 2002-2003;103.

Bressler NM, Lim J, Potter MJ, Bradley BR, Williams GA. Guidelines for using verteporfin (Visudyne®) in photodynamic therapy to treat choroidal neovascularization due to age-related macular degeneration and other causes. Retina 2002; 22: 6-18.

Bressler NM, Bressler SB, Congdon NG et al. Potential public health impact of Age-Related Study results: AREDS report no. 11. Arch. Ophthalmol 2003; 121:1621-1624.

Congdon N, O'Colmain B, Klaver CC et al. Causes and prevalence of visual impairment among adults in the United States. Arch Opthalmol 2004;122:477-485.

D'Amico DJ, Goldberg MF, Hudson H, Jerdan JA, Krueger DS, Luna SP, Robertson SM, Russell S, Singerman L, Slakter JS, Yannuzzi L, Zilliox P; Anecortave Acetate Clinical Study Group. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. Ophthalmology. 2003;110:2372-2378.

Dvorak HF, Dvorak AM, Manseau EJ, Wiberg L, Churchill WH. Fibrin gel investment associated with line 1 and line 10 solid tumor growth, angiogenesis, and fibroplasia in guinea pigs. Role of cellular immunity, my fibroblasts, microvascular damage, and infarction in line 1 tumor regression. J Natl Can Inst . 1979:62:1459-1472.

Dvorak HF, Orenstein NS, Carvalho AC, Churchill WH, Dvorak AM, Galli SJ, Feder J, Bitzer AM, Rypysc J, Giovinco P. Induction of a fibrin-gel investment: an early event in line 10 hepatocarcinoma growth mediated by tumor-secreted products. J Immunol. 1979:122;166-74.

The Early Treatment Diabetic Retinopathy Study Group: Photocoagulation for diabetic macular edema, ETDRS Report No. 1. Arch Ophthalmol 1985, 103:1644-1652.

The EyeTech Study Group: Preclinical and phase 1A clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. Retina 2002, 22:143-152.

Ferrara N. VEGF: an update on biological and therapeutic aspects. Current Opinion in Biotechnology 2000:11;617-624.

Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr. Rev. 1997;18:4-25.

Ferrara N, Leung DW, Cachianes G, Winer J, Henzel WJ. Purification and cloning of vascular endothelial growth factor secreted by pituitary folliculostellate cells. Methods Enzymol. 1991;198:391-405.

Gordon MS, Margolin K, Talpaz M, Sledge GW, Holmgren E, Benjamin R, Stalter S, Shak S, Adelman DC. Phase I safety and pharmacokinetic study of recombinant human anti- vascular endothelial growth factor in patients with advanced cancer. J Clin. Oncol. 2001:19;843-850.

Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer D. Pegaptanib for Neovascular Age-Related Macular Degeneration. N Eng. J Med 2004;351:2805.

Heier JS, Sy JR, McCluskey ER, rhuFab V2 Study Group. RhuFab V2 in Wet AMD – 6 Month Continued Improvement Following Multiple Intravitreal Injections. Proc ARVO 2003.

Higgins RD, Yan Y, Geng Y, Zasloff M, Williams JI. Regression of retinopathy by squalamine in a mouse model. Pediatr Res. 2004;56:144-149.

Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, Boland P, Leidich R, Hylton D, Burova E, Ioffe E, Huang T, Radziejewski C, Bailey K, Fandl JP, Daly T, Wiegand SJ, Yancopoulos GD, Rudge JS. VEGF-Trap: A VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002; 99:11393–11398.

Hurwitz H, Fehrenbacher L, Cartwright T, Hainsworth J, Heim W, Berlin J, Griffing S, Novotny W, Holmgren E, Kabbinavar F. Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouriacil, leucovorin) as first-line therapy in patients with metastatic CRC. Abstract presented at the 39th Annual Meeting of the American Society for Clinical Oncology (ASCO), June 1, 2003.

Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NM, Li W, Connolly E, O'Neill CA, Miller JW: Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002, 120: 338-346.

Kwak N, Okamoto N, Wood JM, Campochiaro PA: VEGF is an important stimulator in a model of choroidal neovascularization. Invest Ophthalmol Vis Sci 2000, 41: 3158-3164.

Langmuir V, Cobleigh M, Herbst R, Holmgren E, Hurwitz H, Kabbinavar F, Miller K, Novotny W. Successful long-term therapy with bevacizumab (AvastinTM) in solid tumors: Preliminary report on extension study AVF0778g. Proc Am Soc Clin Oncol 2002.

The Macular Photocoagulation Study Group: Argon laser photocoagulation for neovascular maculopathy: Five year results from randomized clinical trials. Arch

Ophthalmol 1991; 109: 1109-1114.

Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology. 2005;112(6):1035-1047.

Nambu H, Nambu R, Melia M, Campochiaro PA. Combretastatin A-4 phosphate suppresses development and induces regression of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003; 44:3650.

Nussenblatt RB; Palestine AG; Chan CC; Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985 April; 92:467-71.

Ohno-Matsui, Hirose K, Yamamoto S, Saikia J, Okamot N, Gehlbach P, Duh EJ, Hackett S, Chang M, Bok D, Zack DJ, Campochiaro PA: Inducible Expression of Vascular Endothelial Growth Factor in Adult Mice Causes Severe Proliferative Retinopathy and Retinal Detachment. Am J Pathol 2002;160:711-719.

Rahmani B, Tielsch JM, Katz J, Gottsch J, Quigley H, Javitt J, Sommer A. The cause-specific prevalence of visual impairment in an urban population. The Baltimore Eye Survey. Ophthalmology. 1996; 103:1721-1726.

Rakic JM, Lambert V, Devy L, Luttun A, Carmeliet P, Claes C, Nguyen L, Foidart JM, Noel A, Munaut C. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci. 2003;44:3186-3193.

Rasmussen H, Chu KW, Campochiaro P, Gehlbach PL, Haller JA, Handa JT, Nguyen QD, Sung JU. Clinical protocol. An open-label, phase I, single administration, dose-escalation study of ADGVPEDF.11D (ADPEDF) in neovascular age-related macular degeneration (AMD). Hum Gene Ther. 2001;12:2029-2032.

Rechtman E, Danis RP, Pratt LM, Harris A Intravitreal triamcinolone with photodynamic therapy for subfoveal choroidal neovascularisation in age related macular degeneration. Br J Ophthalmol. 2004 Mar;88(3):344-347.

Reich SJ, Fosnot J, Kuroki A, Tang W, Yang X, Maguire AM, Bennett J, Tolentino MJ. Small interfering RNA (siRNA) targeting VEGF effectively inhibits ocular neovascularization in a mouse model. Mol Vis. 2003 30;9:210-216.

Rosenfeld PJ, Villate N. Feuer1 WJ, Puliafito CA, McCluskey ER. RhuFab V2 (Anti-VEGF Antibody Fragment) in Neovascular AMD: Safety, Tolerability, and Efficacy of Multiple, Escalating Dose Intravitreal Injections. Proc. ARVO 2003.

Saishin Y, Saishin Y, Takahashi K, Lima e Silva R, Hylton D, Rudge JS, Wiegand SJ, Campochiaro PA. VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiol 2003; 195:19:241-248.

Schmidt-Erfurth U, Miller JW, Sickenberg M, Laqua H, Barbazetto I, Gragoudas ES, Zografos L, Piguet B, Pournaras CJ, Donati G, Lane AM, Birngruber R, van den Berg H,

Strong HA, Manjuris U, Gray T, Fsadni M, Bressler NM: Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of retreatments in a phase 1 and 2 study. Arch Ophthalmol 1999, 117:1177-1187.

Schmidt-Erfurth, U, Scholotzer-Schrehard U, Cursiefen C, Michels S, Beckendorf A, Naumann GO. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. Invest Opththalmol Vis Sci. 2003;44:4473-4480.

Shen J, Samul R, Silva RL, Akiyama H, Liu H, Saishin Y, Hackett SF, Zinnen S, Kossen K, Fosnaugh K, Vargeese C, Gomez A, Bouhana K, Aitchison R, Pavco P, Campochiaro PA. Suppression of ocular neovascularization with siRNA targeting VEGF receptor 1. Gene Ther. 2006;13:225-234.

Smith LE, Wesolowski E, McLellan A, Kostyk SK, D'Amato R, Sullivan R, D'Amore PA. Oxygen-induced retinopathy in the mouse. Invest Ophthalmol Vis Sci. 1994; 35:101-111.

Thickett DR, Armstrong L, Millar A B. Vascular endothelial growth factor (VEGF) in inflammatory and malignant pleural effusions. Thorax 1999;54:707-710.

Yang JC, Haworth L, Steinberg SM, Rosenberg SA, Novotny W. A randomized trial of bevacizumab, an anti-Vascular Endothelial Growth Factor, for metastatic renal cancer. N Engl J Med 2003;349:427-434.

U.S. Department of Health and Human Services, Food and Drug Administration (FDA) Approved Lucentis™ (Ranibizumab) New Biologic Treatment for Wet Age-Related Macular Degeneration June 30, 2006.
http://www.fda.gov/bbs/topics/NEWS/2006/NEW01405.html

17 Investigator's Agreement

I have read the attached protocol: ***A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration*** dated ***May 17, 2007,*** and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guideline for Good Clinical Practice and the United States FDA regulations set forth in 21 CFR 50, 54, 56, 312 subpart D, and all applicable federal, state, and local laws, rules, regulations and guidelines relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for Regeneron Pharmaceuticals, Inc. or a partnership in which Regeneron is involved. I will immediately disclose it in writing to Regeneron if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of Regeneron Pharmaceuticals, Inc., which must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Appendix D: Study Drug Administration

ROUTE OF ADMINISTRATION: Intravitreal Injection

Study Drug Dose and Volume for Administration

VEGF Trap is formulated as a sterile liquid to a final concentration of either 10 mg/mL or 40 mg/mL VEGF Trap in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. VEGF Trap study drug will be supplied by Regeneron Pharmaceuticals Inc. in sealed, sterile 3 mL vials each with a "withdrawable" volume of approximately 0.5 mL. The volume of injection will be 50 µl (0.05 mL) for the 0.5 mg dose of VEGF Trap and the 2 mg dose of VEGF Trap. The study drug will be withdrawn using aseptic technique through an 18 gauge needle attached to a 1 mL syringe. The needle will be discarded after withdrawal of the vial contents and should not be used for ITV injection. The needle should be replaced with a sterile 30 gauge needle for the ITV injection. The contents should be expelled until the plunger is aligned with the line that marks 0.05 mL on the syringe.

When VEGF Trap vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

Based on present stability data and the fact that the dosing solution contains no bacteriostatic agents, VEGF Trap dosing solutions may be kept at room temperature (25 °C) for up to 2 hours; the injection of VEGF Trap must be completed within 2 hours of the start of dose preparation.

Sham injections will follow the same preparation procedure described below. The sham

Exhibit 39

Trials@uspto.gov
571-272-7822

Paper No. 93
Entered: October 26, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., CELLTRION, INC., and APOTEX, INC.,
Petitioners,

v.

REGENERON PHARMACEUTICALS INC.,
Patent Owner.

IPR2021-00880 (Patent 9,669,069 B2)[1]
IPR2021-00881 (Patent 9,254,338 B2)[2]

Record of Oral Hearing
Held: August 10, 2022[3]

Before ERICA A. FRANKLIN, JOHN G. NEW, and SUSAN L. C. MITCHELL, *Administrative Patent Judges.*

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[1] IPR2022-00257 and IPR2022-00301 have been joined with this proceeding.
[2] IPR2022-00258 and IPR2022-00298 have been joined with this proceeding.
[3] The consolidated hearing for these cases does not indicate that IPR2021-00880 and IPR2021-00881 have been joined.

IPR2021-00880 (Patent 9,669,069 B2)
IPR2021-00881 (Patent 9,254,338 B2)

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The above-entitled matter came on for hearing on Wednesday, August 10, 2022, commencing at 2:00 p.m. EST, in Hearing Room D.

P R O C E E D I N G S

- - - - -

2:00 p.m.

JUDGE NEW: Good afternoon. Welcome to the Board. My name is Judge New. I am joined today by Judge Mitchell and remotely by Judge Franklin.

