

No. 17-1480

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**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

AMGEN INC., AMGEN MANUFACTURING, LTD., and AMGEN USA, INC.,

*Plaintiffs-Appellees,*

v.

SANOFI, SANOFI-AVENTIS U.S. LLC, AVENTISUB LLC, f/d/b/a AVENTIS  
PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC.,

*Defendants-Appellants.*

On Appeal from the United States District Court for the District of Delaware,  
No. 14-1317-SLR

**EMERGENCY MOTION FOR STAY PENDING APPEAL  
AND EXPEDITED BRIEFING**

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January 13, 2017

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## **CERTIFICATE OF INTEREST**

Counsel for appellants certifies the following:

**1. The full name of every party represented by us is:**

Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc.

**2. The name of the real party in interest represented by us is:**

Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc.

**3. All parent corporations and any other publicly held companies that own 10 percent or more of the stock of the party represented by me are:**

Sanofi has no parent corporation, and no publicly held company owns 10 percent or more of its stock. Sanofi is the parent corporation of sanofi-aventis and Aventisub LLC. Regeneron Pharmaceuticals, Inc. has no parent corporation. Sanofi, through Sanofi's directly and indirectly owned subsidiaries, owns 10 percent or more of Regeneron's stock.

**4. The names of all law firms and the partners or associates that appeared for appellants in trial court or are expected to appear in this court are:**

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Dated: January 13, 2017

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Pursuant to Fed. R. App. P. 8(a) and Fed. Cir. R. 8, Appellants Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (“Appellants”) move for a stay pending appeal of the permanent injunction ordered by the district court on January 5, 2017, set to take effect on February 21, 2017. Ex.A. The district court denied Appellants’ motion to stay on January 9, 2017. Ex.B. Appellants noticed their appeal on January 12, 2017. Ex.C. If the Court’s consideration of this motion extends beyond February 21, 2017, Appellants request a temporary stay of the injunction until the Court decides the motion. Appellants also request expedited consideration of the appeal.<sup>1</sup>

## **INTRODUCTION**

The district court’s permanent injunction orders the total withdrawal from the market of Appellants’ FDA-approved, life-saving cholesterol medicine—a drug used by thousands of patients, most of whom have no available substitute. Remarkably, the district court recognized that this extraordinary remedy was contrary to the public interest, but ordered it anyway, despite the readily available alternative of an ongoing royalty as a remedy for infringement. The district court then doubled down and refused to stay its remarkable injunction to allow this Court to consider the merits of the underlying dispute, which the district court itself described as close and difficult. Commentators immediately described this

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<sup>1</sup> Appellants have discussed this motion with Appellees (“Amgen”). Amgen opposes and will file a response.

medicine-removal injunction as “nearly unprecedented,” “shock[ing],” and “very strange.”<sup>2</sup> It is all of that—and it should be stayed pending this Court’s full review of both the injunction and the underlying final judgment. *See* Exs.D,E.

The drug the district court would remove from the market is Praluent, the first FDA-approved antibody therapy approved to treat high cholesterol. In 18 months on the market, Praluent has been prescribed more than 100,000 times. The only other product in this market is Repatha, a biologically distinct antibody developed by Amgen. Amgen obtained patents that claim not just Repatha but a broad genus of functionally defined antibodies. Despite their sweeping claims, the patents disclose only two antibodies known to meet those claims—Repatha and another antibody with a structure entirely different from Praluent.

In 2014, Amgen alleged that Praluent infringed Amgen’s patents, and Appellants challenged the validity of those patents. Throughout the ensuing litigation, the district court candidly acknowledged that it was “struggling” with the issues, Ex.L 846:21, and its decisions bear this out. For example, to show the insufficiency of Amgen’s written description, Appellants sought to introduce Praluent, whose structure is vastly different from Repatha. The district court ruled,

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<sup>2</sup> Matthew Herper, *Could Amgen’s Patent Victory Be Bad For Medicine?*, Forbes (Jan. 6, 2017), <http://bit.ly/2ioTTmR>; *id.* (quoting Prof. Jacob Sherkow); Prof. Rachel Sachs, *Let’s All Worry About the Effects of Patent Injunctions Against Drug Manufacturers*, Harvard Law Bill of Health Blog (Jan. 6, 2017), <http://bit.ly/2jhLYYM>.

however, that Appellants could not introduce their own antibody—*the very product accused of infringement*—despite this Court’s reliance on precisely such evidence in prior cases. The district court also instructed the jury that it could find Amgen’s patents valid if they disclosed a “newly characterized antigen,” even though this Court has never upheld validity on that theory. Finally, the district court granted judgment as a matter of law (JMOL) to Amgen on obviousness based on a gross misreading of this Court’s precedent.

The district court saved its most remarkable decision for last, however. Nearly nine months after the jury found the patents valid—during which time Praluent remained available to patients—the district court granted Amgen’s extraordinary request to take Praluent off the market, even though the court found that the public interest weighed *against* an injunction. The district court offered not one word explaining how its puzzling, conclusory decision was justified by equitable considerations or any precedent of this Court.

This is a textbook case for a stay pending appeal. Given the district court’s many dubious rulings, both the underlying judgment and the injunction are highly unlikely to survive on appeal. In the meantime, the injuries to Appellants are severe and irreparable. Appellants will be forced to shut down operations for manufacturing and distributing Praluent, void painstakingly-negotiated contracts with insurers and pharmacy benefit managers, and terminate hundreds of

employees with specialized knowledge of Praluent—all while absorbing enormous reputational damage. By contrast, the costs of staying the injunction are minimal for Amgen, which did not even seek a preliminary injunction; a stay would simply preserve the status quo, and royalties remain a remedy if this Court ultimately upholds the rulings below. Appellants, moreover, stand ready to expedite the appellate proceedings to whatever degree this Court deems appropriate.

Most important, as the district court's order underscores, the public interest overwhelmingly favors a stay. Forcing thousands of patients to transition from Praluent to Repatha is disruptive at best and dangerous at worst, as renegotiating contracts and other logistical hurdles will leave many patients without access to either drug during the transition. Even worse, most Praluent patients will have *no* adequate substitute, because they take a low-dose version of Praluent with no Repatha counterpart. And *all* patients will bear the price increases and disruption risks inevitable in the single-product market that the injunction creates. The public interest plainly counsels against forcing innocent patients to absorb such enormous costs before this Court even addresses the merits of the appeal. This injunction is deeply flawed and should never have been granted, but at the very least it should be stayed pending the Court's plenary review.

## BACKGROUND

### A. Praluent

High levels of low-density lipoprotein (LDL) cholesterol are a major risk factor for cardiovascular disease. Doctors often prescribe statins (such as Lipitor) to reduce LDL levels. But for many patients, statins are insufficient, leaving them at high risk for heart attacks and strokes. Ex.O¶5. Praluent is designed to help those patients. The Praluent antibody binds to the naturally occurring protein PCSK9, which in turn prevents PCSK9 from binding to and destroying LDL receptors (“LDLR”) on liver cells responsible for extracting cholesterol from the bloodstream. Praluent thereby enables LDLRs to extract more cholesterol and patients to achieve lower cholesterol.

In July 2015, Praluent became the first anti-PCSK9 antibody approved by FDA. FDA approved Praluent in two doses, a 75-mg biweekly “low dose” that reduces LDL cholesterol by approximately 45 percent, and a 150-mg biweekly “high dose” that reduces LDL cholesterol by approximately 60 percent. *Id.* ¶¶6-7. The choice of doses is significant, because most doctors treat LDL cholesterol to a “target.” *Id.* ¶9. That is, they aim to reduce a patient’s cholesterol to—but *not below*—a certain level, because “too low” LDL cholesterol has uncertain medical effects. *Id.* About 85 percent of Praluent prescriptions have been for the low dose. Ex.S¶7.

## **B. Repatha and the Asserted Patents**

While Appellants were independently developing Praluent, Amgen was developing Repatha. Like Praluent, Repatha prevents PCSK9 from binding to the LDLR. But Repatha is a different antibody with a substantially different structure. And, unlike Praluent, Repatha is not available in an FDA-approved “low dose.” Repatha is offered only in 140-mg biweekly and 420-mg monthly doses, both of which reduce LDL cholesterol by about 60 percent. Ex.O¶¶6-7.

In 2014, Amgen obtained several patents covering Repatha. The asserted patents claim a genus of antibodies that perform two functions: binding to PCSK9 at specific locations (“residues”) and blocking PCSK9’s binding to the LDLR. For example, Claim 1 of Patent No. 8,829,165 covers “[a]n isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, ... and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.” Ex.D at 5.

## **C. Proceedings Below**

In October 2014, Amgen sued Appellants for patent infringement. Appellants stipulated to infringement but challenged validity on written description, enablement, and obviousness grounds. Amgen chose not to pursue a preliminary injunction, but instead sought and obtained an expedited trial.

The district court proceeded to issue a number of significant erroneous

rulings severely prejudicing Appellants' invalidity case. For example, under the guise of a *Daubert* ruling, the court prevented Appellants from introducing evidence of the structural dissimilarities between Praluent and the only two antibodies known to satisfy the claims whose crystal structures are actually disclosed in Amgen's patents (Repatha and an antibody called 31H4). Exs.F,G. Appellants argued that this prohibition was inconsistent with *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014), but the court nevertheless categorically excluded *all* evidence related to antibodies discovered after the patents' January 2008 priority date—including Praluent itself, plus evidence that Amgen had continued searching for antibodies falling within the claimed genus (thus confirming that the inventors did not possess those antibodies in 2008). The court repeatedly expressed reservations about its decision.<sup>3</sup> But the damage was done; the ruling eviscerated critical parts of Appellants' written description and enablement defenses.

The district court also granted JMOL to Amgen on Appellants' obviousness defense. Ex.M 1077:2-3. But it did so only by misconstruing *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375 (Fed. Cir. 2015),

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<sup>3</sup> See, e.g., Ex.J 18:17-18 (“[M]aybe I need to let it all in and not preclude anything. Maybe that is ... better[.]”); *id.* 19:1-2 (“[I]t sounds like I’ve swept too much information away[.]”); Ex.L 846:19-21 (“[T]hat’s a difficult legal issue that I obviously am still struggling with.”).

following one-page submissions by the parties on that case’s relevance. Again, the court expressed doubts about its ruling. Ex.M 1077:4-6 (acknowledging that Appellants “have a good argument the other way”); *id.* 1076:23 (refusing to reconsider *Drinkware* ruling, as “right or wrong, I did make it”); Ex.L 1034:7 (stating, in obviousness context, “there’s nothing easy about this case”).

Finally, the court overruled Appellants’ objection to an instruction that permitted the jury to find Amgen’s patents valid if they describe a “newly characterized antigen”—even though this Court has never upheld that theory as a basis for adequate written description and nothing in Amgen’s patents discloses a “newly characterized antigen.” Ex.H. 25. The jury found the patents valid.

Nearly nine months later, the court denied Appellants’ motions for a new trial and JMOL. Ex.D. In a brief order, the court also granted Amgen’s permanent injunction motion. The court concluded that “[t]he public generally is better served by having a choice of available treatments,” that “taking an independently developed, helpful drug off the market does not benefit the public,” and that “the public interest of having a choice of drugs should prevail.” Ex.A¶11. Yet the court ordered Praluent taken off the market. *Id.* ¶12.

Recognizing the “ramifications of an injunction,” the court delayed imposition by 30 days to allow Appellants “the opportunity to appeal and request expedited review.” *Id.* The court denied Appellants’ motion to stay pending appeal

but extended the injunction's imposition by 15 days. Ex.B¶2. Appellants appealed. Ex.C. This Court has jurisdiction under 28 U.S.C. §§1292(c)(1) and 1295(a)(1).

### LEGAL STANDARD

The stay factors are well-established: “(1) whether the stay applicant has made a strong showing that [the applicant] is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies.” *Standard Havens Prods., Inc. v. Gencor Indus., Inc.*, 897 F.2d 511, 512 (Fed. Cir. 1990).

The Court applies these factors on a “sliding scale.” *Id.* at 513. Thus, “[t]he more likely the [applicant] is to win, the less heavily need the balance of harms weigh in his favor.” *Id.* Conversely, if the “harm to applicant is great enough,” the Court “will not require a strong showing that applicant is likely to succeed on the merits.” *Id.* Additionally, because a stay is an equitable remedy, the consideration of the public interest figures prominently. *See Winter v. NRDC*, 555 U.S. 7, 23-26 (2008). This Court has regularly granted stays of permanent injunctions pending appeal. *See, e.g., ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1336 (Fed. Cir. 2012); *i4i Ltd. P'ship v. Microsoft Corp.*, 343 F. App'x 619 (Fed. Cir. 2009); *Nichols Inst. Diagnostics, Inc. v. Scantibodies Clinical Lab., Inc.*, 166 F. App'x 487, 489 (Fed. Cir. 2006) (staying permanent injunction in antibody case).

## **ARGUMENT**

This is a textbook case for a stay pending appeal. The extraordinary injunctive relief ordered by the district court is highly unlikely to withstand review. In the meantime, the injunction will inflict extraordinary, irreparable harm on Appellants and thousands of innocent patients; even the district court recognized that an injunction disserved the public interest. And staying the injunction merely preserves the status quo for Amgen. The case for ordering a stay before a draconian, medicine-withdrawing injunction takes effect could hardly be clearer.

### **I. The Permanent Injunction Is Highly Likely To Be Vacated On Appeal.**

The district court's permanent injunction is highly likely to be vacated on appeal for two independent reasons. First, there are numerous flaws in the underlying judgment, each independently requiring reversal or vacatur such that there will be no wrong to remedy. Second, the injunction order itself is deeply flawed and would warrant vacatur even if some remedy were appropriate.

#### **A. The Validity Judgment Is Likely To Be Vacated.**

##### **1. Written Description**

While Amgen's patents suffer from many defects, they plainly fail the written description requirement. Amgen's asserted claims are precisely the kind of broad, functional genus claims that this Court has warned are "inherently vulnerable to invalidity challenge for lack of written description support." *AbbVie*, 759 F.3d at 1301. To support a functional genus claim, a patentee must describe

either a “representative number of species falling within the scope of the genus” or “structural features common to the members of the genus,” such that “one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc).

Amgen did not come close to satisfying either test. Amgen did not identify any structural feature “common to” the genus, and there is none. The claims define the genus based on where antibodies *bind*, and scientists indisputably cannot determine an antibody’s structure based on where it binds. Ex.K 549:2-16; Ex.L 836:5-15. At best, Amgen introduced expert testimony focusing on PCSK9’s surface, rather than structural features common to the antibodies. *Id.* 784:5-8,17-19. Amgen fares no better under the “representative species” test. Although the functional language of the claims indisputably encompasses a wide range of structurally diverse antibodies, the specification describes a total of two antibodies known to meet the claims (Repatha and 31H4). Ex.K 644:5-645:13; 650:24-651:14.

The telltale sign of Amgen’s inadequate written description is the same one that doomed the patent in *AbbVie*: the specification does not even describe “some species representative of antibodies that are structurally similar to” the *very product accused of infringement*. 759 F.3d at 1301. Remarkably, however, the district court precluded Appellants from presenting evidence of *Praluent’s own structure*, thereby preventing Appellants from showing the jury that, for example,

Repatha is more structurally similar to antibodies to influenza and the rabies virus than it is to Praluent. Ex.N¶65. Such evidence would have been devastating to Amgen's assertion of sufficient written description to claim an entire genus. The district court rightly expressed concerns over its decision, which it admitted was in tension with *AbbVie*. See n.3, *supra*. Nevertheless, the upshot of its decision is that a patentee can now force an accused product *off the market* without describing even a *single* antibody that is structurally similar to the accused product *or even allowing the accused product to be presented to the jury*. Unless this Court is prepared to accept that astonishing proposition, the verdict is likely to be vacated.

## 2. Newly Characterized Antigen Instruction

The verdict is likely to be vacated for another, independent reason. Over Appellants' objection, the district court instructed the jury that Amgen's patents were valid if they disclosed "a newly characterized antigen by its structure, formula, chemical name, or physical properties." Ex.H 25. That instruction could have comprised the sole basis for the jury's verdict. But this Court has *never* held that the written description requirement for a functional antibody claim is satisfied based solely on the disclosure of a "newly characterized antigen."

At most, this Court has acknowledged the concept in dicta, see *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1351-52 (Fed. Cir. 2011), but the instruction in this case is not even consistent with that dicta. In *Centocor*, the

Court characterized that dicta as “presum[ing] that the applicant is disclosing a novel protein and then claiming *both the protein and* an antibody that binds to it.” *Id.* (emphasis added). But the instruction here did not require the jury to find that Amgen was claiming “both the protein and an antibody that binds to it.” Amgen did not request that instruction, and for good reason: Amgen did not discover PCSK9, which was well-known for years; it is claiming *only* an antibody. *Id.* Because the jury instruction was erroneous and prejudicial, the verdict is likely to be vacated on this basis as well.

### **3. Obviousness**

Yet another issue on which Appellants are likely to prevail on appeal is the district court’s flawed obviousness ruling. Appellants contended that certain Patent Cooperation Treaty (“PCT”) applications rendered the asserted claims obvious, and they relied on the filing dates for the PCT applications’ respective provisional applications to predate Amgen’s priority date. Following one-page briefing, the court held that the PCT applications were not entitled to the provisional filing dates, because, under *Drinkware*, Appellants had to conduct a full-blown written description and enablement analysis for the PCT applications’ claims relative to the disclosures in the corresponding provisional applications. The court’s decision eviscerated Appellants’ obviousness evidence, resulting in JMOL to Amgen.

But *Drinkware* has no relevance here. The asserted prior art in *Drinkware*

was an *issued patent* with *fixed claims*. By contrast, this case involves PCT *applications*, with *unexamined claims* that may be amended or deleted entirely. Extending *Drinkware*'s requirements to PCT applications makes no sense. Even the district court barely endorsed its decision. *See* Ex.M 1077:4-6 (noting that “defendants have a good argument the other way, but it will be made to the Federal Circuit, not to the jury”). Its decision nevertheless resulted in Appellants’ obviousness defense not even reaching the jury, which is plainly prejudicial error.

**B. The Injunction Remedy Is Likely To Be Vacated.**

The district court’s permanent injunction order—with no real reasoning, and in the teeth of a finding that the *public interest counsels against an injunction*—is itself likely to be vacated on appeal. That independently warrants a stay.

“An injunction is a drastic and extraordinary remedy, which should not be granted as a matter of course.” *Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 165 (2010). In *eBay Inc. v. MercExchange*, 547 U.S. 388 (2006), the Supreme Court held that to obtain an injunction following patent infringement, a plaintiff “*must demonstrate*: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; *and* (4) *that the public interest would not be disserved by a permanent injunction.*” *Id.* at 391 (emphases added).

The district court's order is irreconcilable with *eBay*. Amgen did not “demonstrate” all four of the required factors, because the court expressly found that “[t]he public interest factor weighs in favor of” Appellants. Ex.A¶12 (emphasis added); *see id.* ¶11 (“[T]he public interest of having a choice of drugs should prevail.”). Neither the district court nor Amgen cited any precedent from this Court—and Appellants are aware of none—granting a permanent injunction when one of the *eBay* factors, let alone the public interest, *weighs against* injunctive relief. Indeed, even Amgen's proposed injunction order, submitted before the district court's decision, presumed (correctly) that the court must “find[] that the entry of an order of injunction will not disserve the public interest.” Ex.I at 5. This case, involving a lifesaving medication used by thousands of patients, should certainly not be the first in which this Court permits an injunction that is concededly contrary to the public interest. But at a bare minimum, this Court should not allow such unprecedented relief to take effect before this Court can assess the merits of the underlying appeal as to both the merits and remedy. *See, e.g., Jacobson v. Lee*, 1993 WL 262664, at \*5 (Fed. Cir. May 5, 1993) (staying injunction based on “important questions, some of first impression, that deserve careful consideration by this court”).

Furthermore, even if an injunction could be granted over a conflicting *eBay* factor, the district court offered literally no explanation for why such an approach

was justified here. Engaging in no analysis weighing the *eBay* factors, the Court simply followed its finding that “[t]he public interest factor weighs in favor of [Appellants]” with the glaring *ipse dixit* that “Plaintiffs’ motion for a permanent injunction ... is granted.” Ex.A¶12. Just as egregious, the court’s discussion of irreparable harm merely described the parties’ arguments and then stated, absent any reasoning, that the factor “weighs in favor of plaintiffs.” *Id.* ¶7. So too on the balance of hardships, which the court found to be “neutral” with zero explanation, despite the overwhelming hardships that Appellants will face if Praluent is pulled off the market. *Id.* ¶9. The discussion of the adequacy of money damages included at best one sentence of reasoning, itself contradicted by the court’s later suggestion that the parties might “reach an appropriate business resolution,” which presumably would consist of a reasonable royalty. *Id.* ¶¶8, 12.

The court’s perfunctory analysis and wholly unreasoned conclusion are independent reasons the injunction will likely be vacated on appeal and should be stayed in the meantime. *See Winter*, 555 U.S. at 26 (vacating injunction where court analyzed public interest factor “in only a cursory fashion”); *ActiveVideo*, 694 F.3d at 1336-41 (staying and later vacating injunction); *Wang Labs., Inc. v. Clearpoint Research Corp.*, 1992 WL 349339, at \*1 (Fed. Cir. Oct. 21, 1992) (staying injunction where “court’s findings and conclusions ... were abbreviated and conclusory”).

Finally, the district court's decision to grant an injunction is "as inexplicable as it is unexplained." *Felkner v. Jackson*, 562 U.S. 594, 598 (2011). An injunction is an equitable and discretionary remedy, and the cardinal command of a court of equity is to "do equity." *Hecht Co. v. Bowles*, 321 U.S. 321, 329 (1944). Thus, the issuance of an injunction that the issuing court itself views as contrary to the public interest should be the null set. The Supreme Court has recently emphasized the paramount importance of the public interest in the equitable analysis. *See Winter*, 555 U.S. at 23 (finding irreparable injury "outweighed by the public interest"). And this Court has noted that "for good reason, courts have refused to permanently enjoin activities that would injure the public health," and viewed a medicine-removal order as the very archetype of an improper injunction. *Cordis Corp. v. Boston Sci. Corp.*, 99 F. App'x 928, 935 (Fed. Cir. 2004). Indeed, this Court recently dismissed an objection to an injunction favoring Apple because "Apple does not seek to enjoin the sale of lifesaving drugs." *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 647 (Fed. Cir. 2015). Here, however, Amgen seeks precisely that forbidden fruit: "to enjoin the sale of lifesaving drugs." *Id.*

Put simply, this is not a case about cell phones and tablets; it is about heart attacks and strokes. It is no exaggeration to say that the injunction will take lifesaving medicine away from thousands of patients and leave them with no adequate replacement. Absent a rigid presumption in favor of patent infringement

injunctions of the kind the Supreme Court expressly rejected in *eBay*, *see* 547 U.S. at 393-94, there is simply no way to justify the district court’s utterly unreasoned conclusion that the other equitable factors somehow outweigh the public interest in keeping Praluent available to patients. At the very least, the question is sufficiently debatable and the stakes are sufficiently high to warrant a stay pending appeal.

## **II. The Injunction Will Inflict Irreparable Harm On Appellants.**

The injunction ordered by the district court will inflict irreparable harm on Appellants in multiple ways. First, the injunction requires the removal of Praluent from all stages of the supply chain, including manufacturing, packaging, and distribution. Ex.Q¶13; Ex.S¶15. This is a massive, complex, and costly logistical undertaking. Moreover, it cannot simply be “undone” should this Court ultimately vacate the injunction. Reintroducing Praluent to the market after total shutdown is not simply a matter of flipping a switch. It would require an even more massive, complex, and costly operation to bring supply, manufacturing, packaging, and distribution operations back on line. *Id.* The burden on Appellants from both shutdown and restart is incalculable, and even if there were some way to quantify the harm, Appellants could not recover those monetary costs.

Praluent’s withdrawal from the market would also result in the invalidation of Appellants’ contracts with insurers and pharmacy benefits managers. Ex.P¶4. Amgen, as the sole player in the market, would then negotiate its own contracts

with those entities. This extraordinary injury is also irreparable: even if the injunction were vacated and Praluent restored to the market, Appellants would be unable to reinstate their former contracts or regain their market position. *Id.*

The damage to Appellants' human capital—the heart of their businesses as innovators—would be equally irreparable. If the injunction is not stayed, Appellants will have no choice but to lay off hundreds of skilled employees with specialized knowledge of Praluent. Ex.Q¶10; Ex.S¶20. Even if Appellants prevail on appeal, it will be difficult to rehire those employees, as many will have found other jobs or be hesitant to rejoin a company that recently terminated them. Ex.Q¶11; Ex.S¶21. New employees would have to undergo time-consuming and expensive training, which would substantially delay any relaunch of Praluent. *Id.*

Finally, an injunction withdrawing Praluent from the market would inflict enduring, irreparable reputational harm on Appellants. As Dr. Robert Eckel, former president of the American Heart Association, explains, “trust and confidence in both a medicine and its supplier are paramount” in the pharmaceuticals market. Ex.O¶15. Doctors and patients “must have complete trust not only in a medicine’s efficacy, but also in its availability.” *Id.* Appellants’ hard-earned reputation for reliability “will be irreparably harmed the moment Praluent is pulled from the market.” *Id.* That damage cannot be undone even if Appellants succeed on appeal. *Id.*

### **III. A Stay Pending Appeal Will Not Substantially Injure Amgen.**

In stark contrast to the irreparable harm inflicted on Appellants (and patients) if Praluent is pulled off the market, a stay of the injunction pending appeal will not “substantially injure” Amgen. *Standard Havens*, 897 F.2d at 512. To the contrary, staying the injunction will simply preserve the status quo. “[P]reservation of th[e] status quo is an important factor favoring a stay,” and “is preferable to forcing the [appellant] to develop new procedures which might be required only for a short period of time.” *Houchins v. KQED, Inc.*, 429 U.S. 1341, 1346 (1977) (Rehnquist, J., in chambers). That is all the more true here, where Amgen deliberately chose *not* to seek a preliminary injunction that could have prevented Praluent from being marketed. That decision strongly indicates that money damages suffice to compensate Amgen for any harm suffered during litigation, whether at trial or on appeal.

Moreover, damages are the norm in a case between two innovators like this one. An injunction “taking an already approved, available [pharmaceutical] product off the market” is exceedingly rare, occurring “about once a decade.” *Sachs*, n.2, *supra*. Indeed, recently, Merck did not ultimately pursue an injunction pulling Gilead’s Hepatitis C drug off the market after establishing infringement. *Id.* If money damages were enough to satisfy the patentee *permanently* there, they are surely enough to avoid substantial harm to Amgen *pending appeal* here.

#### **IV. The Public Interest Overwhelmingly Favors A Stay Pending Appeal.**

Finally, and critically, “the public interest” points unmistakably in favor of a stay pending appeal. *Standard Havens*, 897 F.2d at 512. If Praluent is withdrawn, transitioning to Repatha will be complex and costly for patients. Many insurance contracts cover *only* Praluent and will have to be renegotiated—a process that often takes months and could leave patients without treatment in the interim. *See* Ex.S¶15; Sachs, n.2, *supra* (“At least some patients will undoubtedly go without the drug during a transition period.”). Even worse, many Praluent patients will be left with *no* realistic option for cholesterol-lowering drugs. As noted, only Praluent is available in a low dose that delivers a 45 percent (rather than a 60 percent) cholesterol reduction. That allows doctors to treat to a “target” and avoid exposing patients to the “unknown” medical effects of “very low” LDL cholesterol—an uncertainty reflected on FDA-approved labels for both Praluent and Repatha. Ex.O¶¶7-9. If Praluent is pulled from the market, thousands of patients now using the low dose of Praluent—85 percent of prescriptions to date—must either take a larger dose than medically necessary, or stop taking an anti-PCSK9 therapy entirely. *Id.* ¶¶10-13. “Neither of these options is medically sound,” yet they are the inevitable result of the injunction here. *Id.* ¶10.

In addition, the injunction will harm the public interest by jeopardizing the completion of FDA-mandated clinical trials measuring the long-term safety and

efficacy of Praluent and, more generally, PCSK9 inhibitors in certain patient sub-populations. If the injunction is not stayed, many trial patients will likely withdraw, reasoning that there is no point in continuing trials for a drug that will not be on the market, thereby compromising the trials. Ex.R¶¶4-6. Likewise, patients will not likely enroll in Appellants' ongoing (and in some instances FDA-mandated) new trials, including trials involving PCSK9 inhibitors in children, adolescents, and diabetics. *Id.* ¶¶7-10. The resulting harm to public health from the forgone medical research is incalculable.

Furthermore, following an injunction, Amgen would have a monopoly in the anti-PCSK9 market, undoubtedly creating upward pressure on prices. Ex.P¶9; *see* Sachs, n.2, *supra*. And if Repatha were recalled for any reason—*e.g.*, safety concerns, manufacturing disruptions, or contamination—there would be no anti-PCSK9 therapy on the market at all, leaving patients with no option for lowering dangerously high cholesterol levels. Ex.O¶14.

Simply put, if the public interest in keeping Praluent on the market is strong enough to counsel against *granting the injunction*, as the district court found, it counsels overwhelmingly in favor of *staying the injunction* pending appeal.

## CONCLUSION

For the foregoing reasons, this Court should stay the injunction pending appeal. If consideration of this motion extends beyond the injunction's effective date—February 21, 2017—Appellants request a temporary stay of the injunction until the Court decides the motion. Appellants also request expedited consideration of the appeal under the following schedule, which halves the times under the default schedule: Appellants' brief 30 days after a schedule is ordered; Amgen's brief 20 days later; and Appellants' reply 7 days later, with oral argument promptly thereafter. Appellants seek to avoid irreparable harm pending appeal, not delay, and will comply with whatever schedule this Court deems appropriate.

Respectfully submitted,

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January 13, 2017

**CERTIFICATE OF COMPLIANCE  
WITH TYPE-VOLUME LIMITATION**

I hereby certify that:

1. This motion complies with the type-volume limitation of Fed. R. App. P. 27(d)(2)(A) because it contains 5,200 words, excluding the parts exempted by Fed. R. App. P. 32(f).

2. This motion complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the typestyle requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in 14-point font.

January 13, 2017

s/Paul D. Clement  
Paul D. Clement

**CERTIFICATE OF SERVICE**

I hereby certify that on January 13, 2017, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system. I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

s/Paul D. Clement  
Paul D. Clement

# **EXHIBIT A**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, )  
LIMITED; AND AMGEN USA, INC )

Plaintiffs, )

v. )

Civ. No. 14-1317-SLR  
(Consolidated)

SANOFI; SANOFI-AVENTIS U.S. LLC; )  
AVENTISUB LLC f/d/b/a AVENTIS )  
PHARMACEUTICALS INC.; and )  
REGENERON PHARMACEUTICALS, )  
INC., )

Defendants. )

**MEMORANDUM ORDER**

At Wilmington this ~~5<sup>th</sup>~~ day of January, 2017, having reviewed the papers filed in connection with plaintiffs' motion for permanent injunction, and having heard oral argument on the same;

IT IS ORDERED that the motion (D.I. 336) is granted, for the following reasons:

1. **Procedural background.**<sup>1</sup> On October 17, 2014, plaintiffs Amgen Inc., Amgen Manufacturing Limited, and Amgen USA Inc. (collectively "plaintiffs") brought this action alleging infringement of certain patents against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively "defendants"). (D.I. 1) On February 22, 2016, defendants stipulated to infringement of certain asserted claims of the patents-in-suit. (D.I. 235) The parties proceeded to trial

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<sup>1</sup> A fuller recitation of the procedural and factual background may be found in the court's post-trial opinion. (D.I. 389)

on March 8, 2016, arguing the validity of the asserted claims. On March 16, 2016, the jury returned a verdict finding the asserted claims of the patents-in-suit valid. (D.I. 302, 304) On March 23 and 24, 2016, the court heard evidence on plaintiffs' request for a permanent injunction. The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a).

2. **Factual background.**<sup>2</sup> Physicians recognize dyslipidemia caused by elevated LDL ("low density lipoprotein" or "bad" cholesterol) as a major risk factor for cardiovascular disease. Starting in 2005, plaintiffs developed Repatha™ ("Repatha"), which uses the active ingredient "evolocumab." Evolocumab is a monoclonal antibody that targets PCSK9<sup>3</sup> to prevent it from engaging the low density lipoprotein receptor ("LDLR") protein and ultimately lowers the levels of LDL in the blood. Plaintiffs filed for FDA approval on August 27, 2014, which they received in August 2015. Plaintiffs then launched Repatha. Repatha is offered in a 140 mg dose and 420 mg dose.

3. Defendants developed PRALUENT® alirocumab ("Praluent"), a monoclonal antibody that reduces LDL cholesterol levels in the blood. Defendants filed for regulatory approval in November 2014 using an orphan drug priority review voucher, and received FDA approval in July 2015. Defendants then launched Praluent, which is provided in a 75 mg low dose and a 150 mg high dose. According to defendants, more than 80% of patients on Praluent are able to hit their LDL target on the low dose.

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<sup>2</sup> The facts and arguments discussed below are taken from the parties' briefing and corresponding hearing transcripts. (D.I. 347, 348, 362, 369, 376)

<sup>3</sup> Proprotein convertase subtilisin kexin type 9 is a specific antibody involved in regulating the levels of the low density lipoprotein receptor protein.

4. **Standard.** In *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006) (vacating and remanding *MercExchange, L.L.C. v. eBay Inc.*, 401 F.3d 1323, 1339 (Fed. Cir. 2005)) (hereinafter “*eBay*”), the Supreme Court overruled the Federal Circuit's longstanding “general rule that courts will issue permanent injunctions against patent infringement absent exceptional circumstances.” The Supreme Court held in *eBay* that permanent injunctions in patent cases must be based on a case-by-case assessment of the traditional equitable factors governing injunctions. *Id.* at 391-92. That is, to be awarded a permanent injunction, a plaintiff must demonstrate: “(1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction.” *Id.* at 391. “[T]he decision whether to grant or deny injunctive relief rests within the equitable discretion of the district courts, and that discretion must be exercised consistent with traditional principles of equity, in patent disputes no less than in other cases governed by such standards.” *Id.* at 394.

5. In *eBay*, the Court specifically cautioned against the application of categorical rules, classifications, and assumptions in these analyses. *Id.* at 392. Nevertheless, courts (presumably struggling to balance the absence of a presumption of irreparable harm with a patentee's right to exclude) have frequently focused upon the nature of the competition between a plaintiff and a defendant in the relevant market in the context of evaluating irreparable harm and the adequacy of money damages. *See, e.g., TruePosition Inc. v. Andrew Corp.*, 568 F. Supp. 2d 500, 531 (D. Del. 2008). Courts

awarding permanent injunctions typically do so under circumstances in which the plaintiff practices its invention and is a direct market competitor.<sup>4</sup> Plaintiffs also frequently succeed when their patented technology is at the core of their business, and/or where the market for the patented technology is volatile or still developing.<sup>5</sup>

6. There is no dispute that both Repatha and Praluent are approved by the FDA to lower LDL cholesterol in a select group of patients. They are the only therapeutics in the PCSK9 inhibitor market, making the parties head-to-head competitors in a targeted and developing market. The parties at bar are large companies with multiple products, both on the market and in the development pipeline. The parties are also each innovators, having independently developed their PCSK9 inhibitor.

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<sup>4</sup> See, e.g., *Muniauction, Inc. v. Thomson Corp.*, 502 F. Supp. 2d 477, 482 (W.D. Pa. 2007) (“Plaintiff and defendants are direct competitors in a two-supplier market. If plaintiff cannot prevent its only competitor's continued infringement of its patent, the patent is of little value.”) (granting permanent injunction); *Johns Hopkins Univ. v. Datascope Corp.*, 513 F. Supp. 2d 578, 586 (D. Md. 2007) (granting permanent injunction where infringing product was plaintiffs’ “only competition” and “thus, its sale reduce[d] the [p]laintiffs’ market share”); *Transocean Offshore Deepwater Drilling, Inc. v. GlobalSantaFe Corp.*, 2006 WL 3813778, \*4 (S.D. Tex. Dec. 27, 2006) (granting permanent injunction requiring structural modifications to infringing deepwater drilling rigs where “the customer base for deep water drill rigs is small, and [defendant] has not only used [its] rigs equipped with the infringing structure to compete for the same customers and contracts as [plaintiff], but also to win contracts over competing bids from [plaintiff]”).