We are convened to hear oral arguments in the matter of IPR2021-00880 and 00881. This hearing relates to claims 1 to 12 of US Patent 9,669,069 B2 in the 00880 IPR; and claims 1, 3 to 11, 13, 14, 16 to 24, and 26 of US Patent 9,254,338 B2 in the 00881 IPR.

Consistent with the hearing order, each party has a total of 60 minutes for its presentation. Petitioner may reserve a portion of their time to respond to arguments presented by Patent Owner. Patent Owner has also been authorized to reserve a portion of time for rebuttal.

Please be mindful that a court reporter is transcribing this hearing and there is no shared display for demonstrative exhibits for Judge Franklin, who is with us remotely. So please, when referring to a particular demonstrative exhibit, identify it clearly by number so that she can follow along with all of us here.

We're in receipt of the parties' objections to various evidence and Petitioner's motion to exclude. However, we will reserve ruling upon the objections and motions at this time.

Lastly, I'd like to remind you all that there are a number of documents and exhibits under seal in these proceedings, and that this hearing and trial transcript will be available to the public. I therefore caution

counsel against discussing or raising any matter that may be under seal and considered confidential.

And with that, Counsel for Petitioner, you may proceed after introducing yourself and indicating any time you would like to reserve for rebuttal.

MR. McGLAUGHLIN: Thank you, Your Honors. Neil McGlaughlin on behalf of Petitioners, Mylan Pharmaceuticals and the joint parties.

We would like to reserve 15 minutes of our time for rebuttal.

We also want to bring the Board's attention to, in case you didn't receive it, the corrected exhibits that Petitioner filed. Do you have copies of those?

JUDGE NEW: We do, yes. Thank you very much.

MR. McGLAUGHLIN: The '069 patent claims are directed to a prior art PRN dosing regimen that was in use by ophthalmologists when administering anti-VEGF agents long before the filing date of the '069 patent.

The '069 claims set forth the same regimen using a prior art molecule, aflibercept, also known as VEGF Trap-Eye, a molecule of known structure and sequence. Petitioner has set forth in this proceeding clear, straightforward grounds of anticipation based on disclosures of use of VEGF Trap-Eye in PRN dosing clinical trials, one example of which is shown here on slide 2.

This is from Exhibit 1006, the Dixon reference, from page 1576, the disclosure of the CLEAR-IT-2 Phase II trial in which VEGF Trap-Eye, also

There were a number of statements that clearly indicate -- this is a quote -- "clearly indicate that aflibercept and VEGF Trap-Eye are not necessarily the same proteins with the same amino acid sequence." And then I'll also refer you to page 113, lines 9 through 24, of Klibanov's deposition, which is Exhibit 1108.

In fact, Mylan's own expert conceded in deposition when confronted with the disclosures of Dixon that the POSA could have concluded that VEGF Trap-Eye and aflibercept were not the same molecule based on Dixon's discussions of two separate Phase I trials.

I don't know if we can pull up Exhibit 2130. Is that possible? Do we have that technology?

JUDGE NEW: 2130?

MS. FISHMAN: It's Exhibit 2130, which a deposition --

JUDGE NEW: I have that here in front of me.

MS. FISHMAN: Okay. Judge Franklin, I'll read into the record starting at line 340, 14. This is a question, my question to Dr. Albini.

But the POSA looking at this disclosure -- this is referring to Dixon, Exhibit 1006. But the POSA looking at this disclosure of one Phase I trial of aflibercept and a separate Phase I trial with VEGF Trap-Eye, is it possible that they would have concluded that these are different molecules?

There's an objection. Answer: Some may have, some may not.

So indeed, there are a number of disclosures in Dixon. And the testimony of Patent Owner's expert is taken as a whole. It was not necessarily the case that VEGF Trap-Eye and aflibercept were one and the same molecule.

JUDGE NEW: But there's no dispute, is there, that VEGF Trap-Eye was the drug being tested in the VIEW 1 and VIEW 2 tests in Dixon; is that correct?

MS. FISHMAN: That's correct.

JUDGE NEW: And it's also clear, as you acknowledged, that claim 1 of the '069 patent cites VEGF Trap-Eye, correct?

MS. FISHMAN: The sequence --

JUDGE NEW: That the sequence is the same?

MS. FISHMAN: Yes, that's correct.

JUDGE NEW: Right. Okay. Therefore, Dixon is teaching the use of that sequence, correct?

MS. FISHMAN: Well, it is known today that it's the sequence. Patent Owner's position is that wasn't known then.

So for example, are we able to pull up Mylan's slide number 10? Mylan has a slide number 10 where they -- there we go. I don't know, Your Honor, if you can see it. Mylan's slide number 10.

To be very clear, this Exhibit 1122, this did not exist in the prior art. This was created for this proceeding by Mylan's expert. They run a sequence comparison comparing the aflibercept and the sequence of the claims with sequences in Regeneron's prior art patent publications and patents. But what that ignores is there were other sequences in those same patents that satisfy Dixon's and Holash's structural description of $VEGFTrap_{R1R2}$ or VEGF Trap-Eye, but do not satisfy these claim limitations and do not align.

So this is with benefit of future knowledge. They go back and they fish out of prior art disclosures a sequence that matches the claims.

It's our position, as set forth in our briefs, that that is not permissible because rather than it being a permitted use of inherency for a property that the POSA necessarily possessed, what they're doing is backfilling an incomplete description in the prior art. And we believe our case law says that that's not permitted.

JUDGE NEW: Would you expect a person of ordinary skill in the art as you define it, which would be a practicing ophthalmologist -- am I correct on that?

MS. FISHMAN: That's correct.

JUDGE NEW: Would you expect them to know the amino acid sequence of a drug they're using?

MS. FISHMAN: It would depend on the --

JUDGE NEW: In other words, if Regeneron says, here's some VEGF Trap-Eye. Go and use it in your VIEW 1 test. And you're using that in the test, is having that amino acid sequence in their mental possession even relevant? If they're using the drug and the drug is being used, do they need to know that? I'm just not persuaded.

MS. FISHMAN: They don't truly possess the drug in the sense that they're under -- presumably, they're under restrictions on what they can do with it. They can't sequence it. Yes, they have it, but there are also restrictions on their use.

So from the perspective of our anticipatory or obviousness case law, their use of the drug would not put it in the public domain. It would not make it available to others.

JUDGE NEW: The claim is for method of use, is it not?

MS. FISHMAN: It's a method of treatment. That's correct.

JUDGE NEW: So it's a method of using the drug, in other words. It's not the drug itself. So using a drug with a particular sequence, that that sequence is going to be part of the drug. It is the drug, or part of it because it's not the entire component of the drug. It's going to be part of the drug however it's used, right?

So in other words, if I say, here's VEGF Trap-Eye. Go use it in your VIEW 1 test. And you use it in your VIEW 1 test, it's going to have that sequence, is it not?

MS. FISHMAN: I guess I'm a little confused by your question. Yes, we know today that VEGF Trap-Eye has the same sequence as the claims. And yes, when that was given to the clinical investigators in the studies that were performed, it had that sequence.

JUDGE NEW: So in other words, it was inherent. It was necessarily part of that drug.

MS. FISHMAN: It was the drug that was tested. I disagree that it was inherent because their use is not an anticipatory use in these proceedings, nor is it an anticipatory use even if we were in District Court because it was an experimental use under confidentiality restrictions. But yes, it was in there. That's true.

JUDGE NEW: It's experimental use but it's printed. It's there in the printed publication, is it not, for using the drug?

MS. FISHMAN: Well, that's where we differ. For anticipation, it has to be with -- it's the four corners that had to put the POSA in possession of it.

Regeneron's clinical investigators that were under confidentiality restrictions. They're not part of the prior art because their use of it, what

they know about it, the information they were provided by Regeneron, that's not public domain. It was tightly controlled by Regeneron.

JUDGE NEW: I see. And is the 10-Q document, the SEC filing, is that not part of the public domain as well?

MS. FISHMAN: That is part of the public domain.

JUDGE NEW: Right. And it basically says that aflibercept is VEGF Trap, and VEGF Trap-Eye is simply a purified VEGF Trap?

MS. FISHMAN: Your Honor, I made the points I have to make on the 1021.

JUDGE NEW: All right.

MS. FISHMAN: In the interest of time, may I move on to Adis also on a related point?

JUDGE NEW: Please do.

MS. FISHMAN: So with respect to Adis' disclosures, it is uncontroverted on this record that the POSA would not have considered Adis to be an accurate or reliable source of information. Adis has no author attribution and no indication of peer review. Adis contains errors and is inconsistent with more authoritative sources.

During questioning of the '338 anticipation grounds, Mr. Salmen said that Adis and Dixon have consistent descriptions of the VIEW trial. That is incorrect. Adis' description of VIEW 1 is inconsistent with Dixon and is inconsistent with more authoritative sources.

Indeed Dr. Albini, Mylan's expert, in his deposition admitted that the description of the VIEW 1 study in Adis was not the dosing regimen of the VIEW study. And this is at Exhibit 2130, Albini's deposition transcript, at

evidence saying that it's not just about the frequency of administration, but it's the frequency of administration coupled with matching the efficacy that had come to be expected in the art.

I see that I'm at time, Your Honors.

JUDGE NEW: You are indeed. Thank you very much.

MS. FISHMAN: Thank you, Your Honors.

JUDGE NEW: I thank you all for a most interesting and stimulating discussion. We also are grateful to our staff for making the hearing possible today.

We are taking the matter under advisement. A decision will be entered in due course.

We stand adjourned, but I'm going to ask you remain just in case our court reporter has any spelling questions.

(Whereupon, the above-entitled matter went off the record at 4:14 p.m.)

IPR2021-00880 (Patent 9,669,069 B2)
IPR2021-00881 (Patent 9,254,338 B2)

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E i it 40

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 28, 2022

VIATRIS INC.
(Exact name of registrant as specified in its charter)

Delaware	001-39695	83-4364296
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I R S. Employer Identification No.)

1000 Mylan Boulevard, Canonsburg, Pennsylvania, 15317
(Address of Principal Executive Offices)

Registrant's telephone number, including area code: (724) 514-1800

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.01 per share	**VTRS**	**The NASDAQ Stock Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 1.01 Entry into a Material Definitive Agreement.

On November 29, 2022, Viatris Inc., a Delaware corporation ("Viatris"), announced that it closed the previously announced transaction with Biocon Biologics Limited, a public limited company incorporated under the India Companies Act, 2013 ("Biocon Biologics"), involving the transfer by Viatris of substantially all of its biosimilars portfolio (the "Biosimilars Business") to Biocon Biologics and its subsidiaries (the "Transaction") in exchange for consideration from Biocon Biologics and its subsidiaries of $3.335 billion on a cash-free, debt-free basis, consisting of (a) $2.0 billion in cash consideration at closing, subject to certain adjustments as set forth in the Transaction Agreement (as defined below), (b) a convertible preferred equity stake in Biocon Biologics initially representing 12.9% of the equity in Biocon Biologics (on a fully diluted basis), which the parties' valued at $1 billion in the Transaction, (c) $160.0 million in future cash consideration, payable on the second anniversary of closing and (d) $175.0 million in future cash consideration, payable on April 8, 2024 (as a result of Biocon Biologics not exercising its right to exclude certain assets and liabilities related to Viatris' aflibercept product candidate from the Transaction). Approximately $150 million of the closing cash consideration was financed by equity commitments from Serum Institute Life Sciences Private Limited and approximately $650 million of the closing cash consideration was financed by equity commitments from Biocon Limited and its affiliate, Biocon Pharma Limited. The consideration is subject to certain post-closing adjustments and indemnities as set forth in the Transaction Agreement.

On November 28, 2022, prior to the closing of the Transaction, Viatris and Biocon Biologics entered into Amendment No. 1 ("Amendment No. 1") to the Transaction Agreement, dated as of February 27, 2022, between Viatris and Biocon Biologics (the "Original Transaction Agreement" and, as amended by Amendment No. 1, the "Transaction Agreement"). Amendment No. 1, among other things, (a) modified certain aspects of the structuring of the Transaction, (b) modified the timing and procedures for determining the purchase price adjustments, including relating to working capital, and (c) increased the amount of the working capital target from $150 million to $225 million. In addition, pursuant to the Transaction Agreement, at the closing of the Transaction, Viatris retained cash and certain current assets otherwise included in the working capital of the Biosimilars Business in an aggregate amount equal to the working capital target. All or a portion of such amounts may become payable to Biocon Biologics in connection with certain events in the future, depending on the valuations attributable to such events.

The foregoing description of the Transaction Agreement, and the transactions contemplated thereby, does not purport to be complete and is subject to, and qualified in its entirety by reference to, the full text of (i) the Original Transaction Agreement, which is attached as Exhibit 2.1 to Viatris' Form 8-K filed with the SEC on February 28, 2022 and incorporated herein by reference, and (ii) Amendment No. 1, which is attached as Exhibit 2.1 hereto and incorporated herein by reference.

The above description of the Transaction Agreement has been included to provide investors and security holders with information regarding the terms of such agreements. It is not intended to provide any other factual information about Viatris and Biocon Biologics and their respective subsidiaries and affiliates, or any of their respective businesses. The Transaction Agreement contains representations and warranties that are solely for the benefit of parties thereto. The assertions embodied in those representations and warranties are qualified by information in confidential disclosure letters that the parties have exchanged in connection with signing the Transaction Agreement as of a specific date. The disclosure letters contain information that modifies, qualifies and creates exceptions to the representations and warranties set forth in the Transaction Agreement. Therefore, investors and security holders should not treat the representations and warranties as categorical statements of fact. Moreover, these representations and warranties may apply standards of materiality in a way that is different from what may be material to investors. They were made only as of the date of the Original Transaction Agreement or such other date or dates as may be specified in the Transaction Agreement and they are subject to more recent developments. Accordingly, investors and security holders should read the representations and warranties in the Transaction Agreement not in isolation but only in conjunction with the other information about Viatris and its respective subsidiaries that the respective companies include in reports and statements Viatris files with the SEC.

Item 2.01 Completion of Acquisition or Disposition of Assets

The information contained in Item 1.01 of this Current Report on Form 8-K is incorporated herein by reference.

Item 7.01 Regulation FD Disclosure

On November 29, 2022, Viatris issued a press release announcing the closing of the Transaction. A copy of the press release is attached hereto as Exhibit 99.1 and is incorporated herein by reference.

The information in this Item 7.01 (including Exhibit 99.1) shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liability of that section, and shall not be incorporated by reference into any registration statement or other document filed under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

Forward-Looking Statements

This Current Report on Form 8-K contains "forward-looking statements". These statements are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements may include, without limitation, statements about the Transaction, including statements about the future cash consideration payable in the Transaction, the post-closing purchase price adjustments and indemnities related to the Transaction, the amounts that may become payable to Biocon Biologics in connection with future events and the sale or conversion of Viatris' equity stake in Biocon Biologics. Forward-looking statements may often be identified by the use of words such as "will", "may", "could", "should", "would", "project", "believe", "anticipate", "expect", "plan", "estimate", "forecast", "potential", "pipeline", "intend", "continue", "target", "seek" and variations of these words or comparable words. Because forward-looking statements inherently involve risks and uncertainties, actual future results may differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to: the Transaction may not achieve its intended benefits; the parties' ability to meet expectations regarding the accounting and tax treatments of the Transaction; changes in relevant tax and other laws; the possibility that Viatris may be unable to achieve expected benefits, synergies and operating efficiencies in connection with the transaction pursuant to which Mylan N.V. ("Mylan") combined with the Pfizer Inc.'s Upjohn business (the "Upjohn Business") in a Reverse Morris Trust transaction (the "Combination") and Upjohn Inc. became the parent entity of the combined Upjohn Business and Mylan business and was renamed "Viatris Inc." or Viatris' global restructuring program within the expected timeframe or at all; the Transaction and other strategic initiatives, including potential divestitures, may not achieve their intended benefits; operational or financial difficulties or losses associated with Viatris' reliance on agreements with Pfizer in connection with the Combination, including with respect to transition services; the potential impact of public health outbreaks, epidemics and pandemics, including the ongoing challenges and uncertainties posed by the COVID-19 pandemic; Viatris' failure to achieve expected or targeted future financial and operating performance and results; actions and decisions of healthcare and pharmaceutical regulators; changes in relevant laws and regulations, including but not limited to changes in tax, healthcare and pharmaceutical laws and regulations globally (including the impact of potential tax reform in the U.S.); the ability to attract and retain key personnel; Viatris' liquidity, capital resources and ability to obtain financing; any regulatory, legal or other impediments to the Viatris' ability to bring new products to market, including but not limited to "at-risk launches"; success of clinical trials and the Viatris' or its partners' ability to execute on new product opportunities and develop, manufacture and commercialize products; any changes in or difficulties with Viatris' manufacturing facilities, including with respect to inspections, remediation and restructuring activities, supply chain or inventory or the ability to meet anticipated demand; the scope, timing and outcome of any ongoing legal proceedings, including government inquiries or investigations, and the impact of any such proceedings on Viatris; any significant breach of data security or data privacy or disruptions to our information technology systems; risks associated with having significant operations globally; the ability to protect intellectual property and preserve intellectual property rights; changes in third-party relationships; the effect of any changes in Viatris' or its partners' customer and supplier relationships and customer purchasing patterns, including customer loss and business disruption being greater than expected following the Combination; the impacts of competition, including decreases in sales or revenues as a result of the loss of market exclusivity for certain products; changes in the economic and financial conditions of Viatris or its partners; uncertainties regarding future demand, pricing and reimbursement for Viatris' products; uncertainties and matters beyond the control of management, including but not limited to general political and economic conditions, inflation rates and global exchange rates; and inherent uncertainties involved in the estimates and judgments used in the preparation of financial statements, and the providing of estimates of financial measures, in accordance with accounting principles generally accepted in the United States and related standards or on an adjusted basis. For more detailed information on the risks and uncertainties associated with Viatris, see the risks described in Part I, Item 1A of Viatris' Annual Report on Form 10-K for the year ended December 31, 2021, as amended, and our other filings with the SEC. You can access Viatris' filings with the SEC through the SEC website at www.sec.gov or through our website, and Viatris strongly encourages you to do so. Viatris routinely posts information that may be important to investors on our website at investor.viatris.com, and we use this website address as a means of disclosing material information to the public in a broad, non-exclusionary manner for purposes of the SEC's Regulation Fair Disclosure (Reg FD). The contents of our website are not incorporated into this filing or our other filings with the SEC. Viatris undertakes no obligation to update any statements herein for revisions or changes after the date of this filing other than as required by law.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits

Exhibit No.	Description
2.1	Amendment No. 1 to Transaction Agreement, dated as of November 28, 2022, by and between Biocon Biologics Limited and Viatris Inc.*
99.1	Viatris press release announcing the closing of the Transaction

* Annexes, schedules and/or exhibits have been omitted pursuant to Item 601(b)(2) of Regulation S-K. Viatris agrees to furnish supplementally a copy of any omitted attachment to the SEC on a confidential basis upon request.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Viatris Inc.

By: /s/ Sanjeev Narula
Name: Sanjeev Narula
Title: Chief Financial Officer

Date: November 29, 2022

AMENDMENT NO. 1
TO
TRANSACTION AGREEMENT

November 28, 2022

Reference is hereby made to that certain Transaction Agreement, dated as of February 27, 2022 (as amended from time to time, the "Agreement"), by and between Biocon Biologics Limited, a public limited company incorporated under the Indian Companies Act, 2013 ("Buyer"), and Viatris Inc., a Delaware corporation ("Seller Parent"). Capitalized terms used but not defined in this Amendment No. 1 to the Transaction Agreement (this "Amendment") shall have the respective meanings assigned to them in the Agreement.

WHEREAS, concurrently with the execution and delivery of this Amendment, the Parties are entering into Amendment No. 1 to the Seller Parent Disclosure Letter; and

WHEREAS, the Parties desire to amend the Agreement in accordance with the terms set forth herein.

NOW, THEREFORE, in consideration of the premises and the representations, warranties, covenants and agreements contained in this Amendment and the Agreement, and subject to the conditions set forth herein and therein, the Parties hereby agree as follows:

1. Amendments of the Agreement.

(a) The third recital of the Agreement is hereby amended and restated in its entirety as follows:

"WHEREAS, prior to the date of this Agreement (a) Mylan Ireland Limited, an Irish private limited company and a Subsidiary of Seller Parent ("Mylan Ireland"), transferred its biosimilars trade (including Transferred Assets and Assumed Liabilities) to Biosimilar Collaborations Ireland Limited, an Irish private limited company (such transfer, the "Irish Spin-Off" and, such transferee, the "Irish Acquired Company") and (b) Mylan Ireland transferred all of the issued and outstanding equity interests in the Irish Acquired Company to the Irish Seller and, as of the date of this Agreement, the Irish Seller is the sole record and beneficial owner of all of the issued and outstanding equity interests (including any preference shares) in the Irish Acquired Company;"

(b) The seventh recital of the Agreement is hereby amended and restated in its entirety as follows:

"WHEREAS, Buyer is the sole record and beneficial owner of all of the issued and outstanding equity interests in the Subsidiary Buyer;"

(c) The eighth recital of the Agreement is hereby amended and restated in its entirety as follows:

"WHEREAS, upon the terms and subject to the conditions set forth in this Agreement, Seller Parent and Buyer desire to cause (a) the sale of the Acquired ROW Equity Interests from ROW Seller to Buyer in exchange for the Stock Consideration, (b) the payment of other amounts as described herein, including, pursuant to the ROW Acquisition, the Irish Future Cash Payment, and (c) (i) the subscription by the Subsidiary Buyer for, and the allotment and issue by the Irish Acquired Company of, the Irish New Equity Interests in exchange for the Irish Closing Cash Consideration and (ii) the redemption by the Irish Acquired Company of the Irish Redemption Equity Interests in exchange for an amount equal to the Irish Closing Cash Consideration;"

(d) The ninth recital of the Agreement is hereby amended and restated in its entirety as follows:

"WHEREAS, concurrently with the execution of this Agreement, as an inducement to and condition of Seller Parent's willingness to enter into this Agreement and the other Transaction Documents to which it is a party, (a) Buyer Parent, Buyer and Seller Parent have duly executed and delivered the Equity Financing Letter, attached as Exhibit I-A hereto (the "Buyer Parent Equity Financing Letter") and (b) Serum, Buyer and Seller Parent have duly executed and delivered the Equity Financing Letter, attached as Exhibit I-B hereto (the "Serum Equity Financing Letter" and, together with the Buyer Parent Equity Financing Letter, the "Equity Financing Letters");"

(e) The Agreement is amended by adding the following as a new recital, immediately after the ninth recital of the Agreement:

"WHEREAS, prior to or concurrently with the execution of this Amendment, as an inducement to and condition of Seller Parent's willingness to enter into this Amendment and the other Transaction Documents to which it is a party, (a) Buyer Parent, Buyer, BPL and Seller Parent have duly executed and delivered the Amendment to Equity Financing Letter, attached as Exhibit I-C hereto (the "Buyer Parent Equity Financing Letter Amendment"; the Buyer Parent Equity Financing Letter, as amended by the Buyer Parent Equity Financing Letter Amendment, the "Buyer Parent Amended Equity Financing Letter"), and pursuant to the Buyer Parent Amended Equity Financing Letter, upon the terms and subject to the conditions set forth therein, prior to the Closing, Buyer Parent, BPL and Buyer shall consummate the Buyer Parent Equity Financing and (b) Serum, Buyer and Seller Parent have duly executed and delivered the Amendment to Equity Financing Letter, attached as Exhibit I-D hereto (the "Serum Equity Financing Letter Amendment"; the Serum Equity Financing Letter, as amended by the Serum Equity Financing Letter Amendment, the "Serum Amended Equity Financing Letter" and, the Serum Amended Equity Financing Letter together with the Buyer Parent Amended Equity

Financing Letter, the "Amended Equity Financing Letters"), and pursuant to the Serum Amended Equity Financing Letter, upon the terms and subject to the conditions set forth therein, prior to the Closing, Serum and Buyer shall consummate the Serum Equity Financing;"

(f) The first sentence of Section 1.01 of the Agreement is hereby amended and restated in its entirety as follows:

"Closing. The closing of (a) the ROW Acquisition, (b) the repayment in full the ROW Note, (c) the Irish Subscription and (d) the Irish Redemption (the "Closing") shall take place remotely via the electronic exchange of documents and signature pages at 10:00 a.m., New York City time, on the second (2nd) Business Day following the date of satisfaction (or, to the extent permitted by Law, waiver by the Parties entitled to the benefit thereof) of all of the conditions set forth in Article VI (other than those conditions which by their terms are to be satisfied at the Closing, but subject to satisfaction or waiver of such conditions), or at such other place, time and date as shall be agreed in writing between Buyer and Seller Parent."