<sup>5</sup> See, e.g., *Martek Biosciences Corp. v. Nutrinova Inc.*, 520 F. Supp. 2d 537, 558-59 (D. Del. 2007) (granting permanent injunction where plaintiff was a direct competitor “likely to lose market share that it may not be able to recapture,” as plaintiff’s patented technology was its primary revenue source, and defendant was plaintiff’s only competitor and was “targeting [plaintiffs] customers in that industry”); *TiVo, Inc. v. EchoStar*, 446 F. Supp. 2d 664 (E.D. Tex. 2006) (granting permanent injunction where: (1) parties were direct competitors; (2) “plaintiff [was] losing market share at a critical time in the market's development;” (3) the parties agreed that customers in the relevant market tend to remain customers of the company they first purchased from; and (4) as a “relatively new company with only one primary product,” plaintiff’s “primary focus is on growing a customer base specifically around the product” competing with the infringing product).

7. **Irreparable harm.** Plaintiffs present traditional evidence of loss of market share and momentum. Specifically, plaintiffs allege that they have been forced to compete with defendants for contracts with insurers and exclusive formulary positions, particularly since defendants were first to market. Plaintiffs argue that defendants' market position is causing harm to their reputation as the innovator in the PCSK9 cholesterol-lowering medicine, and defendants' marketing of Praluent as "The First U.S. FDA-Approved PCSK9 Inhibitor" compounds such harm. Defendants respond that it is well known that plaintiffs were the first to file a biologics license application with the FDA and receive regulatory approval worldwide for Repatha. According to defendants, Repatha would have faced pricing pressures even without competition from Praluent. This factor weighs in favor of plaintiffs.

8. **Remedies at law.** Plaintiffs assert that patent protection is fundamental to their business model and they will not be able to fully recoup their investment in Repatha without an injunction. Monetary damages will not suffice under the present circumstances, as plaintiffs intended to use their patent to maintain market exclusivity. Moreover, the developing PCSK9 inhibitor market, together with the reputational harm, make monetary damages speculative. In contrast, defendants allege that plaintiffs have not suffered reputational harm and, even if they did, such harm is measurable. Defendants maintain that monetary damages are sufficient, in as much as the parties' experts quantified the extent of past financial injury during the liability phase of the case. This quantification, however, does not include reputational harm and defendants do not offer any method of calculation. This factor weighs in favor of plaintiffs.

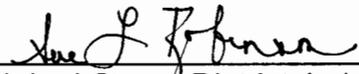
9. **Balance of hardships.** Both parties have spent billions of dollars and over a decade of work to bring their respective products to market. If an injunction does not issue, plaintiffs lose the market share occupied by defendants and face continued competition. If an injunction issues, defendants lose business going forward and the ability to make and market Praluent. This factor is neutral.

10. **Public interest.** Plaintiffs rely on the traditional notions of being a patent holder and a verdict winner. Plaintiffs point to the FDA's approval of Repatha to treat all patients covered by the Praluent label to assuage the consequence of an injunction on patients. (JTX 392) Defendants rely heavily on the availability of (and physicians' alleged preference for) the low 75 mg dose of Praluent to argue that an injunction would harm the treatment of patients. Defendants also point to Praluent's label stating that "[t]he recommended starting dose for Praluent is 75 mg." (PTX 5012)

11. The court will not substitute its judgment for that of the FDA, nor delve into weighing testimony on the propriety of treating patients with the 75 mg dose of Praluent (instead of the 150 mg dose or the 140 mg dose of Repatha). The public generally is better served by having a choice of available treatments. Therefore, the court finds itself between a rock and a hard place, i.e., being a patent holder and a verdict winner should be a meaningful factor in the balancing test, but taking an independently developed, helpful drug off the market does not benefit the public. "[T]he touchstone of the public interest factor is whether an injunction, both in scope and effect, strikes a workable balance between protecting the patentee's rights and protecting the public from the injunction's adverse effects." *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 863 (Fed. Cir. 2010), *aff'd*, 564 U.S. 91 (2011). The court concludes that the public

interest of having a choice of drugs should prevail. This factor weighs in favor of defendants.

12. **Conclusion.** For the aforementioned reasons, plaintiffs have demonstrated irreparable harm, as well as the inadequacy of money damages. The public interest factor weighs in favor of defendants. Plaintiffs' motion for a permanent injunction (D.I. 336) is granted. Given the ramifications of an injunction, the court will delay its imposition for thirty (30) days to allow defendants the opportunity to appeal and request expedited review of this ruling by the Federal Circuit, and/or to encourage the parties to reach an appropriate business resolution.

  
United States District Judge

# **EXHIBIT B**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, )  
LIMITED; AND AMGEN USA, INC )

Plaintiffs, )

v. )

Civ. No. 14-1317-SLR  
(Consolidated)

SANOFI; SANOFI-AVENTIS U.S. LLC; )  
AVENTISUB LLC f/d/b/a AVENTIS )  
PHARMACEUTICALS INC.; and )  
REGENERON PHARMACEUTICALS, )  
INC., )

Defendants. )

**MEMORANDUM ORDER**

At Wilmington this 9th day of January, 2017, having reviewed the papers filed in connection with defendants' motion to stay entry of the permanent injunction;<sup>1</sup>

IT IS ORDERED that the motion (D.I. 394) is denied, for the reasons that follow:

1. **Standard.** A court may stay an injunction pending appeal pursuant to Federal Rule of Civil Procedure 62(c). In exercising its discretion to issue such a stay, the Federal Circuit has indicated that a court must consider four factors: "(1) whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies." *Standard Havens Prods. v. Gencor Indus.*, 897 F.2d 511, 512 (Fed. Cir. 1990) (citations omitted). The Federal Circuit also has opined that

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<sup>1</sup>Including an exchange of emergency emails with the court. (D.I. 400)

each factor need not be given equal weight, instead, a court should use a flexible balancing approach. *Id.* at 513. In deciding whether to grant a stay pending appeal, a court should “assess[] the movant’s chances of success on the merits and weigh[] the equities as they affect the parties and the public.” *Essex Electro Engineers, Inc. v. United States*, 433 F. App’x 901 (Fed. Cir. 2011) (citing *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 835 F.2d 277, 278 (Fed. Cir. 1987)).

2. As reflected in the court’s order on the permanent injunction, the court has essentially weighed the above factors and entered a limited stay. Although the court declines to grant the relief requested (a stay pending appeal), the court will extend the 30-day stay to 45 days, to provide ample opportunity for an appeal of the instant order.

3. **Conclusion.** For the aforementioned reasons, defendants’ motion to stay the permanent injunction (D.I. 394) pending appeal is denied. The permanent injunction is stayed for 45 days.

  
\_\_\_\_\_  
United States District Judge

# **EXHIBIT C**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC.; AMGEN MANUFACTURING, )  
LIMITED; AND AMGEN USA, INC., )  
)  
Plaintiffs, )  
)  
v. )  
)  
SANOFI, SANOFI-AVENTIS U.S. LLC, )  
AVENTISUB LLC, f/d/b/a AVENTIS )  
PHARMACEUTICALS INC., and )  
REGENERON PHARMACEUTICALS, INC., )  
)  
Defendants. )

C.A. No. 14-1317-SLR  
(Consolidated)

**NOTICE OF APPEAL**

Notice is hereby given that Defendants Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. in the above-named case hereby appeal to the United States Court of Appeals for the Federal Circuit from (1) the final judgment entered in this action on January 3, 2017 (D.I. 391) (and all orders antecedent to that judgment); and (2) the order granting Plaintiffs’ motion for a permanent injunction, entered in this action on January 5, 2017 (D.I. 392).

ASHBY & GEDDES

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Dated: January 12, 2017

# **EXHIBIT D**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, )  
LIMITED; AND AMGEN USA, INC )

Plaintiffs, )

v. )

Civ. No. 14-1317-SLR  
(Consolidated)

SANOFI; SANOFI-AVENTIS U.S. LLC; )  
AVENTISUB LLC f/d/b/a AVENTIS )  
PHARMACEUTICALS INC.; and )  
REGENERON PHARMACEUTICALS, )  
INC., )

Defendants. )

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**MEMORANDUM OPINION**

Dated: January 3, 2017  
Wilmington, Delaware

  
ROBINSON, District Judge

## I. INTRODUCTION

On October 17, 2014, plaintiffs Amgen Inc., Amgen Manufacturing Limited, and Amgen USA Inc. (collectively “plaintiffs”) brought this action alleging infringement of U.S. Patent Nos. 8,563,698; 8,829,165 (“the ‘165 patent”); and 8,859,741 (“the ‘741 patent”) against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively “defendants”). (D.I. 1) Plaintiffs filed an amended complaint on November 17, 2014. (D.I. 10) Defendants answered the complaint on December 15, 2014. (D.I. 18, 19, 20) The court held a *Markman* hearing on September 17, 2015, and issued a claim construction order on October 25, 2015 construing certain disputed limitations of the ‘165 and ‘741 patents. (D.I. 151) On January 29, 2016, the court granted plaintiffs’ motion to amend the complaint, which amended complaint was filed the same day consolidating into a single complaint plaintiffs’ pleadings from four lawsuits (resulting in the addition of U.S. Patent Nos. 8,871,913; 8,871,914; 8,883,983; and 8,889,834). (D.I. 183, 184) Defendants answered the amended complaint on February 16, 2016. (D.I. 220) On February 22, 2016, defendants stipulated to infringement of the asserted claims of the patents-in-suit.<sup>1</sup> (D.I. 235) The court held a final pretrial conference on February 22, 2016.

The parties proceeded to trial on March 8, 2016, arguing the validity of the asserted claims. The court decided a series of evidentiary issues and *Daubert* motions before and during trial. (D.I. 226, 249, 250, 264, 269, 280) On March 16, 2016, the court granted defendants’ judgment as a matter of law regarding willful infringement.

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<sup>1</sup> Claims 2, 7, 9, 15, 19, and 29 of the ‘165 patent and claim 7 of the ‘741 patent.

(D.I. 302) On March 16, 2016, the jury returned a verdict finding the asserted claims of the patents-in-suit valid. (D.I. 304) Presently before the court are defendants' motions for a new trial and judgment as a matter of law on written description and enablement (D.I. 331, 332), and plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338). The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a).

## **II. BACKGROUND**

### **A. Parties**

Amgen Inc. and Amgen USA Inc. are corporations organized under the laws of the State of Delaware, with a principal place of business in Thousand Oaks, California. Amgen Manufacturing, Limited is a corporation organized under the laws of Bermuda with its principal place of business in Juncos, Puerto Rico. Sanofi is a company organized under the laws of France with its principal headquarters in Paris, France. Sanofi-Aventis U.S. LLC is a company organized under the laws of the State of Delaware with its principal place of business in Bridgewater, New Jersey. Aventisub LLC is a company organized under the laws of the State of Delaware having its principal place of business in Greenville, Delaware.<sup>2</sup> Regeneron Pharmaceuticals, Inc. is a corporation organized under the laws of the State of New York with its principal place of business in Tarrytown, New York. (D.I. 184 at ¶¶ 2-8, 12)

### **B. Technology**

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<sup>2</sup> Aventisub is the surviving entity from a June 2014 merger involving Aventis Pharmaceuticals Inc. and has assumed the assets, liabilities, and/or responsibilities of Aventis Pharmaceuticals Inc. Aventis Pharmaceuticals Inc. was a Delaware corporation having a principal place of business in Bridgewater, New Jersey.

## 1. The patents-at-issue

The '165 patent issued on September 9, 2014 and the '741 patent issued on October 14, 2014 (collectively "the patents-at-issue"). (JTX 2, 3) The patents-at-issue are titled "Antigen binding proteins to proprotein convertase subtilisin kexin type 9 (PCSK9)" and share a specification.<sup>3</sup> Proprotein convertase subtilisin kexin type 9 ("PCSK9") is a specific antibody involved in regulating the levels of the low density lipoprotein receptor ("LDLR") protein. (1:57-59) Monoclonal antibodies have a known "Y-shaped" structure made up of "two identical pairs of polypeptide chains," each pair having a heavy chain and a light chain. The carboxy-terminal portion of each chain typically defines a constant region. "The amino-terminal portion of each chain typically includes a variable region of about 100 to 110 or more amino acids that typically is responsible for antigen recognition." This allows different antibodies to bind to different antigens. (33:1-27) The specification describes monoclonal antibodies that bind to a specific region of PCSK9. (3:5-6)

The specification provides that 3000 human monoclonal antibodies were "rescreened for binding to wild-type PCSK9 to confirm stable hybridomas were established," and "a total of 2441 positives repeated in the second screen." (78:4-6, 35) Of these, "384 antibodies . . . blocked the interaction between PCSK9 and the LDLR well [and] 100 antibodies blocked the interaction strongly," "inhibit[ing] the binding interaction of PCSK9 and LDLR [at] greater than 90%." (80:22-26) The "screen of the 384 member subset identified 85 antibodies that blocked interaction between the PCSK9 mutant enzyme and the LDLR [at] greater than 90%." (80:35-37) The

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<sup>3</sup> All references are to the '165 patent unless otherwise indicated.

specification provides the amino acid sequence of over two dozen of the identified antibodies. (Figures 2A-2D, 3A-3JJ, 15A-15D, 17:60-18:3, 20:1-8, 85:7-43) The specification describes the use of “epitope binning assays”<sup>4</sup> to characterize the different epitopes on PCSK9. 21B12 and 31H4 are representative members of two epitope bins that do not compete with each other for binding to PCSK9. (88:34-89:19) X-ray crystallography experiments were used to characterize the 21B12 and 31H4 binding sites. (99:56-103:60)

The claims reference specific amino acids at designated positions in SEQ ID NO: 1 and/or 3, which are specific amino acid sequences of PCSK9. (124-133) Claim 1 of the ‘165 patent recites:

An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

(427:47-52) Claim 1 of the ‘741 patent recites:

An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

(‘741 patent, 427:36-40) At trial, defendants argued that the asserted claims were invalid for lack of written description and enablement and were obvious in light of the prior art.

## 2. Repatha™ and PRALUENT®

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<sup>4</sup> Epitope binning assays are used to determine the ability of an antibody to block another’s binding to the antigen. Antibodies with similar blocking profiles are grouped into a bin, indicating these antibodies bind to the same or overlapping epitopes. (88:34-89:37; D.I. 344 at 799:7-800:16)

Physicians recognize dyslipidemia caused by elevated LDL (“low density lipoprotein” or “bad” cholesterol) as a major risk factor for cardiovascular disease. Plaintiffs developed Repatha™ (“Repatha”), which uses an active ingredient “evolocumab” (identified as “21B12” in the specification). As described in the specification, evolocumab is a monoclonal antibody that targets PCSK9 to prevent it from engaging LDLR and ultimately lowers the levels of LDL in the blood. The FDA approved Repatha in August 2015. (D.I. 184; D.I. 342 at 241:15-24; D.I. 362 at 5) Defendants developed PRALUENT® alirocumab (“Praluent”), a monoclonal antibody that reduces LDL cholesterol levels in the blood. The FDA approved Praluent in July 2015. (D.I. 342 at 347:6-9, 350:23-351:5; D.I. 362 at 5)

### **III. STANDARDS OF REVIEW**

#### **A. Renewed Motion for Judgment as a Matter of Law**

The Federal Circuit “review[s] a district court’s denial of judgment as a matter of law under the law of the regional circuit. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1325 (Fed. Cir. 2016) (citation omitted). In the Third Circuit, a “court may grant a judgment as a matter of law contrary to the verdict only if ‘the record is critically deficient of the minimum quantum of evidence’ to sustain the verdict.” *Acumed LLC v. Advanced Surgical Servs., Inc.*, 561 F.3d 199, 211 (3d Cir. 2009) (citing *Gomez v. Allegheny Health Servs., Inc.*, 71 F.3d 1079, 1083 (3d Cir. 1995)); see also *McKenna v. City of Philadelphia*, 649 F.3d 171, 176 (3d Cir. 2011). The court should grant judgment as a matter of law “sparingly,” and “only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability.” *Marra v.*

*Philadelphia Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007) (citing *Moyer v. United Dominion Indus., Inc.*, 473 F.3d 532, 545 n.8 (3d Cir. 2007)). “In performing this narrow inquiry, [the court] must refrain from weighing the evidence, determining the credibility of witnesses, or substituting [its] own version of the facts for that of the jury. *Id.* (citing *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)). Judgment as a matter of law may be appropriate when there is “a purely legal basis” for reversal “that does not depend on rejecting the jury’s findings on the evidence at trial.” *Acumed*, 561 F.3d at 211.

#### **B. Motion for a New Trial**

Federal Rule of Civil Procedure 59(a) provides, in pertinent part:

A new trial may be granted to all or any of the parties and on all or part of the issues in an action in which there has been a trial by jury, for any of the reasons for which new trials have heretofore been granted in actions at law in the courts of the United States.

Fed. R. Civ. P. 59(a). The decision to grant or deny a new trial is within the sound discretion of the trial court and, unlike the standard for determining judgment as a matter of law, the court need not view the evidence in the light most favorable to the verdict winner. *See Allied Chem. Corp. v. Daiflon, Inc.*, 449 U.S. 33, 36 (1980); *Leonard v. Stemtech Int’l Inc.*, 834 F.3d 376, 386 (3d Cir. 2016) (citing *Olefins Trading, Inc. v. Han Yang Chem. Corp.*, 9 F.3d 282 (3d Cir. 1993)); *LifeScan Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 345, 350 (D. Del. 2000) (citations omitted); *see also* 9A Wright & Miller, *Federal Practice and Procedure* § 2531 (2d ed. 1994) (“On a motion for new trial the court may consider the credibility of witnesses and the weight of the evidence.”). Among the most common reasons for granting a new trial are: (1) the jury’s verdict is against the clear weight of the evidence, and a new trial must be granted to prevent a

miscarriage of justice; (2) newly-discovered evidence exists that would likely alter the outcome of the trial; (3) improper conduct by an attorney or the court unfairly influenced the verdict; or (4) the jury's verdict was facially inconsistent. See *Zarow-Smith v. N.J. Transit Rail Operations*, 953 F. Supp. 581, 584-85 (D.N.J. 1997) (citations omitted). The court must proceed cautiously, mindful that it should not simply substitute its own judgment of the facts and the credibility of the witnesses for those of the jury. Rather, the court should grant a new trial “only when the great weight of the evidence cuts against the verdict and a miscarriage of justice would result if the verdict were to stand.” *Leonard*, 834 F.3d at 386 (citing *Springer v. Henry*, 435 F.3d 268, 274 (3d Cir. 2006) and *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1352-53 (3d Cir. 1991)) (internal quotation marks omitted).