(g) Section 1.02(a) of the Agreement is hereby amended and restated in its entirety as follows:

"ROW Acquisition. Seller Parent shall cause the ROW Seller to sell, assign, transfer, convey and deliver to Buyer, and Buyer shall purchase and accept from the ROW Seller, the Acquired ROW Equity Interests, in each case, in accordance with Section 1.03 and Section 1.04 (the "ROW Acquisition"), free and clear of Liens, other than (A) transfer restrictions under applicable Securities Laws and (B) those arising pursuant to this Agreement or from acts of Buyer or its Affiliates (including any Liens related to the Debt Financing). The aggregate consideration payable in respect of the ROW Acquisition shall be the Stock Consideration (payable when and as set forth in Section 1.04). In addition, Buyer shall cause the ROW Acquired Company to repay in full the ROW Note and to pay the ROW Future Cash Payment (payable when and as set forth in Section 1.05). Further, pursuant to the ROW Acquisition, Buyer shall cause the Subsidiary Buyer to pay the Irish Future Cash Payment (payable when and as set forth in Section 1.05 and subject to Section 1.10)."

(h) The last sentence of Section 1.02(b) of the Agreement is hereby amended by adding the words "when and" immediately before the words "as set forth".

(i) The last sentence of Section 1.02(c) of the Agreement is hereby amended by adding the words "when and" immediately before the words "as set forth".

(j) Section 1.03 of the Agreement is hereby amended and restated in its entirety as follows:

"Allocation of Cash Consideration and Acquired Equity Interests. (i) An amount equal to the Irish Closing Cash Consideration shall be paid to the Irish Seller by the Irish Acquired Company in consideration for the Irish Redemption, (ii) the Stock Consideration shall be paid to the ROW Seller by Buyer, (iii) the Adjustment Amount shall be paid (A) to the ROW Seller by the ROW Acquired Company or to the Irish Seller by the Subsidiary Buyer, as applicable, or (B) by the ROW Seller and the Irish Seller, as applicable, to the ROW Acquired Company or the Subsidiary Buyer, in the case of each of clauses (A) and (B), with the ROW Seller and the Irish Seller receiving or paying, as applicable, the portion of the Adjustment Amount related to the ROW Acquired Company and the Irish Acquired Company, respectively, (iv) the ROW Future Cash Payment shall be paid to the ROW Seller by the ROW Acquired Company and (v) the Irish Future Cash Payment shall be paid to the Irish Seller by the Subsidiary Buyer, in the case of each of clauses (i) through (v), at such times as specified in this Agreement."

(k) Section 1.04(a)(i) of the Agreement amended and restated in its entirety as follows:

"consummate each Equity Financing in accordance with the Amended Equity Financing Letter for such Equity Financing, and immediately thereafter contribute $800,000,000 (eight hundred million dollars) to the Subsidiary Buyer (the "Subsidiary Buyer Contribution");"

(l) Section 1.04(a)(ii) of the Agreement is hereby amended and restated in its entirety as follows:

"(A) pursuant to the ROW Acquisition convey and deliver to the ROW Seller book-entry interests representing the Stock Consideration, together with duly executed instruments of issuance, sale and delivery in respect thereof, in form and substance reasonably acceptable to Seller Parent, evidencing the issuance, sale and delivery of the Stock Consideration, (B) immediately after the conveyance and delivery to Buyer of duly executed instruments of assignment in respect of the Acquired ROW Equity Interests pursuant to Section 1.04(b)(i), cause the Subsidiary Buyer to pay, or to cause to be paid (out of the proceeds of the Subsidiary Buyer Contribution), to the ROW Acquired Company, by wire transfer of immediately available funds to the account(s) designated in writing by Buyer (such designation to be set forth in the ROW Letter of Direction), an amount equal to $212,000,000 (two hundred twelve million dollars), in exchange for the ROW Acquired Company allotting and issuing to Subsidiary Buyer new ordinary shares or preference shares of the ROW Acquired Company (the "Buyer ROW Contribution"), and (C) immediately after the Buyer ROW Contribution, cause the ROW Acquired Company to pay (which payment shall be in part out of the proceeds of the Buyer ROW Contribution), to the

ROW Seller, by wire transfer of immediately available funds to the account(s) designated in writing by Seller Parent (such designation to be set forth in the ROW Letter of Direction), an amount equal to the amount required to repay in full the ROW Note;"

(m) Section 1.04(a)(iii) of the Agreement is hereby amended by replacing the words "writing by Seller Parent at least two (2) Business Days prior to the Closing Date" with the words "the Irish Letter of Direction".

(n) The first sentence of Section 1.04(b) of the Agreement is hereby amended by replacing the words "upon receipt of the Estimated Closing Cash Consideration and the Stock Consideration" with the words "upon (x) the substantially concurrent receipt of the Stock Consideration and immediately available funds described in Section 1.04(a)(ii) and (y) the substantially concurrent receipt of the immediately available funds described in Section 1.04(a)(iii)".

(o) Section 1.04(b)(i) of the Agreement is hereby amended and restated in its entirety as follows:

"pursuant to the ROW Acquisition, cause the ROW Seller to convey and deliver to Buyer duly executed instruments of assignment, in form and substance reasonably acceptable to Buyer, evidencing the sale, assignment, transfer, conveyance and delivery of the Acquired ROW Equity Interests;"

(p) Section 1.04(b)(iii) of the Agreement is hereby amended by replacing the words "writing by Seller Parent at least two (2) Business Days prior to the Closing Date" with the words "the Irish Letter of Direction"

(q) The heading of Section 1.05 of the Agreement is hereby amended by replacing the words "Future Cash Consideration" with the words "Future Cash Payments".

(r) Section 1.05(a) of the Agreement is hereby amended by deleting the phrase "(or, at Seller Parent's election, any other wholly owned Subsidiary of Seller Parent as may be designated in writing by Seller Parent at least two (2) Business Days prior to April 8, 2024)" from the first sentence thereof.

(s) Section 1.05(b) of the Agreement is hereby amended and restated in its entirety as follows:

"If the Closing occurs, then, subject to Section 8.09, within two (2) Business Days following the Second Anniversary Date, Buyer shall take all actions to cause the ROW Acquired Company to pay to the ROW Seller, by wire transfer of immediately available funds to the account(s) designated in writing by Seller Parent at least two (2) Business Days prior to the Second Anniversary Date, an amount equal to $160,000,000 (one hundred sixty

million dollars) (the "ROW Future Cash Payment" and, together with the Irish Future Cash Payment, the "Future Cash Payments")."

(t) The heading of Section 1.06 of the Agreement is hereby amended by replacing the words "Purchase Price Adjustment" with the words "Adjustment Amounts".

(u) Section 1.06 of the Agreement is hereby amended by replacing each reference to "Final Closing Cash Consideration" with a reference to "Final Adjustment Amount".

(v) Section 1.06(a) of the Agreement is hereby amended by (i) replacing the words "Not less than five (5) Business Days prior to the Closing Date," with the words "Within five (5) Business Days after the Closing Date," and (ii) replacing the words "Estimated Closing Cash Consideration" with the words "Estimated Adjustment Amount".

(w) Section 1.06(b) of the Agreement is hereby amended by replacing the words "forty-five (45)" with the words "sixty (60)".

(x) Section 1.07(a) of the Agreement is hereby amended by replacing the word "Sellers" with the words "Irish Seller and the ROW Acquired Company to pay to the ROW Seller, as applicable".

(y) Section 1.07(b) of the Agreement is hereby amended by (i) replacing the word "Sellers" with the words "ROW Seller to pay to the ROW Acquired Company and the Irish Seller to pay to the Subsidiary Buyer, as applicable" and (ii) deleting the words "to pay to the Subsidiary Buyer" immediately following the parenthetical thereof.

(z) Section 2.03(a) of the Agreement is hereby amended and restated in its entirety as follows:

"As of immediately prior to the Closing and after giving effect to the Business Internal Reorganization, (i) the ROW Seller will be the sole record and beneficial owner of all of the issued and outstanding equity interests in ROW Newco, (ii) the ROW Seller will have good and valid title to all of the Acquired ROW Equity Interests, free and clear of Liens other than (A) transfer restrictions under applicable Securities Laws and (B) those arising from acts of Buyer or its Affiliates (including any Liens related to the Debt Financing), and (iii) the ROW Seller will be the record and the beneficial owner of all such Acquired ROW Equity Interests. Assuming Buyer has the requisite power and authority to be the lawful owner of the Acquired ROW Equity Interests, upon (i) delivery by the ROW Seller to Buyer at the Closing of the items described in Section 1.04(b)(i) and (ii) delivery by Buyer and the ROW Acquired Company, as applicable, to the ROW Seller of the consideration required to be paid by Buyer and the ROW Acquired

Company at the Closing, as described in Section 1.04(a)(iii), good and valid title to the Acquired ROW Equity Interests will pass to Buyer at the Closing, free and clear of Liens, other than (i) transfer restrictions under applicable Securities Laws and (ii) those arising pursuant to this Agreement or from acts of Buyer or its Affiliates (including any Liens related to the Debt Financing), and the Acquired ROW Equity Interests, together with the equity interests in the ROW Acquired Company to be issued to the Subsidiary Buyer in the Buyer ROW Contribution, will constitute 100% of the issued share capital of the ROW Acquired Company immediately following the Closing. Upon issuance, each Acquired ROW Equity Interest will be (in each case, to the extent such concepts are applicable) duly authorized, validly issued, fully paid and nonassessable, and will not be issued or transferred in violation of any purchase option, call option, right of first refusal, preemptive right, subscription right or other similar right under any provision of the Applicable Business Organization Law or the organizational or similar documents of Seller Parent or any of its Subsidiaries (including the ROW Seller and the ROW Acquired Company)."

(aa) Section 3.01 of the Agreement is hereby amended and restated in its entirety as follows:

"(a) Each of Buyer and its Subsidiaries (i) is duly organized, validly existing and in good standing (with respect to jurisdictions that recognize such concept) under the Applicable Business Organization Law, (ii) has full corporate or similar power and authority to own, lease or license, and to operate, its properties and assets and to operate its business as currently operated and (iii) is duly qualified or licensed to do business as a foreign company and in good standing (with respect to jurisdictions that recognize such concept) in each jurisdiction where the character of the properties owned, leased or operated by it or the nature of its business makes such qualification or licensing necessary, in the case of each of clauses (i), (ii) and (iii), in all material respects.

(b) True, correct and complete copies of the organizational or similar documents of Buyer and each of its Subsidiaries, as in effect on the date of this Agreement, have been made available to Seller Parent. Each such organizational or similar document is in full force and effect in all material respects, and none of Buyer or its Subsidiaries is in material violation of any provisions thereof."