#### **IV. MOTION FOR JMOL**

##### **A. Procedural Issue**

Defendants renew their motion for JMOL on the issue of lack of written description and enablement, arguing that the evidence presented at trial was legally sufficient to show that the specification lacked written description and was not enabled. Plaintiffs challenge the propriety of the renewed motion as defendants did not formally move for JMOL under Rule 50(a) during trial. Fed. R. Civ. P. 50(a).

Rule 50(a) requires the movant to “specify the judgment sought and the law and facts that entitle the movant to judgment.” Fed. R. Civ. P. 50(a). “The purpose of th[is] requirement is to afford the opposing party an opportunity to cure the defects in proof that might otherwise preclude the party from taking the case to the jury.” See *Duro-Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1105 (Fed. Cir. 2003). The caselaw

indicates that a Rule 50(b) JMOL motion is properly founded where an oral Rule 50(a) motion was lodged; or a mere technical failure to comply with Rule 50(a) occurred, i.e., “the party clearly challenged the sufficiency of the evidence on the disputed issue at some point during trial, thereby alerting the opposing party as to the grounds on which the evidence is allegedly insufficient.” *Id.* at 1106. The level of specificity required to give the opposing party notice has been the subject of interpretation, and may vary depending on the circumstances of the case. *See Fresenius Medical Care Holdings, Inc. v. Baxter Intern., Inc.*, 2007 WL 518804, \*5 (N.D. Cal. Feb. 13, 2007) (collecting Federal Circuit authority).

At the close of defendants’ case, on March 10, 2016, the court indicated that the parties should move on to the rest of the case postponing any motion practice until the jury was excused. (D.I. 343 at 720:17-19) After resolving an evidentiary issue outside the presence of the jury, the court stated that “if [plaintiffs] want to do [their] placeholder motion, [plaintiffs] should just say [that they] make a motion, and I will reserve judgment. No need to do much more than that.” Plaintiffs moved for JMOL arguing that defendants did not present a sufficient evidentiary basis for a reasonable juror to find for defendants with respect to their invalidity defenses of obviousness, lack of written description, and enablement relating to the . . . asserted claims of the patents-in-suit.” The court reserved judgment, and stated that there was “[n]o need for defendants to even respond” to plaintiffs’ motion. (D.I. 343 at 725:15-726:8) On March 14, 2016, after further discussion with counsel, the court granted plaintiffs’ motion for JMOL on obviousness. (D.I. 345 at 1076:21-1077:6) With this grant, the court issued a short instruction to the jury to explain why the testimony of plaintiffs’ expert was cut off. (*Id.* at

1110:9-17) Plaintiffs then rested their case. Defendants did not formally move for JMOL on the issues of written description and invalidity and moved on to their rebuttal case. (*Id.* at 1100:18-23)

“The district court [is] in the best position to judge the sufficiency of [a] Rule 50(a) motion in the context of the trial . . . .” *Gaus v. Conair Corp.*, 363 F.3d 1284, 1287 (Fed. Cir. 2004). Throughout the trial, the crux of the invalidity dispute was defendants’ contention of lack of written description and invalidity. Indeed, only these issues went to the jury (defendants having stipulated to infringement and the court having resolved the issue of willful infringement and obviousness). Under the circumstances, the court concludes that plaintiffs were apprised during trial of defendants’ allegations of insufficient evidence of written description and enablement, therefore, defendants may proceed with the renewed JMOL.<sup>5</sup>

**B. Standard**

The statutory basis for the enablement and written description requirements, 35 U.S.C. § 112, provides in relevant part:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

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<sup>5</sup> In contrast, in *TruePosition Inc. v. Andrew Corp.*, 568 F. Supp. 2d 500 (D. Del. 2008) (cited by plaintiffs), the court found that defendant’s pre-verdict JMOL motions regarding infringement (no offer for sale and failure of proof on claims 1 and 22) and damages, together with its counsel’s statements, were insufficient to support the post-trial renewed JMOL motion on several other claims (willfulness; no lost profits damages based on the existence of non-infringing alternatives; government use; fraud; and promissory estoppel)).

35 U.S.C. § 112 ¶1. “The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without ‘undue experimentation.’” *Strech, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). “While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The specification need not teach what is well known in the art. *Id.* (citing *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). A reasonable amount of experimentation may be required, so long as such experimentation is not “undue.” *ALZA Corp. v. Andrx Pharmaceuticals, Inc.*, 603 F.3d 935, 940 (Fed. Cir. 2010).

“Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). The Federal Circuit has identified several factors that may be utilized in determining whether a disclosure would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. These factors are sometimes referred to as the “*Wands* factors.” A court need not consider

every one of the *Wands* factors in its analysis, rather, a court is only required to consider those factors relevant to the facts of the case. See *Streck, Inc.*, 655 F.3d at 1288 (citing *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)).

The enablement requirement is a question of law based on underlying factual inquiries. See *Green Edge Enterprises, LLC v. Rubber Mulch Etc., LLC*, 620 F.3d 1287, 1298-99 (Fed. Cir. 2010) (citation omitted); *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1323 (Fed. Cir. 2009) (citation omitted). The burden is on one challenging validity to show, by clear and convincing evidence, that the specification is not enabling. See *Streck, Inc.*, 665 F.3d at 1288 (citation omitted).

A patent must also contain a written description of the invention. 35 U.S.C. § 112, ¶ 1. The written description requirement is separate and distinct from the enablement requirement. See *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2011). It ensures that “the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed.” *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005). The Federal Circuit has stated that the relevant inquiry – “possession as shown in the disclosure” – is an “objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.” *Ariad*, 598 F.3d at 1351.

This inquiry is a question of fact; “the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Id.* (citation omitted). In this regard, defendant must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. See *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008) (citation omitted).

### **C. Evidence**

#### **1. 21B12 and 31H4**

The parties agreed that the patent described the screening of about 3,000 antibodies to determine which ones block the binding of PCSK9 to the LDL receptor. The inventors chose 384 antibodies, which blocked PCSK9 “well” for further testing. Of these, 100 antibodies were identified that blocked PCSK9 at over 90%. (D.I. 342 at 283; D.I. 343 at 637:18-639:3, 742) The parties also agreed that the patents-in-suit disclose two antibodies (21B12 and 31H4) that bind to a specific region (the “binding region”) of PCSK9.<sup>6</sup> The inventors identified the binding region using X-ray crystallography of 21B12 and 31H4. (D.I. 342 at 283-286:11, 411:4-9, 415:15-21; D.I. 343 at 550:7-17; D.I. 344 at 881:19-882:4, 916:6-8) The specification only provides X-ray crystallography data for 21B12 and 31H4. (D.I. 342 at 283:10-14; D.I. 343 at 645:4-13; D.I. 344 at 882:5-8, 937:24-938:6)

#### **2. Defendants’ evidence**

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<sup>6</sup> The court will refer to this region as “the binding region,” rather than the list of names used by the various witnesses including, but not limited to: region, zone, hot zone, central patch, patch, specific area, and sweet spot.

Defendants' expert, Dr. Michael Eck ("Dr. Eck"), testified that the patent disclosed the topography of PCSK9 and the fifteen residue binding region, as well as the crystal structure. (D.I. 343 at 562:19-563:4, 579:1-11; see *a/so* D.I. 344 at 633:22-634:22, 676:2-677:10) He explained that 21B12 and 31H4 "bind to very defined spots on the surface of PCSK9, [21B12] on one spot, sort of at the edge . . . of the [binding] region [and] 31H4 on the opposite edge." (D.I. 343 at 540:9-541:2; D.I. 345 at 1114:5-1116:13) He stated that 21B12 "probably interacts with probably eighteen amino acids on the surface," four of which are in the binding region. 31H4 interacts with about thirty amino acids total and three in the binding region. (D.I. 343 at 556-557) There are residues in the "middle" of the binding region that are not bound by either 21B12 or 31H4. (D.I. 343 at 546:4-19, 556:4-557:4; D.I. 345 at 1115:10-13) He opined that there are "many different positions on the surface of PCSK9, including this region in the middle, where one would expect antibodies to [be] able to bind, and we see here in [plaintiffs'] patent exactly two examples of antibodies that we know bind in this general vicinity, both on the edge." (D.I. 343 at 541:3-10) There is no example of an antibody "that interacts with the middle and binds [S]153 or likewise D238 or I369 or V380." (D.I. 345 at 1118:14-1119:12) Defendants' other expert, Dr. Donald Siegel ("Dr. Siegel"), similarly concluded that the patents-in-suit do not show the structure of an antibody that binds centrally to the binding region and opined that such an antibody "would have to have a different amino acid sequence or structure than either" 21B12 or 31H4. Moreover, it "would be interacting in a different way." (D.I. 343 at 634:6-25, 645:14-24)

Dr. Eck further explained that there are other possible antibodies, which would have different structures and mechanisms of binding with the binding region. Such

antibodies “[m]ight interact with many of the same residues on PCSK9, but [also with] a few different residues.” That a certain antibody binds to a particular amino acid on PCSK9 “does not tell you anything at all about the structure,” “only about its function.” Moreover, there are no developed methods for working back from a binding target “to reliably predict how to make an antibody to bind there.” (*Id.* at 547:18-549:16, 564:14-17) Nor can one predict where an antibody would bind on PCSK9 from its structure. (*Id.* at 558:6-9, *see also* 684:3-18) For example, one would expect that “many antibodies with very different chemical structures could bind to PCSK9 and” bind to “D238, but do it in very different ways, with many different antibody structures.” (D.I. 343 at 580:11-22, 587:20-588:3, 588:18-590:5)

Dr. Eck testified that the specification disclosed eleven other antibodies that have essentially the same sequence as 21B12. He opined that if the multiple copies of 21B12 are “binding at all, they have to be binding right where [21B12] is.” (D.I. 343 at 558:12-559:1) Dr. Eck also testified that there are “on the order of thousands of different versions of . . . 21B12,” and the patent does not describe any “examples of antibodies that bind centrally across the middle” of the binding region. (D.I. 345 at 1112:24-1113:19) Dr. Eck briefly described that an antibody may “contact” an amino acid without binding to the amino acid, such that 21B12 contacts the middle amino acid of the EGF-A region (the region of the LDL receptor that binds and interacts with PCSK9). (D.I. 343 at 557, 565:1-18)

Yet another of defendants’ experts, Dr. Jeffrey Ravetch (“Dr. Ravetch”), testified that the antibody technology was extremely well developed and a “mature technology.” The use of “transgenic mice and phage display,” as well as other laboratory methods,

were routine techniques. (D.I. 342 at 409:7-11, 413:3-20, 414-415) Dr. Siegel explained that the asserted claims were not limited to human antibodies, but could be mouse or camel antibodies. The structures of such non-human antibodies would be “much different” than human antibodies. (D.I. 343 at 632:20-633:12) He also explained that the asserted claims (excepting claim 29 of the ‘165 patent) do not specify a particular level of blocking, such that “any small amount of blocking would define an antibody that fit in the genus of antibodies.” (*Id.* at 632:15-19)

Dr. Eck explained that to determine similarities of antibodies, a person of ordinary skill considers “their chemical structure, their composition, their primary amino acid sequence and their three-dimensional structure.” (*Id.* at 577:21-578:4) He concluded that there are “many antibodies that will meet [the asserted] claims that have nevertheless very diverse and different three-dimensional structures and primary amino acid sequences.” He could not “visualize or recognize” these based on the teachings of the specification. Further, “having the expectation that there are many antibodies that will bind [to the binding region] is different than being able to know precisely what those structures are and to be able to realize and make and use any of those structures.” (*Id.* at 583:13-584:14) The specification does not offer “clear evidence” of antibodies binding to the “many ways one could have antibodies binding, covering this central region, as well, for example, as binding to the north edge, or binding to the south edge.” (D.I. 345 at 1117:2-21)

Dr. Siegel explained that the claims of the patents-in-suit “are very broad” and “cover a large number of antibody structures, not limited in any way.” He opined that the specification does not “provide a description of [the] invention.” (D.I. 343 at 612:9-

17) Moreover, the claims reciting an antibody that binds to at least one residue (for example D238), do not provide information about the structure or sequence of such antibody. (*Id.* at 630:9-12) He testified that there are no “common structural features . . . described that would make one understand . . . the structures of other antibodies.” (*Id.* at 659:3-22) Dr. Siegel concluded that the two antibodies are not representative of antibodies that would bind in the middle of the binding region. (*Id.* at 650:24-651:10) He also opined that the 20 or more sequences reported in the specification are insufficient to represent the diversity of antibodies covered by the asserted claims. (*Id.* at 707:18-22)

As to the enablement requirement, Dr. Siegel testified that it would not be possible to start with the amino acid sequences listed in the specification and make “the full diversity of antibodies that are covered by the claims,” because “[i]t’s a very unpredictable process” and would require trial and error. (*Id.* at 662:19-663:10) He stated that the methods were known (*id.* at 664-668:9) but, in his opinion, the process would involve undue experimentation, as “there are a lot of steps involved” and there is nothing in the specification to help a researcher “hone in on an antibody that satisfies the claims.” (*Id.* at 668:10-669:13) The specification has not disclosed a “quick way of doing” the research, or “taught . . . anything special.” (*Id.* at 701:4-8) That the binding region is known is not useful in making the antibodies, as the antibodies must be made and tested to determine where they bind. (*Id.* at 672:22-673:20, 714:10-12) He stated that “even today, we’re talking about how immature the art is where you can’t take an antigen and figure out how to make an antibody that will bind to it.” (*Id.* at 695:5-9)

### **3. Plaintiffs’ evidence**

Plaintiffs' scientific director, Dr. Simon Jackson ("Dr. Jackson"), testified that the crystallography data "showed . . . the specific amino acids that were . . . binding" and "that the antibodies were binding in a small region side by side on PCSK9." (D.I. 342 at 285) Plaintiffs' expert, Dr. Gregory Petsko ("Dr. Petsko"), testified that when the antibodies bind, they cover "a footprint." (D.I. 344 at 799) Dr. Petsko disagreed with the characterization of 21B12 and 31H4 as "edge binders." He described the antibodies as "very large objects" with "a pretty big footprint on the" binding region, that "don't really hang onto the edge at all." (*Id.* at 805) He explained that the 15 residues that constitute the binding region are covered "virtually perfectly, including . . . [F]379" by 21B12 and 31H4. (*Id.* at 806) On cross-examination, Dr. Petsko was asked: "Based on the information available in the patent as of January 9, 2008, one cannot determine that any of the antibodies disclosed bind to PCSK9 in between where 21B12 and 31H4 bind; is that correct?" He explained that "when a scientist hears the word 'determined,' a scientist often thinks about doing experiments." He responded that without experiments, however, he didn't "know for sure that there are any such antibodies." (*Id.* at 862:19-863:15)

Dr. Petsko testified that example 11 in the patent describes the blocking data for the antibodies, i.e., the ability of the antibody to prevent the LDL receptor from binding to PCSK9. Example 3 of the patent discloses that the inventors were in possession of 85 antibodies that blocked at more than 90%. He explained that the 384 member subset blocked quite reasonably. (*Id.* at 796-797) Dr. Jackson explained that "[b]inning is a way to group antibodies . . . depending on how they bind and where they bind to the protein, in this case PCSK9." (D.I. 342 at 267) Antibodies that co-bin cannot bind "at

the same time,” instead they “compete against each other for binding to the site.” (*Id.* at 269) The specification uses 21B12 as a representative antibody for bin 1 and 31BH4 for bin 3. (D.I. 344 at 270) Dr. Petsko testified that “binning experiments . . . tell you whether antibodies have overlapping footprints on the surface of PCSK9.” (*Id.* at 798:15-17) He explained that bin 1 (containing seventeen antibodies) and bin 3 (containing seven antibodies) “represent the collection of antibodies that co-bin with 21B12 and the collection that co-bin with 31H4,” respectively.<sup>7</sup> (*Id.* at 798-802)

Chadwick King (“King”), one of the named inventors on the patents-in-suit, testified that the screening process used in the patent allowed plaintiffs to “identify . . . antibodies that are highly active, have a function of interest, but also have sequence diversity.” Sequence diversity helps ensure that there are “enough molecules [so] that one of them can potentially make it through the later stage steps of drug development . . . [and] testing.” He opined that the panel of thirty antibodies “had nice sequence diversity” and “cover[ed] multiple epitopes.” He concluded that “comparisons of [the] antibody sequences to the germline consensus region” resulted in “good diversity in germline usage.” (D.I. 343 at 744-746)

According to Dr. Petsko, 21B12 and 31H4 are sufficiently representative of the asserted claims, as they provide “all the information” needed “to define the part of PCSK9 where the antibodies need to bind in order to block.” (D.I. 344 at 806-807, 811) He described generally how an antibody comes together with PCSK9 and that there are different types of chemical interactions possible with an amino acid (for example D238).

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<sup>7</sup> Dr. Siegel answered a short series of questions regarding co-binning on cross examination, and conceded that the “epitopes would overlap if [the antibodies] co-bin.” (D.I. 343 at 688:14-691:25)

(*Id.* at 808-809) Dr. Petsko agreed that antibodies could have different kinds of chemical interactions with a particular residue, but disagreed with the characterization that such differences result in a significant difference in structure. (*Id.* at 808:24-809:23) Using S153 as an example, Dr. Petsko described “the noncovalent interaction that contributes to the affinity of the antibody for PCSK9.” (*Id.* at 815-16) He reasoned that 21B12 binds to S153, R194, R237, D238, D374, T377, and F379 and, therefore, falls within the scope of claims 2, 7, 19, and 29 of the ‘165 patent and claim 7 of the ‘741 patent. 31H4 binds to D374 and V380, with a possibility of binding to S381 and, therefore, falls within the scope of claims 15, 19, and 29 of the ‘165 patent.<sup>8</sup> (*Id.* at 817)

Dr. Petsko explained that using the binning and blocking data, it is “more likely than not that one or more of those [antibodies] are going to make interactions with the residues” of the binding region. He identified which of the co-binned antibodies identified in the patent would “more likely than not” meet the claim limitations of claims 19 and 29 of the ‘165 patent. (*Id.* at 818-21, 824-25, 827) He opined that although the specification does not disclose “a crystal structure [for] an antibody that binds to I369,” the inventors were in possession of such an antibody, because the patent discloses a list of “strong blockers,” which would contain antibodies that are likely to bind I369. (*Id.* at 830-32) In other words, the “inventors are in possession of a large number of antibodies and we’ve described two that cover quite a bit of the [binding region], and we’ve also indicated the likely presence of antibodies that will interact with even more residues in the [binding region].” (*Id.* at 831-32)

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<sup>8</sup> Dr. Eck disagreed with the detail of Dr. Petsko’s analysis (but can “understand where he’s coming from”) that 21B12 and 31H4 interact with D374. (D.I. 345 at 1120:5-10)

Dr. Petsko testified that, although one could not sit at a desk and write out all the sequences, a scientist would use the information provided to find antibodies that bind to the binding region on PCSK9. (*Id.* at 836:5-837:14) The specification provided sufficient information to conclude that 21B12 and 31H4 are representative. (*Id.* at 818-819) On cross-examination, Dr. Petsko agreed that there could be “many antibodies that recognize the same epitope,” and the specification does not provide “the formula” for all of them, but added that “nobody could do that.” (*Id.* at 869:14-23) He also conceded that whether an antibody would bind with a particular residue is “not certain at all” from co-binning data. (*Id.* at 880-881, *see also* D.I. 343 at 594:23-595:6, 600:22-601:3) Dr. Jackson concluded that using the X-ray crystallography of 21B12 and 31H4 and the binning data, plaintiffs “knew that the other antibodies were binding in” the binding region. (D.I. 342 at 291-292)

Another of plaintiffs’ experts, Dr. Anthony Rees (“Dr. Rees”), also described using binning data to make antibodies and screening them against 21B12 to see if they compete. (D.I. 344 at 917-18) He testified that, from a scientific perspective, making additional antibodies did not require undue experimentation. With “a particular series of steps . . . to follow,” it is “routine experimentation with some surprises along the way, but which [a person of ordinary skill] can solve in routine ways.” (*Id.* at 920) He evaluated the diversity of the patent’s antibodies and concluded that the sequences, which lead to differences in protein sequence and structure, result in “seven different families.” He reasoned that this was “quite an extensive diversity.” (*Id.* at 923-26) He concluded that a skilled person in the art “would understand that [plaintiffs’] antibodies are representative of the” antibodies of claim 19, based on the disclosure of “detailed three-

dimensional structure” of 21B12 and 31H4, and the twenty-two “other antibodies that are disclosed with respect to their competition or their binning behavior.” (*Id.* at 937:17-938:6)

As to a structure-function relationship, Dr. Petsko opined that antibodies can bind through “noncovalent interactions,” which “hold them together more often than not.” (*Id.* at 791-92) He explained that a “different amino acid sequence might approach a particular residue from a different direction . . . to make a noncovalent interaction with the residue,” but this does not affect the structure-function relationship. (*Id.* at 838-40) Dr. Petsko concluded that the specification describes a structure-function relationship by “describing structure characteristics that the antibodies in the genus have in order to carry out the function of binding to PCSK9, blocking the binding of the LDL receptor.” More specifically, the “structure function relationship is binding to specific residues on the” binding region. (*Id.* at 783:25-784:19) The specification provides a person of skill in the art the ability to visualize and recognize antibodies falling within the claims based on crystal structures and binning experiments. (*Id.* at 836:22-837:23)

Dr. Rees opined that when an antibody binds to PCSK9, it takes on a unique structure and precisely fits together. So “all the antibodies . . . that bind to this region must share structural features . . . that allow them to get the shape fitting that is required.” (*Id.* at 908:10-24, 902:22-903:14, 905:23-906:10) For example, two different amino acid sequences, which bind to the antigen region from influenza may have a different structure, but still share the structural feature of binding to the region. (*Id.* at 910:13-911:18) The “antibodies that fall within the scope of the claims have common structural features.” These structural features lead “to the functions of binding and

blocking” in order to block the binding of PCSK9 to its LDL receptor. “[T]he consequence of that is there must be a correlation between structure and function.” (*Id.* at 912:8-22) On cross-examination, Dr. Rees agreed that the amino acid sequences defined the antibody and the detailed interactions of the amino acids lead to the folded structure. (*Id.* at 986:9-24)

As to the well characterized antigen test, Dr. Petsko testified that he used the term antigen to describe the binding region (part of PCSK9) and that the binding region could be considered a “newly characterized antibody.” Dr. Petsko explained how to design more antibodies from the disclosures in the patent – by using 21B12 as a reference, performing binning experiments, testing to see whether the antibodies block the binding to the LDL receptor, and then using developed techniques to screen the antibodies. (*Id.* at 834:17-836:4, 871:10-20; *see also* 915:13-922:24, 937:11-16)

As to enablement, Dr. Rees testified that the state of antibody and engineering sciences is “mature and well established,” with well-known methods for creating antibodies, such as those described in the specification. In his opinion, the scope of the claims “is pretty narrow,” as they describe “antibodies that bind to a rather small region on the surface of PCSK9.” He opined that the specification is a “comprehensive roadmap to how to make . . . [the] antibodies.” (*Id.* at 940-41; *see also* D.I. 342 at 401:23-402:7, 417:10-21) He explained that a researcher does not use the binding region to make the antibodies, but the specification teaches “how to analyze for antibodies that bind to” it. (D.I. 344 at 942) Dr. Rees explained that other types of antibodies are well known, including mouse monoclonal antibodies, rat antibodies, and camel antibodies. Moreover, those types of antibodies, as well as fragments, may be

made using the information in the specification and routine methods known in the art. (*Id.* at 942-43) On cross-examination, Dr. Rees agreed that the examples of the specification did not describe mouse or camel antibodies. (*Id.* at 981:21-982:12) As to the degree of blocking, Dr. Petsko opined that if an antibody bound to one of the residues, it would be likely that “the big molecule” (with a “pretty big footprint”) would cause some blocking. Moreover, the patent disclosed certain “low blocking” antibodies. (*Id.* at 840:5-25) Dr. Petsko agreed that a small amount of blocking would suffice to meet the requirements of certain of the asserted claims. (*Id.* at 870:11-24)

#### **D. Analysis**

The jury was asked to consider whether defendants presented clear and convincing evidence that the asserted claims of the patents-in-suit lacked written description and enablement. The court instructed the jury that the specification could disclose either “a representative number [of] species falling within the scope of the claimed invention,” or “structural features common to the members of the genus, so that a person of ordinary skill in the art can ‘visualize or recognize’ the members of the claimed invention.” The jury was also instructed that “[i]n the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if” the creation of such “antibodies against such an antigen was conventional or routine.” (D.I. 299 at 24-25)

The parties and their experts largely agreed on what the specification discloses – a screening process used to select 384 antibodies, which blocked PCSK9 “well” for further testing; a certain subset of antibodies that blocked PCSK9 at over 90%; two

antibodies (21B12 and 31H4), which underwent X-ray crystallography analysis; a binding region on PCSK9 of fifteen residues that is the target of such antibodies. The parties' experts also agreed that the art discloses the research techniques necessary to perform antibody development and screening.

The parties' experts analyzed the specification's disclosures and formulated conclusions. Defendants' experts focused on the "middle" portion of the binding region and concluded that insufficient data and examples were disclosed in the specification. Plaintiffs' experts argued the opposite, that is, the examples and disclosures in the patent sufficiently described two antibodies which bind to a large portion of the binding region. An antibody that would bind to the part of the binding region that is not specifically bound by 21B12 and 31H4 is logically within reach using the disclosures of the specification (including the blocking and binning data).

The jury is the finder of fact and is tasked with weighing the evidence and credibility of the witnesses. The parties' experts provided the jury with competing testimony on the interpretation of the data available in the specification. The jury concluded that the asserted claims were not invalid for lack of written description or enablement. Defendants' post-trial arguments essentially ask the court to reevaluate the experts' testimony and reach the opposite conclusion. For example, defendants argue that the two antibodies (21B12 and 31H4) are "plainly insufficient" to represent the genus, and the twenty-two other antibodies that "bin" with 21B12 and 31H4 are not value added as "binning does not allow a person of ordinary skill in the art to determine with any certainty what amino acid an antibody binds to." According to defendants, their experts testified that "nothing disclosed in the [specification] allowed one to visualize or

recognize the structures of the claimed antibodies and to distinguish the claimed antibodies from others.” According to defendants, plaintiffs’ experts “gave purely conclusory testimony” that the specifications did allow such visualization or recognition. (D.I. 367 at 7, 15)

On the record at bar, plaintiffs’ experts provided more than conclusory testimony in order to explain their respective conclusions to the jury. The jury credited such testimony over that of defendants’ experts. The court declines to re-weigh the evidence or the credibility of the experts. Viewing the record in the light most favorable to plaintiffs, substantial evidence supports the jury’s verdict.<sup>9, 10</sup> For these reasons, defendants’ renewed motion for JMOL is denied.

In the alternative, defendants requested a new trial should the court deny the renewed motion for JMOL on written description and enablement. Defendants’ request is premised on the same arguments as its renewed motion for JMOL. Defendants again ask the court to “substitute its own judgment of the facts and the credibility of the witnesses,” and reach the opposite conclusion as the jury. For the reasons discussed

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<sup>9</sup> Defendants argue that *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), requires a finding that the disclosure is insufficient to meet the representative species test. However, the procedural posture of that case, as well as the facts, are different. Reviewing the district court’s findings following a bench trial, the Federal Circuit held that the written description requirement was not met. It reasoned in part that the specification disclosed “only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin.” *Id.* at 1567.

<sup>10</sup> The jury’s verdict is supported by the evidence on the “representative number of species” or “common structural features” tests, therefore, whether the jury credited the evidence on the “well-characterized antigen” test is not dispositive.

above, the jury's verdict is not against the clear weight of the evidence, therefore, the court denies defendants' request for a new trial.

## V. RECONSIDERATION

In their motion for a new trial, defendants argue that the erroneous exclusion of post-January 2008 evidence substantially prejudiced their defenses of lack of written description and enablement; the jury was erroneously instructed on the test for written description (with respect to the court's "well-characterized antigen" instruction); and the court's grant of JMOL as to obviousness was based on an erroneous interpretation and misapplication of *Dynamic Drinkware v. National Graphics*, 800 F.3d 1375 (Fed. Cir. 2015). While filed as part of a motion for a new trial, defendants essentially request reconsideration of each of the above issues.

A motion for reconsideration is the "functional equivalent" of a motion to alter or amend judgment under Federal Rule of Civil Procedure 59(e). See *Jones v. Pittsburgh Nat'l Corp.*, 899 F.2d 1350, 1352 (3d Cir. 1990) (citing *Fed. Kemper Ins. Co. v. Rauscher*, 807 F.2d 345, 348 (3d Cir. 1986)). The standard for obtaining relief under Rule 59(e) is difficult to meet. The purpose of a motion for reconsideration is to "correct manifest errors of law or fact or to present newly discovered evidence." *Max's Seafood Cafe ex rel. Lou-Ann, Inc. v. Quinteros*, 176 F.3d 669, 677 (3d Cir. 1999). A court should exercise its discretion to alter or amend its judgment only if the movant demonstrates one of the following: (1) a change in the controlling law; (2) a need to correct a clear error of law or fact or to prevent manifest injustice; or (3) availability of new evidence not available when the judgment was granted. See *id.* A motion for reconsideration is not properly grounded on a request that a court rethink a decision

already made and may not be used “as a means to argue new facts or issues that inexcusably were not presented to the court in the matter previously decided.”

*Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239, 1240 (D. Del. 1990); see also *Glendon Energy Co. v. Borough of Glendon*, 836 F. Supp. 1109, 1122 (E.D. Pa. 1993). It goes without saying, therefore, that a motion under Rule 59(e) that advances the same arguments already thought through and rejected by the court - rightly or wrongly - should be denied. See, e.g., *Lazaridis v. Wehmer*, 591 F.3d 666, 669 (3d Cir. 2010); *Savage v. Bonavitacola*, 2005 WL 730679 (E.D. Pa. Mar. 29, 2005), at \*1 (citing *Glendon Energy Co. v. Borough of Glendon*, 836 F. Supp. 1109, 1122 (E.D. Pa. 1993)); *Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239, 1240 (D. Del. 1990).

As to the exclusion of post-January 2008 evidence, the complexity of the matter mandated that the court draw lines and stick to them. (D.I. 345 at 1076:6-1077:25) The court entertained both argument and briefing on this dispute, and issued written orders in support of its decision. (D.I. 226, 249) As to the inclusion of the “well-characterized antigen” jury instruction (D.I. 299 at 25), again the parties were provided opportunity to present argument and briefing, which the court considered. (D.I. 291; D.I. 344 at 1063:5-1065:21) As to the courts’ grant of JMOL on obviousness, the court fully considered defendants’ arguments as to the applicability of the *Drinkware* case, both before and during trial. (D.I. 250, 282; D.I. 345 at 1076:21-1077:6, 1089:14-17) While defendants disagree with the court’s decisions and request that it rethink them, the court declines to do so. The court did not arrive at any of these decisions lightly; indeed, it considered fulsome arguments and briefing. Defendants’ request for reconsideration of these issues is denied, as is the motion for a new trial.

For the foregoing reasons, the court denies defendants' motions for a new trial and judgment as a matter of law on written description and enablement (D.I. 331, 332); and denies as moot plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338). An appropriate order shall issue.

# **EXHIBIT E**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, )  
LIMITED; AND AMGEN USA, INC )

Plaintiffs, )

v. )

Civ. No. 14-1317-SLR  
(Consolidated)

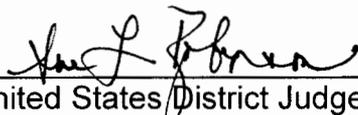
SANOFI; SANOFI-AVENTIS U.S. LLC; )  
AVENTISUB LLC f/d/b/a AVENTIS )  
PHARMACEUTICALS INC.; and )  
REGENERON PHARMACEUTICALS, )  
INC., )

Defendants. )

**FINAL JUDGMENT FOLLOWING POST TRIAL MOTION PRACTICE  
PURSUANT TO FED. R. CIV. P. 54(b)**

For reasons stated in the court's memorandum opinion and order of January 3 ,  
2017;

IT IS ORDERED AND ADJUDGED that judgment be and is hereby entered in  
favor of plaintiffs Amgen, Inc., Amgen Manufacturing, Limited and Amgen USA Inc. and  
against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron  
Pharmaceuticals, Inc.

  
United States District Judge

Dated: 1/3/2017

  
(By) Deputy Clerk

# **EXHIBIT F**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	Civ. No. 14-1317-SLR
	)	(Consolidated)
SANOFI, et al.,	)	
	)	
Defendants.	)	

**MEMORANDUM ORDER**

At Wilmington this 18<sup>th</sup> day of February, 2016, having reviewed the various papers submitted by the parties in connection with their pretrial evidentiary issues;

IT IS ORDERED that:

1. **The UTSW PCSK9 handout** is excluded as being disclosed untimely. In this regard, it would take further discovery to flesh out whether it is prior art, as the facial indicia of such is not sufficient to pass muster. If not prior art, the handout is cumulative and likely to lead to mischief if admitted to demonstrate the state of the art.

2. **Daubert motions: standard of review.** A qualified expert may testify in the form of an opinion if (1) the testimony is based on sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.<sup>1</sup> Fed. R. Evid. 702. As summarized by the Third Circuit in *Elcock v. Kmart Corp.*, 233 F.3d 734 (3d Cir.

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<sup>1</sup>Of course, an expert must be qualified as well, an issue not in dispute presently.

2000), “Rule 702 embodies three distinct substantive restrictions on the admission of expert testimony: qualifications, reliability, and fit.” *Id.* at 741. The burden of persuading the judge to allow the expert to testify is on the party tendering the expert, and is by a preponderance of the evidence. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 743-45 (3d Cir. 1994). As noted by the Supreme Court, “the trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable.” *Kumbo Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999).

3. **Cross *Daubert* motions regarding post-priority date evidence.** Both parties have filed *Daubert* motions to exclude post-priority date evidence. Plaintiffs’ motion seeks to exclude expert testimony regarding the structure of post-priority date antibodies that were not disclosed in the selected patents. (D.I.191) Defendants’ motion seeks to exclude expert testimony that relies on later-developed evidence to demonstrate the structure of the disclosed antibodies. (D.I.185) Although characterized differently, both motions relate to defendants’ written description defense.

4. In this case, the patent claims<sup>2</sup> asserted against defendants are directed to genres of antibodies. Claim 1 of the ‘165 patent, for example, recites:

1. An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S81 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

Defendants argue that such claims as that recited above are invalid for lack of written

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<sup>2</sup>Selected claims of U.S. Patent Nos. 8,829,165 (“the ‘165 patent”), 8,859,741 (“the ‘741 patent”), and 8,871,914 (“the ‘914 patent”).

description pursuant to 35 U.S.C. §112, ¶ 1 because: (1) the claimed antibodies are defined by their function, not by their structure; (2) although the patents identify representative examples of the antibodies encompassed by the asserted claims, the examples are identified only by their amino acid sequences, not by their structure; (3) information about their structure is necessary to determine where these antibodies bind to PCSK9; (4) the only structural information provided by plaintiffs is comprised of post-priority date x-ray crystallography analysis. Plaintiffs respond in kind as follows: (1) the claims “clearly recite several structural features;” (2) the structure of the selected antibodies is an “inherent property” of where they bind to PCSK9; (3) “inherently disclosed properties” are deemed present in the specification. (D.I. 202 at 1, 3)

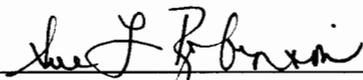
4. To satisfy the written description requirement, “the applicant must ‘convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,’ and demonstrate that by disclosure in the specification of the patent.” *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (citation omitted); *see also Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011). “[T]he hallmark of written description is disclosure,” and “the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). A written description of an invention involving a chemical genus “requires a precise definition, such as by structure, formula, [or] chemical name” of the claimed subject matter sufficient to distinguish it

from other materials. *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Support for a genus claim requires either a “representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350; *Regents*, 119 F.3d at 1568. “[A]n applicant can claim an antibody to novel protein X without describing the antibody when (1) the applicant fully discloses the novel protein and (2) generating the claimed antibody is so routine that possessing the protein places the applicant in possession of an antibody.” *Centocor*, 636 F.3d at 1351-52. Because “each patented advance has a novel relationship with the state of the art from which it emerges,” the written description inquiry “is a question of fact” with the law being “applied to each invention at the time it enters the patent process.” *Ariad*, 598 F.3d at 1351. As explained by the Federal Circuit in *Ariad*, “requiring a written description of the invention limits patent protection to those who actually perform the difficult work of ‘invention’ - that is, conceive of the complete and final invention with all its claimed limitations - and disclose the fruits of that effort to the public.” *Id.* at 1353.