(bb) Section 3.02(a) of the Agreement is hereby amended and restated in its entirety as follows:

"Buyer has all necessary corporate or similar power and authority to execute and deliver this Agreement, each of Buyer and Subsidiary Buyer has all necessary corporate or similar power and authority to execute and deliver

any other Transaction Document to which it is, or is specified to be, a party, and to perform its obligations hereunder and thereunder and to consummate the Transactions to be consummated by it. Without limiting the generality of the foregoing, each of Buyer and Subsidiary Buyer has all necessary corporate or similar power and authority to cause each of its Subsidiaries (including, at and following such time as they become Subsidiaries of Buyer, the Business Companies) to perform the respective obligations under this Agreement and the other Transaction Documents required to be performed by such Subsidiaries and to consummate the Transactions to be consummated by such Subsidiaries (in the case of the Business Companies, at and following such time as they become Subsidiaries of Buyer). The execution, delivery and performance by Buyer of this Agreement, and the execution, delivery and performance by each of Buyer and Subsidiary Buyer of any other Transaction Document to which it is, or is specified to be, a party, and the consummation of the Transactions to be consummated by it, have been duly authorized by all necessary corporate or similar action by Buyer and Subsidiary Buyer, as applicable. This Agreement has been, and each other Transaction Document to which Buyer or Subsidiary Buyer is, or is specified to be, a party will, at or prior to the Closing, be, duly executed and delivered by Buyer and Subsidiary Buyer, as applicable. Assuming the due authorization, execution and delivery by the other parties thereto, this Agreement constitutes, and each other Transaction Document to which Buyer or Subsidiary Buyer is, or is specified to be, a party will constitute, a legal, valid and binding obligation of Buyer and such Subsidiary Buyer, as applicable, enforceable against Buyer and such Subsidiary Buyer, as applicable, in accordance with its terms, except as enforcement thereof may be limited by the Enforceability Exceptions."

(cc) Section 3.03(a) of the Agreement is hereby amended by (i) replacing the reference to "Section 1.04(a)(ii)(B)" with the reference "Section 1.04(a)(ii)(A)" and (ii) replacing the words "the Applicable Buyers" with the word "Buyer", in each case, in the first sentence thereof.

(dd) Section 3.03(c) of the Agreement is hereby amended by replacing the words "From and after its formation until the Closing, Buyer will be" in the last sentence thereof with the words "Buyer is".

(ee) Section 3.03(d) of the Agreement is hereby amended by replacing the words "Buyer Parent Equity Financing Letter" with the words "Buyer Parent Amended Equity Financing Letter" in the first sentence thereof.

(ff) Section 3.04(a) of the Agreement is hereby amended by deleting the phrase "(or, in the case of Subsidiary Buyer, following its formation will be)".

(gg) Section 3.21(a) of the Agreement is hereby amended and restated in its entirety as follows:

As of the date of this Agreement, (i) each of the Equity Financing Letters has not been amended, supplemented or modified, and no such amendment, supplement or modification is contemplated, and (ii) the covenants and agreements contained in each of the Equity Financing Letters have not been withdrawn, terminated or rescinded in any respect, and no such withdrawal, termination or rescission is contemplated. As of the date of this Amendment, (i) each of the Amended Equity Financing Letters has not been amended, supplemented or modified, and no such amendment, supplement or modification is contemplated, and (ii) the covenants and agreements contained in each of the Amended Equity Financing Letters have not been withdrawn, terminated or rescinded in any respect, and no such withdrawal, termination or rescission is contemplated. Except for the Amended and Restated Governance Documents, any escrow arrangement entered into in connection with the Serum Equity Financing or as set forth in Section 3.21(a) of the Buyer Disclosure Letter, there are no side letters, Contracts or other arrangements or understandings related to any Equity Financing or any Amended Equity Financing Letter. The execution, delivery and performance of each of the Amended Equity Financing Letters will not (i) conflict with or violate any provision of the organizational or similar documents of Buyer or any of its Subsidiaries, (ii) require any Consent of, or Filing with, any Governmental Entity that has not been made or obtained, (iii) conflict with or violate any Order or Law applicable to Buyer or any of its Subsidiaries or by which any property or asset of Buyer or any of its Subsidiaries is bound, (iv) require any Consent by any Person that has not been obtained under, result in a breach of, loss of a benefit or constitute a default (or an event that with notice or lapse of time or both would become a default) under, or give to others (immediately or with notice or lapse of time or both) any right of termination, amendment, acceleration or cancellation of, any Contract of Buyer or any of its Subsidiaries or (v) result (immediately or with notice or lapse of time or both) in the creation of any Lien (other than a Permitted Lien) on any property or asset of Buyer or any of its Subsidiaries, except, in the case of clauses (ii), (iii), (iv) and (v) above, as would not, individually or in the aggregate, reasonably be expected to be material to Buyer and its Subsidiaries, taken as a whole."

(hh) Section 3.21(b) of the Agreement is hereby amended by replacing each reference to "Equity Financing Letters" with a reference to "Amended Equity Financing Letters".

(ii) Section 3.21(c) of the Agreement is hereby amended by replacing the words "any adjustment thereto" with the words "the Adjustment Amount".

(jj) Section 3.21(c)(ii)(A) of the Agreement is hereby amended by replacing the words "pay the aggregate Estimated Closing Cash Consideration" with the words "repay the ROW Note and pay the Irish Closing Cash Consideration".

(kk) Section 4.02(b)(i)(a)(1) of the Agreement is hereby amended by replacing the reference to "Equity Financing Letter" with a reference to "Amended Equity Financing Letter".

(ll) Section 5.03 of the Agreement is hereby amended and restated in its entirety as follows:

"SECTION 5.03. Business Internal Reorganization.

(a) Prior to the Closing, subject to Section 1.09, Seller Parent shall, and shall cause its Subsidiaries to, consummate the transactions as described in the Business Steps Plan (the "Business Internal Reorganization"), which Business Internal Reorganization will result in, among other things, the biosimilars business not already held by the Irish Acquired Company (which business consists solely of Transferred Assets and Assumed Liabilities not already held by the Irish Acquired Company) being transferred to and assumed by the ROW Acquired Company immediately prior to the Closing. Seller Parent shall provide Buyer with a reasonable opportunity to review and comment on the material operative documentation effecting the Business Internal Reorganization and shall accept reasonable comments of Buyer that will not prevent or impede the Intended Tax Treatment. Except as otherwise expressly provided by Section 1.09, Seller Parent shall be permitted to amend the Business Steps Plan only (i) with the prior written consent of Buyer (such consent not to be unreasonably withheld, delayed or conditioned), (ii) if Seller Parent reasonably determines that such amendment is necessary or appropriate to achieve the Intended Tax Treatment or achieve a tax efficient structure for Seller Parent or its Affiliates (provided that any such amendment shall not impose any material costs or expenses on Buyer or any Business Company (unless Seller Parent agrees to indemnify and hold harmless Buyer or the applicable Business Company for any such costs or expenses) or materially impair or delay the consummation of the transactions contemplated hereby) or (iii) if Seller Parent determines such amendment is reasonably necessary or appropriate to effect the Transactions and such amendment would not reasonably be expected to (A) be material and adverse to Buyer or (B) materially impair or delay the consummation of the Transactions.

(b) Seller Parent shall take all actions required to ensure that, following their formation, the Business Companies are at all times, between the date of this Agreement and the Closing Date, Affiliates of the Seller Parent. Prior to the Closing, Buyer will make the election, with an effective date on or prior to the Closing Date, with respect to the Subsidiary Buyer pursuant to U.S. Treasury Regulation Section 301.7701-3 to treat the Subsidiary Buyer as an entity disregarded as separate from its owner for U.S. federal income tax purposes.

(c) The assignments and transfers of the Business Registered Intellectual Property pursuant to the Business Internal Reorganization shall be recorded and filed by Buyer, with the appropriate Governmental Entity following the Closing. Following the Closing, at Buyer's reasonable request, Seller Parent shall use reasonable best efforts to provide assistance necessary for Buyer to achieve such recordings and filings. The recordation and filing fees pursuant to this Section 5.03(c) shall be borne 50% by Seller Parent and 50% by Buyer."

(mm) Section 5.06(a)(iii)(A)(1) of the Agreement is hereby amended by replacing the words "the ROW Acquisition" with the words "the ROW Acquisition, the repayment of the ROW Note, the ROW Future Cash Payment".

(nn) Section 5.06(c)(ii) of the Agreement is hereby amended and restated in its entirety as follows:

"From and after the Closing until the date of the payment of the ROW Future Cash Payment, none of Buyer, the Subsidiary Buyer or any of Buyer's other Affiliates shall revoke or amend the election under Section 301.7701-3 of the U.S. Treasury Regulations or take any other actions to cause the Subsidiary Buyer to be treated as an entity other than an entity disregarded from Buyer (its owner) for U.S. federal income tax purposes (including any actions taken after the date of the ROW Future Cash Payment that have a retroactive effect to the date of the ROW Future Cash Payment), without the prior written consent of Seller Parent. From and after the Closing until after the date of the payment of the ROW Future Cash Payment, none of Buyer, the Subsidiary Buyer or any of Buyer's other Affiliates shall revoke or amend the election under Section 301.7701-3 of the U.S. Treasury Regulations or take any other actions to cause the ROW Acquired Company to be treated as an entity other than an entity disregarded from Buyer (its owner) for U.S. federal income tax purposes (including any actions taken after the date of the ROW Future Cash Payment that have a retroactive effect to the date of the ROW Future Cash Payment), without the prior written consent of Seller Parent."

(oo) Section 5.08 of the Agreement is hereby amended by adding the following new clause immediately after clause (d) thereof:

"After the Closing, Buyer shall, and shall cause its Subsidiaries to, at the request of Seller Parent, provide reasonable cooperation to Seller Parent and its Subsidiaries relating to the Insulin Investigations and the Insulin Actions, including by (i) retaining and, upon request of Seller Parent, providing Seller Parent with any books, records and other data or information relating to any of the Insulin Investigations or the Insulin Actions and (ii) upon request of Seller Parent, making their respective employees, and using reasonable best efforts to make their respective consultants and independent contractors, reasonably available to assist with the Insulin Investigations

and the Insulin Actions (including in connection with any investigation, prosecution, pretrial activities or trial relating to, or any compromise, settlement or other discharge of, any of the Insulin Investigations or the Insulin Actions). As used herein, "Insulin Investigations" shall have the meaning given in Item 10 of Section 9.02(b) of the Seller Parent Disclosure Letter."

(pp) Section 5.13(a)(ii) of the Agreement is hereby amended by replacing the words "Equity Financing Letters" with the words "Amended Equity Financing Letters".

(qq) Section 5.15 of the Agreement is hereby amended by adding the following sentence immediately after the last sentence thereof:

"Notwithstanding the foregoing, Seller Parent and Buyer acknowledge and agree that Buyer shall not be required to (a) replace a Credit Support Item or (b) indemnify and hold harmless Seller Parent and its Subsidiaries from and against any claims, losses, liabilities, damages, judgments, fines, penalties, costs and expenses, in each case, pursuant to this Section 5.15 until after Seller Parent has identified such Credit Support Item to Buyer."

(rr) The second sentence of Section 5.19 of the Agreement is hereby amended and restated in its entirety as follows:

"Notwithstanding the immediately preceding sentence, if mutually agreed by Seller Parent and Buyer prior to the Closing, all or certain of the Seller Parent/Buyer Contracts may instead be assigned to Buyer or its Subsidiaries at the Closing or assigned to ROW Acquired Company or Irish Acquired Company prior to or at the Closing, rather than being terminated effective as of the Closing."

(ss) Section 6.03(d) of the Agreement is hereby amended by replacing the words "Equity Financing Letter" with the words "Amended Equity Financing Letter".

(tt) Section 8.05(b) of the Agreement is hereby amended by adding the following sentence immediately after the last sentence thereof:

"For the avoidance of doubt, Seller Parent shall have sole control over the Insulin Investigations and the Insulin Actions, with full authority over such matters (including full authority over the defense, prosecution and settlement or other resolution or disposition of the same), and Seller Parent shall be responsible for all expenses or costs incurred by Seller Parent and its Subsidiaries in connection with Seller Parent's control over the Insulin Investigations and the Insulin Actions (including any such expenses or costs incurred by Seller Parent and its Subsidiaries in the defense, prosecution or settlement or other resolution or disposition of the same). Without limiting the foregoing, Seller Parent shall keep Buyer reasonably informed regarding any material developments in the Insulin Investigations."

(uu) Section 8.07 of the Agreement is hereby amended by (i) replacing the words "adjustments of the Estimated Adjustment Amount" with the words "the Final Adjustment Amount" and (ii) replacing the words "Final Closing Cash Consideration" with "Final Adjustment Amount".

(vv) Section 8.10 of the Agreement is hereby amended by replacing the words "the Final Closing Cash Consideration" with the words "amounts paid under this Agreement for the ROW Acquired Company".