5. The case law cited above gives broad leeway to the court in terms of admitting evidence that illuminates the state of the art **at the time of filing** in order to determine whether there is sufficient disclosure of the claimed invention, in this case, a genus. Given the complexity of the technology at issue and the “considerable leeway” I have as a judge to determine whether an expert’s knowledge will help the jury understand the evidence and determine issues of fact, I conclude that the clearest,

most consistent result is to grant both motions and preclude the use of any such evidence in connection with the issue of written description.

6. **Daubert motions relating to damages.** As per the normal course of events, both plaintiffs and defendants accuse the opposing experts of basing their economic analyses on inappropriate data. Both experts agree that there are no comparable bare license agreements. In order to base their respective opinions on some modicum of real-world data, plaintiffs' expert resorted to using distributor fees as relevant comparables and defendants' expert resorted to using collaboration agreements and cross-license agreements as relevant comparables. With the exception of the Dezima acquisition agreement and the Genentech/Regenron settlement agreement,<sup>3</sup> I am satisfied that the experts have adequately explained in their reports the relevance of their respective data vis a vis the various *Georgia-Pacific* factors.<sup>4</sup> Therefore, defendants' motion as to the reasonable royalty opinions of Dr. Meyer (D.I. 185) is denied, and plaintiffs' motion to exclude the expert testimony of Dr. Stevens (D.I. 187) is granted in part and denied in part.

  
United States District Judge

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<sup>3</sup>Identified by Dr. Stevens. I will preclude these business arrangements as being too far afield from a bare patent license to be relevant comparables.

<sup>4</sup>Including those factors relating to the parties' licensing practices and the fact that plaintiff "does not out-license its patent rights to a competitor where the technology covered by the patent rights is technology that Amgen itself intends to commercialize in the same geographic area and for the same therapeutic use." (D.I. 188, ex. 4, ¶ 146)

# **EXHIBIT G**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN	)	
MANUFACTURING, LIMITED, and	)	
AMGEN USA, INC.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	Civ. No. 14-1317-SLR
	)	(Consolidated)
SANOFI, SANOFI-AVENTIS U.S., LLC,	)	
AVENTISUB LLC, and REGENERON	)	
PHARMACEUTICALS, INC.,	)	
	)	
Defendants.	)	

**MEMORANDUM ORDER**

At Wilmington this 2nd day of March, 2016, having heard argument on the motion for reargument filed by defendants, and having reviewed the papers filed in connection therewith;

IT IS ORDERED that said motion (D.I. 231) is granted to the extent I have entertained further argument on the issues presented, but denied as to its substantive request, for the reasons that follow:

1. I issued a memorandum order on February 18, 2016 that addressed various pretrial evidentiary issues in the above captioned litigation, including whether evidence regarding the structure of antibodies that did not exist at the time of filing (and, therefore, were not disclosed in the patents-in-suit) should be excluded for purposes of defendants' written description defense. I concluded that, because the written

description requirement is tested as of the filing date, such evidence should be excluded. Defendants contend that my decision is contrary to the law, particularly, the Federal Circuit's reasoning in *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc. and Centocor Biologics, LLC*, 759 F.3d 1285 (Fed. Cir. 2014). The Court in *AbbVie* upheld a jury's finding of invalidity of genus claims that were functionally defined based on lack of written description. The Court reasoned that

[w]hen a patent claims a genus using functional language to define a desired result, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented a species sufficient to support a claim to the functionally defined genus." . . . We have held that "a sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."

*Id.* at 1299 (citations omitted). The question presented was whether the patents at issue described representative species to support the entire genus. Without apparent objection, defendant "presented expert testimony that the antibodies described in the patents were structurally similar, but that they differed from [the accused antibody] in many respects." *Id.* at 1293. According to the Federal Circuit,

the jury heard ample evidence that AbbVie's patents only describe one type of structurally similar antibodies and that those antibodies are not representative of the full variety or scope of the genus . . . . [More specifically, the accused antibody] differs considerably from the Joe-9 antibodies described in AbbVie's patents. . . . Centocor's expert testified that antibodies with 80% sequence similarity to J695 could bind to completely different antigens, . . . thus illustrating the significant structural differences between [the accused antibody] and the Joe-9 antibodies and the unpredictability of the field of invention. Centocor also presented evidence of other differences between [the accused antibody] and the Joe-9 antibodies, such as CDR length and epitope binding site.

*Id.* at 1300. The Court concluded that there was “no evidence to show any described antibody to be structurally similar to, and thus representative of [the accused antibody]. There is also no evidence to show whether one of skill in the art could make predictable changes to the described antibodies to arrive at other types of antibodies such as [the accused antibody].” *Id.* at 1301.

2. By giving its imprimatur to the jury's verdict, the Federal Circuit arguably departed from its own precedent, established in *In re Hogan*, 559 F.2d 595 (C.C.P.A. 1977), that later-developed or later-discovered products should not be used to test compliance with 35 U.S.C. § 112.<sup>1</sup> In this regard, the Court in *Hogan* reasoned that,

to now say that appellants should have disclosed in 1953 the amorphous form which on this record did not exist until 1962, would be to impose an impossible burden on inventors and thus on the patent system. . . .

The business of the PTO is patentability, not infringement. . . . The courts have consistently considered subsequently existing states of the art as raising question of infringement, **but never of validity.**

*Id.* at 607 (emphasis added). See also *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247 (Fed. Cir. 1989); *Schering Corp. v. Amgen, Inc.*, 222 F.3d 1347 (Fed. Cir. 2000); *Amgen, Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313 (Fed. Cir. 2003); *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed.

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<sup>1</sup>It is important to keep in mind that the district judge in the *AbbVie* case had consolidated an infringement action filed by AbbVie with an appeal by Centocor from an interference proceeding in which AbbVie's [6,914,128] patent was awarded priority over Centocor's patent application covering the accused antibody. In other words, it may not be surprising that the *AbbVie* record does not contain the kind of evidentiary issues that have arisen instantly, and that the Federal Circuit simply decided the issues presented - on the record presented - without attending to the more significant question of whether it is ever or always appropriate to use post-priority evidence of an embodiment that was not known or even in existence at the time of filing to invalidate a patent based on lack of written description support.

Cir. 1991); *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004); *Biogen Idec, Inc. & Genentech, Inc. v. Glaxo Smith Kline LLC*, 713 F.3d 1090 (Fed. Cir. 2013). See also Goldstein, Jorge, “*AbbVie Deutschland* and Unknown Embodiments: Has the Written Description Requirement for Antibodies Gone Too Far?,” 9 LSLR 399 (Bloomberg BNA, Apr. 3, 2015). This leaves me between a rock - the written description requirement has always been anchored in the state of the art at the time of filing - and a hard place - *AbbVie* arguably has imposed the “impossible burden”<sup>2</sup> on inventors to “at least describe some species representative of antibodies that are structurally similar to” unknown future embodiments. *AbbVie*, 759 F.3d at 1301.

3. Without a specific recognition by the Court in *AbbVie* that it was so dramatically changing the law on written description, I choose to interpret it narrowly and limit it to its unusual facts and procedural posture. Therefore, while I appreciate the arguments made by defendants, I decline to change my ruling precluding the admission of any post-priority date evidence on written description.<sup>3</sup>

  
United States District Judge

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<sup>2</sup>*Hogan*, 559 F.2d at 606.

<sup>3</sup>I note in closing that this significant issue was not addressed during claim construction or in the context of infringement which, absent the dramatic change in perspective arguably foretold by the *AbbVie* decision, would be the most sensible way of addressing broad genus claims and future embodiments not foretold and described in the specification.

# **EXHIBIT H**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN )  
MANUFACTURING, LIMITED, and )  
AMGEN USA INC., )  
 )  
Plaintiffs, )

v. )

Civ. No. 14-1317-SLR  
(Consolidated)

SANOFI; SANOFI-AVENTIS U.S. LLC; )  
AVENTISUB LLC f/d/b/a AVENTIS )  
PHARMACEUTICALS INC.; and )  
REGENERON PHARMACEUTICALS, )  
INC., )  
 )  
Defendants. )

**FINAL JURY INSTRUCTIONS**

Dated: March 14, 2016

## **GENERAL INSTRUCTIONS**

### **INTRODUCTION**

Members of the jury, now it is time for me to instruct you about the law that you must follow in deciding this case. I will start by explaining your duties and the general rules that apply in every civil case. I will explain some rules that you must use in evaluating particular testimony and evidence. I will explain the positions of the parties and the law you will apply in this case. Last, I will explain the rules that you must follow during your deliberations in the jury room. Please listen very carefully to everything I say.

You will have a written copy of these instructions with you in the jury room for your reference during your deliberations. You will also have a verdict form, which will list the interrogatories, or questions, that you must answer to decide this case.

## **JURORS' DUTIES**

You have two main duties as jurors. The first one is to decide what the facts are from the evidence that you saw and heard here in court. Deciding what the facts are is your job, not mine, and nothing that I have said or done during this trial was meant to influence your decision about the facts in any way.

Your second duty is to take the law that I give you, apply it to the facts, and decide which party should prevail on the issues presented. I will instruct you about the burden of proof shortly. It is my job to instruct you about the law, and you are bound by the oath that you took at the beginning of the trial to follow the instructions that I give you, even if you personally disagree with them. This includes the instructions that I gave you before and during the trial, and these instructions. All the instructions are important, and you should consider them together as a whole.

Perform these duties fairly. Do not let any bias, sympathy or prejudice that you may feel toward one side or the other influence your decision in any way.

## **EVIDENCE DEFINED**

You must make your decision based only on the evidence that you saw and heard here in the courtroom. Do not let rumors, suspicions, or anything else that you may have seen or heard outside of court influence your decision in any way. The evidence in this case includes only what the witnesses said while they were testifying under oath (including deposition testimony that has been played or read to you), the exhibits that I allowed into evidence, and any facts that the parties agreed to by stipulation.

Nothing else is evidence. The lawyers' statements and arguments are not evidence. Their questions and objections are not evidence. My legal rulings are not evidence. None of my comments or questions are evidence. The notes taken by any juror are not evidence.

Certain charts and graphics have been used to illustrate testimony from witnesses. Unless I have specifically admitted them into evidence, these charts and graphics are not themselves evidence even if they refer to, identify, or summarize evidence.

During the trial I may not have let you hear the answers to some of the questions that the lawyers asked. I also may have ruled that you could not see some of the exhibits that the lawyers wanted you to see. And sometimes I may have ordered you to disregard things that you saw or heard. You must completely ignore all of these things. Do not speculate about what a witness might have said or what an exhibit might have shown. These things are not evidence, and you are bound by your oath not to let them influence your decision in any way.

Make your decision based only on the evidence, as I have defined it here, and nothing else.

## **DIRECT AND CIRCUMSTANTIAL EVIDENCE**

Some of you may have heard the terms “direct evidence” and “circumstantial evidence.”

Direct evidence is simply evidence like the testimony of any eyewitness which, if you believe it, directly proves a fact. If a witness testified that he saw it raining outside, and you believed him, that would be direct evidence that it was raining.

Circumstantial evidence is simply a chain of circumstances that indirectly proves a fact. If someone walked into the courtroom wearing a raincoat covered with drops of water and carrying a wet umbrella, that would be circumstantial evidence from which you could conclude that it was raining.

It is your job to decide how much weight to give the direct and circumstantial evidence. The law makes no distinction between the weights that you should give to either one, nor does it say that one is any better evidence than the other. You should consider all the evidence, both direct and circumstantial, and give it whatever weight you believe it deserves.

## **CONSIDERATION OF EVIDENCE**

You should use your common sense in weighing the evidence. Consider it in light of your everyday experience with people and events, and give it whatever weight you believe it deserves. If your experience tells you that certain evidence reasonably leads to a conclusion, you are free to reach that conclusion.

## **USE OF NOTES**

You may use notes taken during the trial to assist your memory. Remember that your notes are for your personal use. They may not be given or read to anyone else. Do not use your notes, or any other juror's notes, as authority to persuade fellow jurors. Your notes are not evidence, and they are by no means a complete outline of the proceedings or a list of the highlights of the trial. Some testimony that is considered unimportant at the time presented and, thus, not written down, may take on greater importance later on in the trial in light of all the evidence presented. Your notes are valuable only as a way to refresh your memory. Your memory is what you should be relying on when it comes time to deliberate and render your verdict in this case.

## **CREDIBILITY OF WITNESSES**

You, the jurors, are the sole judges of the credibility, or the believability, of the witnesses you have seen during the trial and the weight their testimony deserves.

You should carefully scrutinize all the testimony each witness has given and every matter of evidence that tends to show whether he or she is worthy of belief. Consider each witness's intelligence, motive, and state of mind, as well as his or her demeanor while on the stand. Consider the witness's ability to observe the matters as to which he or she has testified and whether he or she impresses you as having an accurate recollection of these matters. Consider also any relation each witness may bear to each side of the case, the manner in which each witness might be affected by the verdict, the interest any witness may have in the verdict, and the extent to which, if at all, each witness is either supported or contradicted by other evidence in the case.

Discrepancies in the testimony of different witnesses may, or may not, cause you to discredit such testimony. Two or more persons witnessing an incident or transaction may see or hear it differently. Likewise, in determining the weight to give to the testimony of a witness, you should ask yourself whether there was evidence tending to prove that the witness testified falsely about some important fact, or whether there was evidence that at some other time the witness said or did something, or failed to say or do something, that was different, or inconsistent, from the testimony that he or she gave during the trial. It is the province of the jury to determine whether a false statement or a prior inconsistent statement discredits the witness's testimony.

You should remember that a simple mistake by a witness does not mean that the witness was not telling the truth. People may tend to forget some things or remember

other things inaccurately. If a witness has made a misstatement, you must consider whether it was simply an innocent lapse of memory or an intentional falsehood, and that may depend upon whether it concerns an important fact or an unimportant detail.

### **NUMBER OF WITNESSES**

One more point about the witnesses. Sometimes jurors wonder if the number of witnesses who testified makes any difference. Do not make any decisions based only on the number of witnesses who testified. What is more important is how believable the witnesses were, and how much weight you think their testimony deserves. Concentrate on that, not the numbers.

## **EXPERT WITNESSES**

When knowledge of technical subject matter might be helpful to the jury, a person who has special training or experience in that technical field – he or she is called an expert witness – is permitted to state his or her opinion on those technical matters. However, you are not required to accept that opinion. As with any other witness, it is up to you to judge the credentials and credibility of the expert witness and decide whether to rely upon his or her testimony.

You should consider each expert opinion received in evidence in this case, and give it such weight as you think it deserves. If you decide that the opinion of an expert witness is not based upon sufficient education and experience, or if you conclude that the reasons given in support of the opinion are not sound, or if you feel that the opinion is outweighed by other evidence, you may disregard the opinion in whole or in part.

## **DEPOSITION TESTIMONY**

During the trial, certain testimony was presented to you through depositions that were read into evidence or electronically played. This testimony must be given the same consideration you would give it had the witness personally appeared in court. Like the testimony of a live witness, the statements made in a deposition are made under oath and are considered evidence that may be used to prove particular facts.

## THE PARTIES AND THEIR CONTENTIONS

I will now review for you the parties in this action and the positions of the parties that you will have to consider in reaching your verdict.

Plaintiffs are Amgen Inc., Amgen Manufacturing, Limited and Amgen USA Inc. I will refer to plaintiffs collectively as “plaintiff.”

Defendants are Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, f/d/b/a Aventis Pharmaceuticals Inc., and Regeneron Pharmaceuticals, Inc. I will refer to these parties collectively as “defendants.”

Plaintiff Amgen Inc. is the owner, and plaintiffs Amgen Manufacturing, Limited and Amgen USA Inc. are exclusive licensees, of U.S. Patent No. 8,829,165, which I will refer to as “the ‘165 patent” and U.S. Patent No. 8,859,741, which I will refer to as “the ‘741 patent.”

Defendants have made, marketed, used and/or sold alirocumab, an antibody that is used in a product called Praluent®.

The parties agree that alirocumab and Praluent® infringe claims 2, 7, 9, 15, 19 and 29 of the ‘165 patent and claim 7 of the ‘741 patent. These claims may be referred to as the “asserted claims” of the patents. I will explain in more detail what patent claims are in a moment.

Defendants contend that the asserted claims are invalid due to lack of sufficient written description and lack of enablement. I will explain what written description and enablement mean a little later. You will be asked to determine the issues of validity according to instructions I will give you in a moment.

## **BURDENS OF PROOF**

In any legal action, facts must be proven by a required standard of evidence, known as the “burden of proof.” In this patent case, the burden of proof is called “clear and convincing” evidence. Clear and convincing evidence is evidence that produces an abiding conviction that the truth of a fact is highly probable. You must decide, as to each of the asserted claims, whether defendants have proven that the asserted claims are invalid for lack of written description or lack of enablement. I will explain these concepts to you further in a moment. For each of these two defenses, defendants must prove them by clear and convincing evidence.

## **THE PATENT CLAIMS**

### **PATENT CLAIMS GENERALLY**

Before you can decide whether or not any of the asserted claims are invalid, you will have to understand what patent “claims” are. Patent claims are the numbered paragraphs at the end of a patent.

The purpose of the claims is to provide notice to the public of what a patent covers and does not cover. The claims are “word pictures” intended to define, in words, the boundaries of the invention described and illustrated in the patent.

Claims are usually divided into parts, called “limitations.” For example, a claim that covers the invention of a table may recite the tabletop, four legs, and the glue that secures the legs to the tabletop. The tabletop, legs and glue are each a separate limitation of the claim. A claim covering the invention of a table is called an apparatus claim.

## **DEPENDENT AND INDEPENDENT CLAIMS**

There are two different types of claims in a patent. The first type is called an “independent” claim. An independent claim does not refer to any other claim of the patent. An independent claim is read alone to determine its scope.

For example, claim 1 of the ‘165 patent is an independent claim. You know this because claim 1 does not refer to any other claims. Accordingly, the words of this claim are read by themselves in order to determine what the claim covers.

The second type, a “dependent” claim, refers to at least one other claim in the patent and, thus, incorporates whatever that other claim says. Accordingly, to determine what a dependent claim covers, you must read both the dependent claim and the claim or claims to which it refers.

For example, claim 2 of the ‘165 patent is a dependent claim. If you look at claim 2, it refers to claim 1. Therefore, to determine what claim 2 of the ‘165 patent covers, you must consider both the words of claims 1 and 2 together. Likewise, claim 7 of the ‘741 patent refers to claim 2, and claim 2 refers to claim 1. Therefore, to determine what claim 7 of the ‘741 patent covers, you must consider the words of claims 1, 2 and 7 of the ‘714 patent together.

## CLAIM CONSTRUCTION

It is my duty under the law to define what the patent claims mean and to instruct you about that meaning. You must accept the meanings I give you and use the meaning of each claim for your decision on validity. You must ignore any different interpretation given to these terms by the witnesses or by attorneys. I instruct you that the following claim terms have the following definitions.

### **With respect to the asserted claims of the '741 and '165 patents:**

**“An isolated monoclonal antibody”** means: “Composition of intact immunoglobulins of any isotype (or fragments thereof that can compete with the intact immunoglobulin for specific binding to the target antigen) having identical amino acid sequences, i.e., essentially free of nonidentical amino acid sequences.”

**“Binds [to]” residues** means: “Interacts with [residues] and contributes to the affinity of the PCSK9-antibody interaction.”

**“PCSK9”** means: “Polypeptide as set forth in SEQ ID NO: 1 and/or 3 or fragments thereof.”

**“Wherein the monoclonal antibody blocks binding of PCSK9 to LDLR”**  
means: “Wherein the claimed antibody prevents binding of PCSK9 to LDLR.”

### **With respect only to the '741 patent:**

**“An epitope on PCSK9 comprising at least one of residues 237 or 238”**  
means: “A region on PCSK9 that is recognized by an antibody, wherein the region includes at least one of residues 237 or 238.”

**“Wherein the epitope is a functional epitope”** means: “Wherein the epitope has those residues that directly contribute to the affinity of the interaction (e.g., hydrogen bonds, ionic interactions).”

**“Wherein the isolated monoclonal antibody is a neutralizing antibody”** means: “Wherein the claimed antibody reduces a biological effect of PCSK9.”

**With respect only to the ‘165 patent:**

**“Wherein the monoclonal antibody blocks binding of PCSK9 to LDLR by at least 80%”** means: “Wherein the claimed antibody prevents binding of PCSK9 to LDLR by at least 80%.”

If I have not provided a specific definition for a given term, you are to use the ordinary meaning of that term.

## **VALIDITY**

### **INTRODUCTION**

As I stated previously, defendants contend that the asserted claims are invalid. I will now explain to you each of the grounds for invalidity that were presented by defendants at trial. A party must meet its burden of proof on only one ground in order to invalidate a claim. In making your determination as to invalidity, you should consider each claim separately.

## **AFFIRMATIVE DEFENSE OF INVALIDITY GENERALLY**

For a patent to be valid, the invention claimed in the patent must be adequately enabled, and must have a sufficient written description. The terms “enablement” and “written description” have special meanings under the patent laws. I will explain these terms to you as we discuss defendants’ grounds for asserting invalidity.

Defendants have challenged the validity of the asserted claims on a number of grounds. Although the patent was granted by the Patent and Trademark Office, it is your job to determine whether defendants have proven, by clear and convincing evidence, that the legal requirements for patentability were not met.

I will now explain to you defendants’ grounds for invalidity in detail. In making your determination as to invalidity, you should consider each claim separately.

## ENABLEMENT

The patent law contains certain requirements for the part of the patent called the specification, which is the entirety of the patent before its claims. Defendants contend that the asserted patent claims are invalid because the specification does not contain a sufficiently full and clear description of how to make and use the full scope of the claimed invention and that, therefore, the asserted claims are invalid. To be sufficiently full and clear, the description must contain enough information to have allowed a person having ordinary skill in the field of the technology of the patent to make and use the full scope of the claimed invention at the time of the priority date of the patent claim, which in this case is January 9, 2008. This is known as the “enablement” requirement. If a patent claim is not enabled, it is invalid.

In order to be enabling, the patent must permit persons having ordinary skill in the field of technology of the patent to make and use the full scope of the claimed invention without having to conduct undue experimentation. However, some amount of experimentation to make and use the invention is allowable. A patent specification need not include the information already known to and available to one of ordinary skill in the art.

In deciding whether a person having ordinary skill would have to experiment unduly in order to make and use the invention, you may consider several factors:

- (1) The time and cost of any necessary experimentation;
- (2) How routine any necessary experimentation is in the field of antibody technology;

(3) Whether the patent discloses specific working examples of the claimed invention;

(4) The amount of guidance presented in the patent;

(5) The nature and predictability of the field of antibody technology;

(6) The level of ordinary skill in the field of antibody technology;

(7) The scope of the claimed invention; and

(8) The state of the prior art.

No one or more of these factors is alone dispositive. Rather, you must make your decision whether or not the degree of experimentation required is undue based upon all of the evidence presented to you. You should weigh these factors and determine whether or not, in the context of this invention and the state of the art at the time of the priority date (January 9, 2008), a person having ordinary skill would need to experiment unduly to make and use the full scope of the claimed invention.

## WRITTEN DESCRIPTION

The patent law contains another requirement for the specification called the written description requirement. Defendants contend that the asserted claims of plaintiff's patents are invalid because the specifications of the patents do not contain an adequate written description of the claimed invention. To succeed in this defense, defendants must show by clear and convincing evidence that the specifications fail to meet the law's requirements for written description of the claimed invention.

In deciding whether the specifications satisfy the written description requirement, you must consider the description from the viewpoint of a person having ordinary skill in the field of technology of the patent when the application was filed. The written description requirement is satisfied if a person having ordinary skill in the art at the time of the priority date – here, January 9, 2008 – would have recognized that the specifications describe the full scope of the claimed invention as it is finally claimed in the issued patents and that the inventor actually possessed the full scope of the invention on or before the priority date.

The written description requirement may be satisfied by any combination of the words, structures, figures, diagrams, formulas, etc., contained in the patent specification. The specification is not required to expressly include what is well-known to a person of ordinary skill in the art at the priority date. The level of required disclosure depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and other considerations appropriate to the subject matter. The written

description requirement does not demand either examples or an actual reduction to practice.

In this case, the patent claims are directed to a specific class of antibodies, which can be referred to as a “genus.” One way to consider whether the combination of words, structures, figures, diagrams, formulas, etc., contained in the specifications at issue is sufficient for a genus is to assess whether the specifications include a representative number species falling within the scope of the claimed invention, or by structural features common to the members of the genus, so that a person of ordinary skill in the art can “visualize or recognize” the members of the claimed invention.

With respect to satisfying written description by the disclosure of a representative number of species, there are no hard and fast rules concerning the number of species that constitutes a “representative number.” The specifications need not describe every species in a genus in order to meet the written description requirement. Instead, the specifications need to show that the inventors have truly invented the genus, i.e., that one has conceived and described sufficient representative species encompassing the breadth of the genus. When there is a substantial variation within the claimed genus, the specifications must describe a sufficient variety of species to reflect the variation within the genus.

With respect to disclosing structural features common to the members of the genus, the written description requirement is met when there is an established correlation between structure and function. Functional claim language can meet the written description requirement when a reasonable structure-function correlation is

established by the inventor as described in the specifications or by what was known in the art at the time of the filing date.

In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine.

## **DELIBERATION AND VERDICT**

### **INTRODUCTION**

Let me finish up by explaining some things about your deliberations in the jury room, and your possible verdicts.

Once you start deliberating, do not talk to the jury officer, or to me, or to anyone else except each other about the case. If you have any questions or messages, you must write them down on a piece of paper, sign them, and then give them to the jury officer. The officer will give them to me, and I will respond as soon as I can. I will have to talk to the lawyers about what you have asked, so it may take me some time to get back to you. Any questions or messages normally should be sent to me through your foreperson, who by custom of this Court is the juror seated in the first seat, first row.

One more thing about messages. Do not ever write down or tell anyone how you stand on your votes. For example, do not write down or tell anyone that you are split 4-4, or 5-3, or whatever your vote happens to be. That should stay secret until you are finished.

## UNANIMOUS VERDICT

Your verdict must represent the considered judgment of each juror. In order for you as a jury to return a verdict, it is necessary that each juror agree to the verdict.

Your verdict must be unanimous.

It is your duty, as jurors, to consult with one another and to deliberate with a view towards reaching an agreement, if you can do so without violence to your individual judgment. Each of you must decide the case for yourself, but do so only after an impartial consideration of the evidence with your fellow jurors. In the course of your deliberations, do not hesitate to reexamine your own views and change your opinion, if convinced it is erroneous. But do not surrender your honest conviction as to the weight or effect of evidence solely because of the opinion of your fellow jurors, or for the purpose of returning a verdict. Remember at all times that you are judges – judges of the facts. Your sole interest is to seek the truth from the evidence in the case.

A form of verdict has been prepared for you. The verdict form asks you a series of questions about the parties' claims. Unless you are directed otherwise in the form of the verdict, you must answer all of the questions posed, and you all must agree on each answer. When you have reached a unanimous agreement as to your verdict, you will return your verdict to the courtroom deputy.

It is proper to add the caution that nothing said in these instructions and nothing in the form of verdict is meant to suggest or convey in any way or manner what verdict I think you should find. What the verdict shall be is the sole and exclusive duty and responsibility of the jury.

## **DUTY TO DELIBERATE**

Now that all the evidence is in and the arguments are completed, you are free to talk about the case in the jury room. In fact, it is your duty to talk with each other about the evidence and to make every reasonable effort you can to reach a unanimous agreement. Talk with each other, listen carefully and respectfully to each other's views and keep an open mind as you listen to what your fellow jurors have to say.

Try your best to work out your differences. Do not hesitate to change your mind if you are convinced that other jurors are right and your original position was wrong. But do not ever change your mind just because other jurors see things differently, or just to get the case over with. In the end, your vote must be exactly that – your own vote. It is important for you to reach unanimous agreement, but only if you can do so honestly and in good conscience.

If any member of the jury took notes, let me remind you that notes are not given any greater weight than the memory or impression of each juror as to what the testimony may have been. Whether you took notes or not, each of you must form and express your own opinion as to the facts of the case.

No one will be allowed to hear your discussions in the jury room, and no record will be made of what you say. So you should all feel free to speak your minds.

Listen carefully to what the other jurors have to say, and then decide for yourself.

We generally end our business day at 4:30 p.m. If we do not hear from you by 4:30, I will be sending you a note to see whether you are close enough to a verdict to want to deliberate after 4:30 or whether you are going to recess for the evening and

resume your deliberations on the next business day. You will need to respond in writing to that question.

I am going to remind you now, if you go home this evening and resume your deliberations on the next business day, you are not to talk about the case among yourselves or with anyone else during the evening recess. You may not read or listen to any news about the case in a newspaper, online or on television during the evening recess.

You may talk about the case only while you are in the jury room and everyone on the jury is present. Unless I hear from you that you have a different schedule in mind, I will expect you all to come back the next business day at 9:00. You are not to start deliberating until you are all present in the jury room and participating together.

Because the lawyers have to make themselves available to respond to questions or receive the verdict, I generally give them between 12:30 and 1:30 to step away from the phone. So whenever you are deliberating over the lunch hour, let me remind you, if you ask a question during this time, you probably will not get an answer right away because we are all going to be stepping away from our phones.

**COURT HAS NO OPINION**

Let me finish up by repeating something that I said to you earlier. Nothing that I have said or done during this trial was meant to influence your decision in any way. You must decide the case yourselves based on the evidence presented.

Finally, if I have read any of these instructions inconsistently with the written text, you are to rely on the written instructions in your deliberations.

# **EXHIBIT I**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC.; AMGEN MANUFACTURING, )  
LIMITED; and AMGEN USA INC. )

Plaintiffs, )

v. )

SANOFI; SANOFI-AVENTIS U.S. LLC; )  
AVENTISUB LLC, f/d/b/a AVENTIS )  
PHARMACEUTICALS INC., and REGENERON )  
PHARMACEUTICALS, INC., )

Defendants. )

C.A. No.: 14-1317-SLR  
(CONSOLIDATED)

**[PROPOSED] ORDER OF PERMANENT INJUNCTION**

WHEREAS, the Court entered a stipulated order (D.I. 235, 235a) on February 22, 2016 that the acts by Defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, f/d/b/a Aventis Pharmaceuticals Inc., and Regeneron Pharmaceuticals, Inc. (collectively “Defendants”) of making, using, offering for sale, selling and importing the antibody drug substance alirocumab and the drug product containing it, PRALUENT<sup>®</sup>, infringe claims 2, 7, 9, 15, 19, and 29 of U.S. Patent No. 8,829,165 B2 (the “’165 Patent”), and claim 7 of U.S. Patent No. 8,859,741 (the “’741 Patent”);

WHEREAS, as a result of the entry of the stipulated order (D.I. 235, 235a), the Court’s ruling on Amgen’s Rule 50(a) motion with respect to Defendants’ obviousness defense under 35 U.S.C. § 103 (D.I. 282, and March 14, 2016 Transcript at 1076:6-1077:12 (reflected in March 16, 2016 Oral Order entry on the docket)), and an agreement among the parties, the only issues tried to the jury were the validity of claims 2, 7, 9, 15, 19, and 29 of the ’165 Patent and claim 7 of the ’741 Patent under the enablement and written description requirements of 35 U.S.C. § 112;

WHEREAS, following the jury trial, the jury returned a verdict on March 16, 2016 (D.I. 304) finding that Defendants failed to prove that claims 2, 7, 9, 15, 19, or 29 of the '165 Patent or claim 7 of the '741 Patent are invalid under 35 U.S.C. § 112;

WHEREAS, the Court entered a Judgment Following a Jury Verdict Pursuant to Fed. R. Civ. P. 58(b) on March 18, 2016 (D.I. 308);

WHEREAS, on March 23 and 24, 2016, the Court held a permanent injunction hearing;

WHEREAS, Plaintiffs Amgen Inc., Amgen Manufacturing, Limited, and Amgen USA Inc. (collectively "Amgen") have moved pursuant to 35 U.S.C. § 283 for entry of a permanent injunction against Defendants' continued infringement of the '165 Patent and the '741 Patent, and the Court has considered all briefing submitted in connection with Amgen's motion;

WHEREAS, the Court finds that Amgen has suffered and will continue to suffer irreparable harm resulting from Defendants infringement of the '165 Patent and the '741 Patent, which harm cannot be fully compensated through a payment or payments of monetary damages;

WHEREAS, the Court finds that the balance of hardships weighs in favor of Amgen and the entry of an order of injunction; and

WHEREAS, the Court finds that the entry of an order of injunction will not disserve the public interest:

**IT IS HEREBY ORDERED THAT:**

1. Amgen's motion for a permanent injunction is **GRANTED**, and that Defendants and each of their officers, agents, servants, employees, attorneys, and any other persons who are in active concert or participation with them, are hereby permanently enjoined from infringing in any way claims 2, 7, 9, 15, 19, and 29 of the '165 Patent and claim 7 of the '741 Patent, including by making, using, offering for sale, selling or importing the antibody drug substance

alirocumab or the drug product containing it, PRALUENT<sup>®</sup>, in the United States and its territories, until the respective expiration of each patent, including any USPTO extensions granted thereon (excluded from this injunction are those acts within the scope of 35 U.S.C. § 271(e)(1));

2. The undersigned expressly retains jurisdiction to enforce the judgment and permanent injunction pertaining to this action.

**IT IS SO ORDERED**, this \_\_\_ day of \_\_\_\_\_, 2016.

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The Honorable Sue L. Robinson

01:18609301.1

# **EXHIBIT J**

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IN THE UNITED STATES DISTRICT COURT  
IN AND FOR THE DISTRICT OF DELAWARE

- - -

AMGEN INC., : CIVIL ACTION  
:   
Plaintiff, :   
:   
vs. :   
:   
SANOFI; SANOFI-AVENTIS U.S. :   
:   
LLC; AVENTISUB LLC, f/d/b/a :   
:   
AVENTIS PHARMACEUTICALS :   
:   
INC., and REGENERON :   
:   
PHARMACEUTICALS, INC., :   
:   
Defendants. : NO. 14-1317 (SLR)

- - -

Wilmington, Delaware  
Monday, February 22, 2016  
3:25 o'clock, p.m.

- - -

BEFORE: HONORABLE SUE L. ROBINSON, U.S.D.C.J.

- - -

APPEARANCES:

YOUNG CONAWAY STARGATT & TAYLOR LLP  
BY: MELANIE K. SHARP, ESQ. and  
JAMES L. HIGGINS, ESQ.