(ww) The Agreement is amended by replacing each reference to "Irish Estimated Closing Cash Consideration" with a reference to "Irish Closing Cash Consideration".

(xx) The Agreement is amended by replacing each reference to "TSA Management Committee" with a reference to "Transition Management Committee".

(yy) The Agreement is amended by replacing each reference to "Future Cash Consideration" with a reference to "Future Cash Payments".

(zz) Section 9.02 of the Agreement is hereby amended by adding the following definitions in the appropriate alphabetical order therein:

"Amendment Liabilities" means all obligations and liabilities to the extent arising out of, relating to or otherwise in respect of (a) any of the amendments to Item 1 of the Business Steps Plan or to Section 1.01, Section 1.02, Section 1.03, Section 1.04, Section 1.05(b), Section 1.07 or Section 9.02 to the extent the amendments to Section 9.02 are related to the amendments to the aforementioned sections of Article I, (b) Item 4 of the Business Steps Plan and (c) any Taxes arising out of, relating to or otherwise in respect of the Business Steps Plan, in each case that would not have arisen absent the amendments to the Agreement effected by this Amendment; provided, however, that the Amendment Liabilities shall not include (i) any of the obligations and liabilities of Seller Parent and its Affiliates, or any of the advisors thereof (including Existing Counsel), in respect of evaluating, negotiating or documenting this Amendment, (ii) obligations and liabilities to the extent arising out of, relating to or otherwise in respect of Seller Parent or any of its Affiliates not performing their obligations under this Amendment or the Business Steps Plan or (iii) obligations and liabilities to the extent arising out of, relating to or otherwise in respect of the failure to achieve the Intended Tax Treatment.

"BPL" means Biocon Pharma Limited, a company incorporated under the provisions of the Companies Act, 1956 and a wholly owned Subsidiary of Buyer Parent.

"Estimated Adjustment Amount" means (a) the Estimated Working Capital Adjustment Amount (which may be a negative number), minus (b) the

Estimated Assumed Indebtedness Amount, plus (c) the Estimated Closing Collaboration Adjustment Amount (which may be a negative number).

"Final Adjustment Amount" means (a) the Working Capital Adjustment Amount (which may be a negative number) as finally determined pursuant to Section 1.06, minus (b) the Assumed Indebtedness Amount as finally determined pursuant to Section 1.06, plus (c) the Closing Collaboration Adjustment Amount (which may be a negative number) as finally determined pursuant to Section 1.06.

"Irish Closing Cash Consideration" means $588,000,000 (five hundred eighty-eight million dollars).

"Irish Letter of Direction" means the Funds Flow Letter of Instruction and Direction, dated on or about the Closing Date, by and among Buyer, Subsidiary Buyer, Irish Seller and the Irish Acquired Company.

"ROW Letter of Direction" means the Funds Flow Letter of Instruction and Direction, dated on or about the Closing Date, by and among Buyer, Subsidiary Buyer, ROW Seller and the ROW Acquired Company.

"ROW Note" means the promissory note, to be issued by ROW Acquired Company in favor of the ROW Seller pursuant to Item 4 of the Business Steps Plan, in substantially the form attached hereto as Exhibit X.

"Transition Management Committee" has the meaning set forth in Annex D.

(aaa) Section 9.02 of the Agreement is hereby amended by amending and restating the following definitions to have the following meanings:

"Adjustment Amount" means a number (which may be a negative number) equal to the Final Adjustment Amount.

"Applicable Buyer" means, with respect to any Acquired Equity Interests, the purchaser of such Acquired Equity Interests (which, for the avoidance of doubt, shall be (a) Buyer in the case of the Acquired ROW Equity Interests and (b) the Subsidiary Buyer in the case of the Irish New Equity Interests).

"Assumed Liabilities" means all of Seller Parent's and its Subsidiaries' obligations and liabilities to the extent arising out of, relating to or otherwise in respect of the Business, the Acquired Equity Interests or the Irish Redemption Equity Interests (in each case, including the ownership or operation thereof), whether any such obligation or liability arises before, at or after the Closing, is known or unknown or is contingent or accrued, including (a) the Amendment Liabilities and (b) all obligations and liabilities of Seller Parent or any of its Affiliates to the extent arising out of, relating to

or otherwise in respect of the ROW Note or any Assumed Indebtedness but excluding any obligation or liability set forth on Section 9.02(b) of the Seller Parent Disclosure Letter (the "Business Retained Liabilities").

"Buyer Parent Equity Financing" means the consummation of the Equity Transactions (as defined in the Buyer Parent Amended Equity Financing Letter) in accordance with the Buyer Parent Amended Equity Financing Letter, pursuant to which Buyer, Buyer Parent and BPL have agreed, on the terms and subject to the conditions set forth in the Buyer Parent Amended Equity Financing Letter, that (a) Buyer will issue (i) 145,011,221 newly issued shares of Buyer Common Stock to Buyer Parent in exchange for an approximately $500,000,000 (five hundred million dollars) payment from Buyer Parent to Buyer and (ii) 43,334,580 newly issued shares of Buyer Common Stock to BPL in exchange for an approximately $150,000,000 (one hundred fifty million dollars) payment from BPL to Buyer and (b) Buyer Parent and Buyer will convert the Buyer OCRPS into Buyer Common Stock, in the case of clause (a), immediately prior to the Closing.

"Customer Contract" means each Contract between Seller Parent or any of its Subsidiaries, on the one hand, and any customer of the Business (for the avoidance of doubt, including distributors) (in its capacity as such), on the other hand, to the extent relating to the Business.

"Serum Equity Financing" means the funding of the Equity Commitment (as defined in the Serum Amended Equity Financing Letter) in accordance with the Serum Amended Equity Financing Letter, pursuant to which Buyer and Serum have agreed, on the terms and subject to the conditions set forth in the Serum Amended Equity Financing Letter, that Buyer will issue 34,733,743 newly issued shares of Buyer Common Stock to Serum in exchange for a $150,000,000 (one hundred fifty million dollars) payment from Serum to Buyer, in each case, immediately prior to the Closing.

"Subsidiary Buyer" means Biocon Biologics UK Limited, a private limited company registered in England and Wales.

"VAT" means (a) any tax imposed (i) in compliance with the Council Directive of 28 November 2006 on the common system of value added tax (EC Directive 2006/112), (ii) under the (Indian) Goods and Services Tax Act, 2017, or (iii) under the (UK) Value Added Tax Act 1994 or legislation or regulations supplemental thereto and (b) any other tax of a similar nature, however denominated, to the taxes referred to in clause (a) above, whether imposed in a member state of the European Union in substitution for, or levied in addition to, the taxes referred to in clause (a) above, or imposed elsewhere (including goods and services taxes, state or central value added taxes, indirect taxes and any cess, fee or surcharge thereon, but excluding Transfer Taxes).

"Working Capital Target" means $225,000,000 (two hundred twenty-five million dollars).

(bbb) The definition of "Excluded Taxes" set forth in Section 9.02 of the Agreement is hereby amended by (i) amending and restating clause (d) in its entirety as follows "any Transfer Taxes or VAT for which Seller Parent is liable under Section 5.06(b) (it being understood that no Transfer Taxes or VAT shall be included in clause (a), (b) or (c) of this definition)" and (ii) adding the following proviso at the end of such definition "provided that "Excluded Taxes" shall not include any Taxes that are Amendment Liabilities".

(ccc) The definition of "Fundamental Tax Matters" set forth in Section 9.02 of the Agreement is hereby amended by replacing the reference to "Section 5.03(c)" with a reference to "Section 5.03(b)".

(ddd) The definition of "Irish Redemption Equity Interests" set forth in Section 9.02 of the Agreement is hereby amended by adding the parenthetical "(including any preference shares)" immediately after the words "equity interests".

(eee) The definition of "Transaction Documents" set forth in Section 9.02 of the Agreement is hereby amended replacing the reference to "Equity Financing Letter" with a reference to "Amended Equity Financing Letters".

(fff) The definition of "Transfer Taxes" set forth in Section 9.02 of the Agreement is hereby amended by adding the parenthetical "(other than VAT)" immediately after the word "Taxes" at the end of the sentence thereof.

(ggg) Section 9.02 of the Agreement is hereby amended by deleting the following definitions: "Closing Base Cash Consideration", "Estimated Closing Cash Consideration", "Final Closing Cash Consideration" and "TSA Management Committee".

(hhh) Section 9.03 of the Agreement is hereby amended and restated in its entirety as follows:

"Other Definition. For purposes of this Agreement, the terms listed below have the meanings ascribed to them in the respective sections of this Agreement set forth below.

Term	**Location**
Accessed Party	Section 4.03(a)
Accessing Party	Section 4.03(a)
Acquired Companies	Recitals
Acquisition	Section 1.02(c)
Acquisition Engagement	Section 9.16(a)
Agreement	Preamble
Amended Equity Financing Letters	Recitals

Announcement	Section **5.05**
Anticipated Business Employees	Section 2.27(a)
Assumed Indebtedness	Section 5.13(a)
Benefits/Burdens Period	Section 1.09(b)
Business Financial Information	Section 2.10(a)
Business Financial Information Date	Section 2.10(b)
Business Intellectual Property	Section 2.14(b)
Business Interests	Annex A
Business Internal Reorganization	Section **5.03**
Business Key Customers	Section **2.17**
Business Key Suppliers	Section **2.17**
Business Material Contracts	Section 2.16(b)
Business Registered Intellectual Property	Section 2.14(a)
Business Transfer Documents	Section **5.21**
Buyer	Preamble
Buyer Acquisition Engagement	Section 9.17(a)
Buyer Aggregate Cap	Section 8.04(b)(ii)
Buyer Basket Amount	Section 8.04(b)(iv)
Buyer Board	Recitals
Buyer Counsel	Section 9.17(a)
Buyer De Minimis Amount	Section 8.04(b)(iv)
Buyer Debt Amount	Section 6.03(f)
Buyer General Cap	Section 8.04(b)(ii)
Buyer Indemnitees	Section **8.02**
Buyer Intellectual Property	Section 3.12(b)
Buyer Material Contracts	Section 3.14(b)
Buyer Parent Amended Equity Financing Letter	Recitals
Buyer Parent Equity Financing Letter	Recitals
Buyer Parent Equity Financing Letter Amendment	Recitals
Claim	Section 8.04(a)
Closing	Section **1.01**

Closing Date	Section **1.01**
Closing Statement	Section 1.06(b)
Confidentiality Agreement	Section 4.03(c)
Credit Support Items	Section **5.15**
Debt Financing	Section 5.13(a)
Debt Financing Agreements	Section 9.19
Dedicated Business Employees	Section 4.03(d)
Delayed Transfer Company	Section 1.09(d)
Direct Claim	Section **8.06**
Disclosing Party	Section 5.04(b)
DPA	Section **2.20**
Enforceability Exceptions	Section 2.02(a)
Equity Financing Letters	Recitals
Estimated Assumed Indebtedness Amount	Section 1.06(a)
Estimated Closing Collaboration Adjustment Amount	Section 1.06(a)
Estimated Working Capital Adjustment Amount	Section 1.06(a)
Exclusion Right	Section 1.10(b)
Exclusion Right Exercise Date	Section 1.10(b)
Exclusivity Period	Section **5.01**
Existing Counsel	Section 9.16(a)
FCPA	Section 2.19(a)
Financing	Section 5.13(a)
Foreign Antitrust Approvals	Section 5.02(a)(ii)
Foreign Antitrust Laws	Section 2.07(b)
Future Cash Payments	Section 1.05(b)
HSR Act	Section 2.07(b)
HSR Approval	Section 5.02(a)(i)
ICC Rules	Section 9.13(a)
Indemnified Party	Section 8.04(a)
Indemnifying Party	Section 8.04(a)
Independent Adjustment Expert	Section 1.06(c)
Independent Valuation Expert	Section 5.02(e)(i)
Information Security Reviews	Section 2.14(l)
Intended Irish Tax Treatment	Section 5.06(a)(iii)
Intended Tax Treatment	Section 5.06(a)(iii)

Intended U.S. Tax Treatment	Section 5.06(a)(iii)
Ireland Companies Act	Section 3.11(f)
Irish Acquired Company	Recitals
Irish Acquisition	Section 1.02(c)
Irish Future Cash Payment	Section 1.05(a)
Irish Future Cash Payment Conditions	Section 1.05(a)
Irish Redemption	Section 1.02(c)
Irish Seller	Recitals
Irish Spin-Off	Recitals
Irish Subscription	Section 1.02(b)
Labor Actions	Section 2.27(b)
Law	Section 2.07(a)
Legal Impediment	Section 1.09(b)
Legal Impediment Delayed Asset/Liability	Section 1.09(b)
Legal Impediment Delayed Assets/Liabilities	Section 1.09(b)
Legal Impediment Delayed Transfer	Section 1.09(b)
Legal Impediment Delayed Transfer Date	Section 1.09(b)
Licensed Business IP Contracts	Section 2.14(c)
Licensed Buyer IP Contracts	Section 3.12(c)
Liens	Section 2.07(a)
Mylan Ireland	Recitals
Notice of Disagreement	Section 1.06(c)
Order	Section 2.07(a)
Other Approvals	Section 5.02(a)(iii)
Outside Date	Section 7.01(b)(i)
Parties	Preamble
Regulatory Approvals	Section 5.02(a)(iii)
Requesting Party	Section 5.04(b)
Required Payments	Section 3.21(c)
Restraints	Section 6.01(c)
Retained Names Materials	Section **5.07**
Retained Records	Annex A
ROW Acquired Company	Recitals
ROW Acquisition	Section 1.02(a)
ROW Future Cash Payment	Section 1.05(b)
ROW Seller	Recitals
Seller Aggregate Cap	Section 8.04(b)(i)
Seller Basket Amount	Section 8.04(b)(iii)
Seller De Minimis Amount	Section 8.04(b)(iii)
Seller General Cap	Section 8.04(b)(i)

Seller Indemnitees	Section **8.03**
Seller Parent	Preamble
Seller Parent Board	Recitals
Seller Privileges	Section 9.16(b)
Sellers	Recitals
Serum Amended Equity Financing Letter	Recitals
Serum Equity Financing Letter	Recitals
Serum Equity Financing Letter Amendment	Recitals
SHA Joinder	Recitals
Solvent	Section 3.21(d)
Specified Assets	Section 1.10(b)(i)
Specified Courts	Section 9.12(b)
Specified Liabilities	Section 1.10(b)(ii)
Specified Product	Section 1.10(b)(iii)
Stock Rights	Section 2.03(c)
Third Party Claim	Section 8.05(a)
Transferred Business Records	Annex A
Transferred Contracts	Annex A
Transferred IP	Annex A
Transferred IP Licenses	Annex A
Transferred Labeling and Marketing Materials	Annex A
Transferred Organizational Records	Annex A
Transition Period	Section **5.07**
TSA Delayed Asset	Section 1.09(a)
TSA Delayed Transfer	Section 1.09(a)
TSA Delayed Transfer Date	Section 1.09(a)
UKBA	Section 2.19(a)
Underlying Buyer Common Stock	Section 3.03(b)
Voting Debt	Section 2.03(c)
Written Consent	Recitals”

(iii) Section 9.16 of the Agreement is hereby amended by adding the following words “and (iv) Slaughter and May” immediately after the words “Arthur Cox LLP” and replacing the word “and” immediately following the words “Saraf and Partners” with a comma.

(jjj) Section 9.17 of the Agreement is hereby amended by adding the following words “and (iii) Matheson LLP” immediately after the words “Shardul Amarchand

Mangaldas & Co" and replacing the word "and" immediately following the words Goodwin Procter (UK) LLP with a comma."

(kkk) Section 9.18 of the Agreement is hereby amended by replacing both parentheticals thereof with the following parenthetical "(including, at and following such time as they become Subsidiaries of Buyer, the Business Companies)".

(lll) The Agreement is hereby amended by adding the following Section 9.19 as a new section immediately after Section 9.18:

"SECTION 9.19. Debt Financing Sources. Notwithstanding anything in this Agreement to the contrary, each of the Parties on behalf of itself and each of their Affiliates hereby: (a) agrees that all Actions (whether in contract or in tort or otherwise) against the Debt Financing Sources arising out of or relating to this Agreement, the Debt Financing or the definitive agreements providing for the Debt Financing (collectively, the "Debt Financing Agreements") or any of the transactions contemplated hereby or thereby or the performance of any services thereunder shall be governed by, and construed in accordance with, the laws of the State of New York, without giving effect to any choice of law or conflict of law rules or provisions (whether of the State of New York or any other jurisdiction) that would cause the application of the laws of any jurisdiction other than the State of New York except as otherwise provided in any Debt Financing Agreement; (b) agrees that it will not bring or support any Action (whether in contract or in tort or otherwise) against the Debt Financing Sources arising out of or relating to this Agreement, the Debt Financing, the Debt Financing Agreements or any of the transactions contemplated hereby or thereby or the performance of any services thereunder in any forum other than (i) the Supreme Court of the State of New York, County of New York, or, if under applicable Law exclusive jurisdiction is vested in the federal courts, the United States District Court for the Southern District of New York (and the appellate courts thereof), or (ii) as otherwise provided in any Debt Financing Agreement; (c) agrees that service of process delivered in accordance with Section 9.01 shall be effective service of process against it for any such Action brought in any such court; (d) agrees to waive and hereby waives, to the fullest extent permitted by applicable Law, any objection which it may now or hereafter have to the laying of venue of, and the defense of an inconvenient forum to the maintenance of, any such Action in any such court; (e) waives any right to the fullest extent permitted by applicable law to trial by jury with respect to any such Action; (f) agrees that none of the Debt Financing Sources will have any liability to any of Seller Parent and its Affiliates (including, prior to the Closing, the Business Companies) or their respective directors, officers, employees, agents, partners, managers, advisors, members and stockholders, and none of Seller Parent or its Affiliates (excluding, following the Closing, the Business Companies and any other obligor and security provider under the Debt

Financing Agreements) will have any liability to any of the Debt Financing Sources or their respective directors, officers, employees, agents, partners, managers, advisors, members and stockholders, in each case, relating to or arising out of this Agreement, the Debt Financing, the Debt Financing Agreements or any of the transactions contemplated hereby or thereby or the performance of any services thereunder, none of the Seller Parent and its Affiliates (including, prior to the Closing, the Business Companies) and their respective directors, officers, employees, agents, partners, managers, advisors, members and stockholders shall bring or support any Action (whether in contract or in tort or otherwise) against any of the Debt Financing Sources, and none of the Debt Financing Sources and their respective directors, officers, employees, agents, partners, managers, advisors, members and stockholders shall bring or support any Action (whether in contract or in tort or otherwise) against the Seller Parent or any of its Affiliates (excluding, following the Closing, the Business Companies and any other obligor and security provider under the Debt Financing Agreements), in each case, relating to or arising out of this Agreement, the Debt Financing, the Debt Financing Agreements or any of the transactions contemplated hereby or thereby or the performance of any services thereunder; and (g) agrees (x) that the Debt Financing Sources are express third party beneficiaries of, and may enforce, any of the provisions in this Section 9.19 (or any of the defined terms used in this Section 9.19) and (y) to the extent any amendments to any provision of this Section 9.19 (or any of the defined terms used in this Section 9.19 or any other provision of this Agreement to the extent a modification, waiver or termination of such defined term or provision would modify the substance of this Section 9.19 or such defined terms) are adverse to the Debt Financing Sources, such provisions shall not be amended without the prior written consent of the Debt Financing Sources. Notwithstanding anything contained herein to the contrary, nothing in this Section 9.19 shall in any way affect a party's rights and remedies against the Debt Financing Sources or Buyer or its Affiliates under the Debt Financing Agreements to the extent they are a party thereto."

(mmm) Clause (xi) on Annex B of the Agreement is hereby amended and restated in its entirety as follows:

"(xi) Closing Working Capital. In the event that the Closing Working Capital is a positive amount, current assets included in the Closing Working Capital up to a maximum amount equal to the lesser of (A) Closing Working Capital and (B) the Working Capital Target."

(nnn) Annex B of the Agreement is hereby amended by adding the following as a new clause (xiii) immediately after clause (xii) thereof:

"(xiii) Insulin Actions. All Actions, claims and settlements (in each case, whether or not brought, asserted, in existence or pending, and including any

payment of rights accruing from such Actions, claims and settlements) that may be brought or asserted by Seller Parent, any of its Subsidiaries or the Business relating to the commercialization, development or manufacturing of insulin glargine Products (collectively, the "Insulin Actions"), in each case, to the extent arising out of or relating to Seller Parent's operation of the Business prior to the Closing."

(ooo) Part A of Annex C of the Agreement is hereby amended and restated in its entirety to be in the form of Exhibit A hereto.

(ppp) Part B of Annex C of the Agreement is hereby amended by replacing the word "procuring" with the words "to procure".

(qqq) Annex D of the Agreement is hereby amended and restated in its entirety to be in the form of Exhibit B hereto.

(rrr) The Agreement is hereby amended by adding Exhibit I-C and Exhibit I-D as new exhibits to the Agreement in the form of Exhibit C-1 and Exhibit C-2 hereto, respectively.

(sss) Exhibit III is hereby amended and restated in its entirety to read "[RESERVED]".

(ttt) Exhibit V of the Agreement is hereby amended and restated in its entirety to be in the form of Exhibit D hereto.

(uuu) Exhibit VI of the Agreement is hereby amended and restated in its entirety to be in the form of Exhibit E hereto.

(vvv) Exhibit VII of the Agreement is hereby amended and restated in its entirety to be in the form of Exhibit F hereto.

(www) Exhibit VIII of the Agreement is hereby amended and restated in its entirety to be in the form of Exhibit G hereto.

(xxx) The Agreement is hereby amended by adding Exhibit X as a new exhibit to the Agreement in the form of Exhibit H hereto.

2. Effect of Amendment.

(a) Each Party acknowledges and agrees that this Amendment constitutes an instrument in writing on behalf of each of the Parties in accordance with Section 9.05 of the Agreement. For the avoidance of doubt, references to the date of the Agreement, and references to the "date hereof", "the date of this Agreement" or words of similar meaning in the Agreement shall continue to refer to February 27, 2022.

(b) Notwithstanding anything to the contrary in the Agreement: (i) Seller Parent and its Affiliates shall in no event be in breach of any covenant or agreement contained in the Agreement or any other Transaction Document, and the representations and warranties of Seller Parent and its Affiliates contained in the Agreement and the other Transaction Documents shall in no event be determined to be inaccurate, in each case, to the extent resulting from any of the amendments to the Agreement effected by this Amendment (other than, for the avoidance of doubt, (A) to the extent Seller Parent or any of its Affiliates do not perform their respective obligations under this Amendment and (B) to the extent changes are expressly made by this Amendment to provisions in the Transaction Documents (for example, the change to the Working Capital Target)); (ii) in no event shall the ROW Note be included in the Working Capital Adjustment Amount, the Assumed Indebtedness Amount, the Closing Collaboration Adjustment Amount or the Buyer Debt Amount (in each case, including any estimate thereof), or otherwise constitute Indebtedness of Seller Parent, Buyer or any of their respective Affiliates for purposes of the Agreement; (iii) in no event shall the ROW Note (or any accounts, balances, payables, receivables or Indebtedness thereunder) be considered Intercompany Accounts or Business Intercompany Contracts for purposes of the Agreement; (iv) in no event shall the equity interests in the ROW Acquired Company issued pursuant to the Buyer ROW Contribution be considered ROW Acquired Equity Interests for purposes of the Agreement; (v) Buyer and its Affiliates shall in no event be in breach of any covenant or agreement contained in the Agreement or any other Transaction Document, and the representations and warranties of Buyer and its Affiliates contained in the Agreement and the other Transaction Documents shall in no event be determined to be inaccurate, in each case, to the extent resulting from any of the amendments to the Agreement effected by this Amendment (other than, for the avoidance of doubt, to the extent Buyer or any of its Affiliates do not perform their respective obligations under this Amendment); and (vi) this Amendment constitutes (A) the consent of Seller Parent under the Transaction Documents to the Buyer Parent Equity Financing Letter Amendment and the Serum Equity Financing Letter Amendment and (B) the mutual agreement of the Parties that the Buyer Parent Equity Financing Letter Amendment and the Serum Equity Financing Letter Amendment will not prevent or impede the Intended Tax Treatment.

3. Limited Amendment. Except as expressly set forth in paragraphs 1 and 2 above, this Amendment shall not be deemed to amend, waive, affect or otherwise alter any term or provision of the Agreement or the other Transaction Documents, and all terms and provisions of the Agreement and the other Transaction Documents shall continue in full force and effect.

4. Miscellaneous. The provisions set forth in Sections 9.01 and 9.04 through 9.18 of the Agreement (as amended by this Amendment) shall apply to this Amendment, *mutatis mutandis*, and are incorporated by reference as if fully set forth herein.

[*Remainder of page intentionally left blank*]

IN WITNESS WHEREOF, the Parties have duly executed this Amendment, all as of the date first written above.

VIATRIS INC.

by /s/ Anil Amin
Name: Anil Amin
Title: Authorized Signatory

IN WITNESS WHEREOF, the Parties have duly executed this Amendment, all as of the date first written above.

BIOCON BIOLOGICS LIMITED

by /s/ Chinappa M.B.

Name: Chinappa M.B.
Title: Chief Financial Officer

Viatris Completes Biosimilars Transaction with Biocon Biologics

Receives a $2 Billion Cash Payment and $1 Billion of Convertible Preferred Equity Representing a Stake of at Least 12.9% (on a Fully Diluted Basis) in Biocon Biologics

Marks the First in a Series of Expected Initiatives to Reshape and Rebase Viatris, Aimed at Setting it Up for Long-term Growth

PITTSBURGH, Nov. 29, 2022 – Viatris Inc. (NASDAQ: VTRS) today announced that it has closed its transaction with Biocon Biologics Limited ("Biocon Biologics"), creating what Viatris expects to be a unique fully vertically integrated global biosimilars leader. Viatris and Biocon Biologics have entered a Transition Services Agreement (TSA) pursuant to which Viatris will provide commercialization and certain other transition services for an expected two-year period intended to ensure business continuity for patients, customers and colleagues. Upon the completion of the transition services, Biocon Biologics will assume responsibility of commercial, regulatory and other related services.

Viatris Executive Chairman **Robert J. Coury** said: "Today is a very exciting day in the continued evolution of Viatris. The closing today of the Biocon Biologics transaction represents the completion of the first in a series of achievements against the number of initiatives we laid out recently in our strategic update on Nov. 7 as part of our well-defined plan for Viatris. While we will continue to further execute against this plan, we also look forward as now a significant shareholder of Biocon Biologics to supporting Kiran Mazumdar-Shaw, Executive Chairperson of Biocon Limited and Biocon Biologics, and her team to optimize the value of Biocon Biologics."

Viatris President **Rajiv Malik** said: "The closing of our biosimilars transaction with Biocon Biologics marks the next natural step in the evolution of our collaboration together. We are deeply committed to doing our part in helping Biocon Biologics succeed in the creation of what we believe will be a true global, vertically integrated biosimilars leader. As we look to Viatris' future, we are also excited to focus our energy, resources and efforts on executing our own strategy of moving up the value chain and providing access to more complex and novel products."

Under the terms of the transaction agreement, Viatris received $3 billion in consideration in the form of a $2 billion cash payment and $1 billion of convertible preferred equity representing a stake of at least 12.9 % (on a fully diluted basis) in Biocon Biologics. Viatris also is entitled to $335 million of additional cash payments in 2024.

Financial Impact of Completion of the Biosimilars Transaction
As previously stated, the Company's financial guidance ranges for total revenues, adjusted EBITDA and free cash flows for the year ending December 31, 2022, do not include the impact of the closing of the transaction with Biocon Biologics. The Company expects its reported results for the year ending December 31, 2022, to be impacted by the closing of the transaction as follows:

- The Company expects its reported total revenues and adjusted EBITDA for the year to be lower by approximately $80 million and $20 million, respectively.

- The Company expects to report the $2 billion of cash proceeds, offset by the impact of certain deal related adjustments, as cash flows from investing activities. Additionally, the Company expects to incur approximately $400 million of certain deal related expenses, primarily taxes and associated transactions costs. As a result, the Company expects these deal related expenses to lead to lower reported cash flows from operating activities, and consequently free cash flow, for the year.

Capital Allocation
The Company expects to use the net divestiture cash from the biosimilars transaction to:
- Pay down additional short-term debt and accelerate its progress towards $6.5 billion of Phase 1 debt reduction
- And, in combination with cash on hand, to:
  - Fund the previously announced ophthalmology acquisitions totaling approximately $700 to $750 million, anticipated to close in the first quarter of 2023, and
  - Begin to execute on the previously announced share buyback authorization in 2023.

About Viatris
Viatris Inc. (NASDAQ: VTRS) is a global healthcare company empowering people worldwide to live healthier at every stage of life. We provide access to medicines, advance sustainable operations, develop innovative solutions and leverage our collective expertise to connect more people to more products and services through our one-of-a-kind Global Healthcare Gateway®. Formed in November 2020, Viatris brings together scientific, manufacturing and distribution expertise with proven regulatory, medical, and commercial capabilities to deliver high-quality medicines to patients in more than 165 countries and territories. Viatris' portfolio comprises more than 1,400 approved molecules across a wide range of therapeutic areas, spanning both non-communicable and infectious diseases, including globally recognized brands, complex generic and branded medicines, and a variety of over-the-counter consumer products. With approximately 37,000 colleagues globally, Viatris is headquartered in the U.S., with global centers in Pittsburgh, Shanghai and Hyderabad, India. Learn more at viatris.com and investor.viatris.com, and connect with us on Twitter at @ViatrisInc, LinkedIn and YouTube.

Forward-looking Statements

This press release includes statements that constitute “forward-looking statements.” These statements are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Such forward looking statements may include statements about transition services agreements; the closing today of the Biocon Biologics transaction represents the completion of the first in a series of achievements against the number of initiatives we laid out recently in our strategic update on Nov. 7 as part of our well-defined plan for Viatris; while we will continue to further execute against this plan, we also look forward as now a significant shareholder of Biocon Biologics to supporting Kiran Mazumdar-Shaw, Executive Chairperson of Biocon Limited and Biocon Biologics, and her team to optimize the value of Biocon Biologics; we are deeply committed to doing our part in helping Biocon Biologics succeed in the creation of what we believe will be a true global, vertically integrated biosimilars leader; as we look to Viatris’ future, we are also excited to focus our energy, resources and efforts on executing our own strategy of moving up the value chain and providing access to more complex and novel products; under the terms of the transaction agreement, Viatris received $3 billion in consideration in the form of a $2 billion cash payment and $1 billion of convertible preferred equity representing a stake of at least 12.9 % (on a fully diluted basis) in Biocon Biologics; Viatris is entitled to $335 million of additional cash payments in 2024; financial impact of completion of the Biosimilars Transaction; as previously stated, the Company’s financial guidance ranges for total revenues, adjusted EBITDA and free cash flows for the year ending December 31, 2022, do not include the impact of the closing of the transaction with Biocon Biologics; the Company expects its reported results for the year ending December 31, 2022, to be impacted by closing of the transaction as follows: the Company expects its reported total revenues and adjusted EBITDA for the year to be lower by approximately $80 million and $20 million, respectively and the Company expects to report the $2 billion of cash proceeds, offset by the impact of certain deal related adjustments, as cash flows from investing activities; the Company expects to incur approximately $400 million of certain deal related expenses, primarily taxes and associated transactions costs; as a result, the Company expects these deal related expenses to lead to lower reported cash flows from operating activities, and consequently free cash flow, for the year; expects to use the net divestiture cash from the biosimilars transaction to: pay down additional short-term debt and accelerate its progress towards $6.5 billion of Phase 1 debt reduction, and, in combination with cash on hand, to fund the previously announced ophthalmology acquisitions totaling approximately $700 to $750 million, anticipated to close in the first quarter of 2023, and begin to execute on the previously announced share buyback authorization in 2023. Factors that could cause or contribute to such differences include, but are not limited to: the potential impact of public health outbreaks, epidemics and pandemics, including the ongoing challenges and uncertainties posed by the COVID-19 pandemic; that the transaction between Viatris and Biocon Biologics Limited, pursuant to which Viatris contributed its biosimilar products and programs to Biocon Biologics in exchange for cash consideration and a convertible preferred equity interest in Biocon Biologics (the “Biocon Biologics Transaction”) and other strategic initiatives, including potential divestitures, may not achieve their intended benefits; the integration of Mylan N.V. and Pfizer Inc.’s Upjohn business (the “Upjohn Business”), which combined to form Viatris (the “Combination”) and the implementation of our global restructuring initiatives being more difficult, time consuming or costly than expected, or being unsuccessful; the ability to achieve expected benefits, synergies, and operating efficiencies in connection with the Combination or its restructuring initiatives within the expected timeframe or at all; actions and decisions of healthcare and pharmaceutical regulators; changes in healthcare and pharmaceutical laws and regulations in the U.S. and abroad; any regulatory, legal or other impediments to Viatris’ ability to bring new products to market, including but not limited to “at-risk” launches; Viatris’ or its partners’ ability to develop, manufacture, and commercialize products; the scope, timing and outcome of any ongoing legal proceedings, and the impact of any such proceedings; any significant breach of data security or data privacy or disruptions to our information technology systems; risks associated with international operations; the ability to protect intellectual property and preserve intellectual property rights; changes in third-party relationships; the effect of any changes in Viatris’ or its partners’ customer and supplier relationships and customer purchasing patterns; the impacts of competition; changes in the economic and financial conditions of Viatris or its partners; uncertainties and matters beyond the control of management; and the other risks described in Viatris’ filings with the Securities and Exchange Commission (SEC). Viatris routinely uses its website as a means of disclosing material information to the public in a broad, non-exclusionary manner for purposes of the SEC’s Regulation Fair Disclosure (Reg FD). Viatris undertakes no obligation to update these statements for revisions or changes after the date of this release other than as required by law.

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Non-GAAP Financial Measures

This press release includes the presentation and discussion of certain financial information that differs from what is reported under accounting principles generally accepted in the United States ("U.S. GAAP"). These non-GAAP financial measures, including adjusted EBITDA and free cash flow, are presented in order to supplement investors' and other readers' understanding and assessment of the financial performance of Viatris. Free cash flow refers to U.S. GAAP net cash provided by operating activities, less capital expenditures. For the third quarter of 2022, Viatris calculated adjusted EBITDA as U.S. GAAP net earnings (loss) adjusted for income tax provision (benefit), interest expense and depreciation and amortization (to get to EBITDA) and further adjusted for share-based compensation expense, litigation settlements and other contingencies, net and restructuring, acquisition related and other special items.

Viatris has provided reconciliations of historical non-GAAP financial measures to the most directly comparable U.S. GAAP financial measures. Investors and other readers are encouraged to review the related U.S. GAAP financial measures and the reconciliations of the non-GAAP measures to their most directly comparable U.S. GAAP measures set forth in this release on our website at https://investor.viatris.com/financial-information/non-gaap-reconciliations, and investors and other readers should consider non-GAAP measures only as supplements to, not as substitutes for or as superior measures to, the measures of financial performance prepared in accordance with U.S. GAAP.

With regard to the completion of the biosimilars transaction, Viatris is not providing forward-looking disclosures for the expected impact on the most directly comparable U.S. GAAP measure, net earnings (loss), or a quantitative reconciliation of the expected impact on adjusted EBITDA to a projected impact on U.S. GAAP net earnings (loss) because it is unable to predict with reasonable certainty the ultimate outcome of certain significant items, including integration and acquisition-related expenses, restructuring expenses, asset impairments, litigation settlements and other contingencies, such as changes to contingent consideration and certain other gains or losses, as well as related income tax accounting, because certain of these items have not occurred, are out of the Company's control and/or cannot be reasonably predicted without unreasonable effort. These items are uncertain, depend on various factors, and could have a material impact on U.S. GAAP reported results for the period.

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E i it 41

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EXHIBIT 41
[DKT. 466-15]

REDACTED IN FULL