-and-

Valerie J. Gunning  
Official Court Reporter

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**APPEARANCES (Continued):**

**McDERMOTT WILL & EMERY**  
**BY: WILLIAM G. GAEDE, III, ESQ. and.**  
**DAVID L. LARSON, ESQ.**  
**(Menlo Park, California)**

**-and-**

**McDERMOTT WILL & EMERY.**  
**BY: SARAH CHAPIN COLUMBIA, ESQ.**  
**(Boston, Massachusetts)**

**-and-**

**LONDON & MEAD**  
**BY: CHRISTOPHER B. MEAD, ESQ.**  
**(Washington, D.C.)**

**-and-**

**AMGEN INC.**  
**BY: ERICA OSLO, ESQ.,**  
**STUART WATTS, ESQ. and**  
**WENDY A. WHITEFORD, ESQ. and**  
**(Thousand Oaks, California)**

**Counsel for Plaintiff**

**ASHBY & GEDDES**  
**BY: STEVEN J. BALICK, ESQ.**

**-and-**

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**APPEARANCES (Continued) :**

**AKIN GUMP STRAUSS HAUER & FELD LLP**  
**BY: DIANNE B. ELDERKIN, ESQ.,**  
**STEVEN MASLOWSKI, ESQ. and**  
**ANGELA VERRECCHIO, ESQ.,**  
**(Philadelphia, Pennsylvania)**

**-and-**

**STEPTOE & JOHNSON LLP**  
**BY: JOHN J. MOLENDIA, ESQ.,**  
**VISHAL CHANDRA GUPTA, ESQ.**  
**(New York, New York)**

**Counsel for Defendants**  
**Sanofi, Sanofi-Aventis U.S. LLC, and**  
**Aventisub LLC, f/d/b/a Aventis**  
**Pharmaceuticals Inc.**

**SANOFI**  
**BY: STEPHANIE DONAHUE, ESQ.**

**REGENERON**  
**BY: LARRY COURY, ESQ.**

- - -

1 the four corners of the patent, which is what the law  
2 requires, there's nothing to tell somebody skilled in the  
3 art that antibody 184, for example, will meet claim 2 of the  
4 '165 patent.

5 THE COURT: And, again, I mean, I can't tell you  
6 how long I spent going in circles. That to me is, are  
7 issues of fact, and the question is, should I be resolving  
8 those issues of fact in the context of a Daubert motion?

9 The fact that, well, structure is disclosed,  
10 which, of course, the defendants argued it wasn't, but that  
11 the structure doesn't make any difference because you've got  
12 to have these special tests to really determine the claimed  
13 binding, and that those tests were either not available or  
14 simply not done, I'm still not sure of that, until well  
15 after the filing date, those are issues of fact to a great  
16 extent.

17 So for you to ask me -- I mean, maybe I need to  
18 let it all in and not preclude anything. Maybe that is the  
19 better, which was the other option that I was struggling  
20 with. But it's hard for me in the context of a Daubert  
21 motion to accept everything your experts say, which is  
22 somewhat different than the plaintiff's experts say, and say  
23 this, this is necessary to prove this.

24 You know, these are, these are all complex  
25 issues of fact with varying opinions from the expert. So

1 I'm hard pressed to -- I mean, it sounds like I've swept  
2 too much information away, but, on the other hand -- well,  
3 I'm going to try to draw the line as best I can, and I'm  
4 happy we're having this conversation. And I've gone on too  
5 long.

6 So the question is: Aren't I taking your  
7 experts at their word and determining issues of fact if I  
8 preclude plaintiff's testimony, but allow evidence, but  
9 allow your evidence in?

10 MS. ELDERKIN: I don't believe so, your Honor.  
11 And before I go there, let me just apologize for being a  
12 little loose with my terminology. If we referred to the  
13 structure in our motion, we're referring to the crystal  
14 structure. Sometimes the amino acid sequence is also  
15 sometimes referred to as the structure, so I apologize for  
16 that.

17 THE COURT: That certainly wasn't AbbVie, and  
18 that's, you know, just one of my many issues with what I'm  
19 doing here.

20 MS. ELDERKIN: Sure. But going to your  
21 question, plaintiff's expert, Dr. Petsko, relies on crystal  
22 structure data for these Amgen patents, patent examples for  
23 his opinion that they meet the requirements of the claims  
24 that are asserted here.

25 So there's no doubt that they are relying on

# **EXHIBIT K**

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- VOLUME 3 -

IN THE UNITED STATES DISTRICT COURT  
IN AND FOR THE DISTRICT OF DELAWARE

- - -

AMGEN INC., : CIVIL ACTION  
 :  
 Plaintiff, :  
 :  
 vs. :  
 :  
 SANOFI; SANOFI-AVENTIS U.S. :  
 LLC; AVENTISUB LLC, f/d/b/a :  
 AVENTIS PHARMACEUTICALS :  
 INC., and REGENERON :  
 PHARMACEUTICALS, INC., :  
 :  
 Defendants. : NO. 14-1317 (SLR)

- - -

Wilmington, Delaware  
Thursday, March 10, 2016  
8:47 o'clock, a.m.

- - -

BEFORE: HONORABLE SUE L. ROBINSON, U.S.D.C.J., and a jury

- - -

APPEARANCES:

YOUNG CONAWAY STARGATT & TAYLOR LLP  
BY: MELANIE K. SHARP, ESQ.

-and-

Valerie J. Gunning  
Brian Gaffigan  
Official Court Reporters

1 APPEARANCES (Continued):

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McDERMOTT WILL & EMERY  
3 BY: WILLIAM G. GAEDE, III, ESQ.  
4 (Menlo Park, California)

4

5

-and-

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McDERMOTT WILL & EMERY.  
7 BY: SARAH CHAPIN COLUMBIA, ESQ. and  
8 ERIC HAGEN, ESQ.  
(Boston, Massachusetts)

8

9

-and-

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11

LONDON & MEAD  
12 BY: CHRISTOPHER B. MEAD, ESQ.  
(Washington, D.C.)

12

13

-and-

14

15

AMGEN INC.  
16 BY: WENDY A. WHITEFORD, ESQ.  
(Thousand Oaks, California)

16

17

Counsel for Plaintiff

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ASHBY & GEDDES  
21 BY: STEVEN J. BALICK, ESQ.

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-and-

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**STEVEN MASLOWSKI, ESQ.,**  
**MATTHEW PEARSON, ESQ. and**  
**ANGELA VERRECCHIO, ESQ.**  
**(Philadelphia, Pennsylvania)**

**-and-**

**STEPTOE & JOHNSON LLP**  
**BY: JOHN J. MOLENDIA, ESQ. and**  
**VISHAL CHANDRA GUPTA, ESQ.**  
**(New York, New York)**

**Counsel for Defendants**  
**Sanofi, Sanofi-Aventis U.S. LLC, and**  
**Aventisub LLC, f/d/b/a Aventis**  
**Pharmaceuticals Inc.**

**- - -**

Eck - direct

1 acid.

2 Q. So, Dr. Eck, if I told you that an antibody binds to a  
3 particular amino acid on PCSK9, what does that tell you  
4 about the structure of the antibody?

5 A. It does not tell you anything at all about the  
6 structure of the antibody. It tells you something only  
7 about its function. Antibody binds to that residue.

8 Q. So to what extent is it possible to take a look at  
9 PCSK9 and work backwards to try to figure out what the  
10 structure of the antibody would be?

11 A. It's just not possible. Not even today, and certainly  
12 not in 2008. That's a very active area of research. A lot  
13 of people working on that problem would like to be able to  
14 look at a target and be able to use computational tools to  
15 reliably predict how to make an antibody to bind there, but  
16 those methods just aren't there yet.

17 Q. So, Dr. Eck, I want you to be able to explain the  
18 structure we're looking at here in a little bit more detail,  
19 but, first, could you explain what the experiment is that  
20 scientists do to generate these kind of pictures?

21 A. Sure. So method, we've heard about it over the last  
22 couple of days. It's called X-ray crystallography, and as  
23 the name implies, essentially has two parts. A protein  
24 molecule or complex like we see here is too small to analyze  
25 all by itself, so we make a crystal where multiple copies

Siegel - direct

1 A. So for written description, I'm not a lawyer but my  
2 understanding is that for written description, I was  
3 supposed to look, I think they call it four corners of the  
4 patent. I'm supposed to look at the patent to see what  
5 they show me. And I could only find information on two  
6 antibodies, that the information tells me that those two  
7 antibodies satisfies the claims. I don't find information  
8 on other antibodies, structures described in the patents  
9 that satisfies the claims.

10 Q. Now, is that issue related to the binding requirement  
11 of the claims?

12 A. Well, the claims are claims to what antibodies do.  
13 And -- I'm sorry.

14 Q. Would like me to repeat?

15 A. Yes.

16 Q. Each of the claims recites antibodies that bind to an  
17 amino acids?

18 A. Right. It's not restrictive on the structure of the  
19 antibody that binds them.

20 Q. Does this binder requirement or requirement to bind to  
21 an amino acid relate to your conclusion these are the  
22 examples?

23 A. Say that again.

24 Q. Does the requirement for binding to a particular amino  
25 acids relate to your conclusion there is only two examples

Siegel - direct

1 described in the patent?

2 A. Oh, yes. Right.

3 Q. Can you explain that?

4 A. So to be able to say in a patent that antibodies  
5 bind to those particular residues, there had to have been  
6 experiments that showed what residues antibodies bound to.  
7 And the way they did this, and we heard it from Dr. Eck, is  
8 by using x-ray crystallography in which one would be able to  
9 understand what residues or amino acids on PCSK9 the  
10 antibodies are contacting. And the only x-ray structures --  
11 I think Dr. Eck talked about this earlier. The only x-ray  
12 structures that are antibodies that are in the patent are  
13 these two antibodies.

14 Q. Would either of these two antibodies be representative  
15 of an antibody that would bind more centrally to the spot?

16 A. No. I mean, so you can see, you know, this antibody  
17 is over here, this antibody is over here. If it was an  
18 antibody here, we might not see as much of the pink, and  
19 for an antibody to be here, it would be interacting in a  
20 different way with this pink area and it would have to have  
21 a different structure, and the structure of that antibody  
22 and all the other ones that could do that are covered by the  
23 claims, but there is no description in the patent of any of  
24 those antibodies.

25 Q. Now, you talked about looking for experiments in the

Siegel - direct

1 selected for, they sort of prosper. And so that's why  
2 after, that's like sort of when you get a booster shot of a  
3 vaccine, it's sort of inducing this, this higher affinity  
4 splurge of making the antibodies better.

5 And so if you actually look at this collection  
6 of antibodies that are very similar in sequence, in  
7 structure to Repatha, they probably are just these related  
8 antibodies that came from the same original B cell clone in  
9 the mouse.

10 Q. So to what extent is that adding to the diversity of  
11 what's described in the patent?

12 A. At best, it's just giving you more antibodies like  
13 Repatha. At worst -- at worst, we don't know necessarily  
14 what residues -- you know, we can't assume that they are  
15 binding to residues that are covered by the claim.

16 Q. So --

17 THE COURT: And you can look for a stopping  
18 place any time.

19 THE WITNESS: I think we're almost there.

20 THE COURT: Okay.

21 BY MR. PEARSON:

22 Q. All right. Just one more little set of questions  
23 here.

24 Considering the scope of the claims and what  
25 Amgen has described in its patents, what is your conclusion



# **EXHIBIT L**

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- VOLUME 4 -

IN THE UNITED STATES DISTRICT COURT  
IN AND FOR THE DISTRICT OF DELAWARE

- - -

AMGEN INC., : CIVIL ACTION  
 :  
 Plaintiff, :  
 :  
 vs. :  
 :  
 SANOFI; SANOFI-AVENTIS U.S. :  
 LLC; AVENTISUB LLC, f/d/b/a :  
 AVENTIS PHARMACEUTICALS :  
 INC., and REGENERON :  
 PHARMACEUTICALS, INC., :  
 :  
 Defendants. : NO. 14-1317 (SLR)

- - -

Wilmington, Delaware  
Friday, March 11, 2016  
9:00 o'clock, a.m.

- - -

BEFORE: HONORABLE SUE L. ROBINSON, U.S.D.C.J., and a jury

- - -

APPEARANCES:

YOUNG CONAWAY STARGATT & TAYLOR LLP  
BY: MELANIE K. SHARP, ESQ.

-and-

Valerie J. Gunning  
Official Court Reporter

1 APPEARANCES (Continued):

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McDERMOTT WILL & EMERY  
3 BY: WILLIAM G. GAEDE, III, ESQ.  
4 (Menlo Park, California)

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McDERMOTT WILL & EMERY.  
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8 ERIC HAGEN, ESQ.  
(Boston, Massachusetts)

9

10

-and-

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LONDON & MEAD  
12 BY: CHRISTOPHER B. MEAD, ESQ.  
(Washington, D.C.)

13

14

-and-

15

AMGEN INC.  
16 BY: WENDY A. WHITEFORD, ESQ. and  
17 SIMON JACKSON.  
(Thousand Oaks, California)

18

19

Counsel for Plaintiff

20

21

ASHBY & GEDDES  
22 BY: STEVEN J. BALICK, ESQ.

23

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-and-

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**APPEARANCES (Continued) :**

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**ANGELA VERRECCHIO, ESQ.**  
**(Philadelphia, Pennsylvania)**

**-and-**

**STEPTOE & JOHNSON LLP**  
**BY: JOHN J. MOLENDIA, ESQ. and**  
**VISHAL CHANDRA GUPTA, ESQ.**  
**(New York, New York)**

**Counsel for Defendants**  
**Sanofi, Sanofi-Aventis U.S. LLC, and**  
**Aventisub LLC, f/d/b/a Aventis**  
**Pharmaceuticals Inc.**

**- - -**

Petsko - direct

1 Amgen's patent discloses a structure-function relationship  
2 within the patent laws?

3 A. Yes, in my opinion, is that it does.

4 Q. How does it do that?

5 A. It does so by describing structure characteristics  
6 that the antibodies in the genus have in order to carry out  
7 the function of binding to PCSK9, blocking the binding of  
8 the LDL receptor.

9 Q. Okay. You heard Drs. Eck and Siegel say that just the  
10 information about the sweet spot on PCSK9 was not enough to  
11 disclose a structure-function relationship.

12 Do you agree with that?

13 A. No, I don't agree.

14 Q. Why?

15 A. Because I think that information is tremendously  
16 valuable in understanding the structure-function  
17 relationship. The structure-function relationship is  
18 binding to specific residues on the sweet spot, and you need  
19 to know what they are.

20 Q. So adding up all of these subject matters that we  
21 began yesterday afternoon and getting to now, do you have an  
22 opinion as to whether Amgen's patent claims satisfy the  
23 written description requirement of the patent laws from your  
24 perspective as a structural biologist?

25 A. It's my opinion they do.

Petsko - direct

1 A. I'm pointing to the sweet spot, to the pink region on  
2 this blue three-dimensional model of PCSK9. That's what you  
3 didn't know before the Amgen scientists did the work in the  
4 patent.

5 Q. Okay. So if you recall, Drs. Eck and Siegel said,  
6 well, just because Amgen disclosed the sweet spot on PCSK9,  
7 that does not tell you enough about antibodies that would  
8 bind there. You can't sit at your desk and write out the  
9 sequences. I think they said you can't predict.

10 Do you have an opinion about that?

11 A. My opinion is that they're right. You can't sit at  
12 your desk and write out all the sequences, and you can't  
13 predict all the sequences, but I would reply that that does  
14 not matter. That isn't the way any scientist would go about  
15 studying antibodies.

16 What you would do is, you would use the  
17 information here to know that what you need to find are  
18 antibodies that bind to these residues on PCSK9, and that  
19 if you do, you will have an extremely high likelihood that  
20 you will block the interaction of the LDL receptor with  
21 PCSK9.

22 Q. Okay. So taking into account, taking into account the  
23 defense argument that she says is right, you can't sit at  
24 your desk, you can't predict, right, does the disclosure in  
25 the patent allow a person of skill in the art to visualize

1 immunize mice, test thousands of antibodies.

2           So I think he opened the door when he said, yes.  
3 As long as you have the antigen, that's all you need to  
4 know. And, you know, I don't have to go there with him, but  
5 I think I should at least have the ability to go there with  
6 our experts on rebuttal, because he said that, and if we  
7 don't want to go there with him, then when we bring our  
8 witnesses back on rebuttal, we can ask them, were you here  
9 in the courtroom when Dr. Petsko said all you need is the  
10 antigen, the disclosure, the pink spot, whatever, the hot  
11 spot, they can say, well, that's what he said, but I know  
12 otherwise, because I know four years later, this is what  
13 Amgen actually did.

14           THE COURT: Well, I mean, there are marked  
15 contrasts in how the parties are approaching this case, and  
16 as I was sitting here listening, I mean, there may be a  
17 legal issue here setting aside this whole post priority  
18 date, real world versus what a person of skill in the art,  
19 what they would do with the information at the time, and I  
20 still think that's a difficult legal issue that I obviously  
21 am still struggling with. On the other hand, there is a  
22 marked difference in what the defendants, the defendants'  
23 perspective, which their expert seemed to have inferred, if  
24 not directly said to the jury, that this whole written  
25 description perspective has to be to a certainty with a fine

1 sent them our proposed instruction, and they accepted this  
2 one, apparently. And, moreover, we had laid out the  
3 antedating law in our issues of law in the pretrial order.  
4 So this is no, this is nothing that is surprising.

5 THE COURT: Well, a couple things. Number one,  
6 the obvious, there's nothing easy about this case.

7 Number two, it had always been my understanding  
8 that the issues tried had to have been identified not in the  
9 pretrial order, but through the course of discovery so that  
10 everyone was aware there was an issue, everyone could take  
11 appropriate discovery, the experts could opine. You know,  
12 the case should be an open book.

13 So, once again, I'm not -- because I certainly  
14 don't know how this case is tried, I'm not confident that  
15 just listing it and supplying a jury instruction is whether  
16 the kind of notice I would anticipate there being for an  
17 important issue in a complex case.

18 MR. LARSON: Understand, your Honor. For the  
19 record, the plaintiffs have made clear as long ago as, I  
20 think it was last September or so, that we dispute that  
21 these two references are prior art, and we did so when  
22 served with requests for admissions on that very topic. So  
23 that has been on the table for a long time, and it is a  
24 matter of defendants' burden to prove that they are prior  
25 art if the patent owner disputes at this time.

# **EXHIBIT M**

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- VOLUME 5 -

IN THE UNITED STATES DISTRICT COURT  
IN AND FOR THE DISTRICT OF DELAWARE

- - -

AMGEN INC., : CIVIL ACTION  
:  
Plaintiff, :  
:  
vs. :  
:  
SANOFI; SANOFI-AVENTIS U.S. :  
LLC; AVENTISUB LLC, f/d/b/a :  
AVENTIS PHARMACEUTICALS :  
INC., and REGENERON :  
PHARMACEUTICALS, INC., :  
:  
Defendants. : NO. 14-1317 (SLR)

- - -

Wilmington, Delaware  
Monday, March 14, 2016  
8:45 o'clock, a.m.

- - -

BEFORE: HONORABLE SUE L. ROBINSON, U.S.D.C.J., and a jury

- - -

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P R O C E E D I N G S

(Proceedings commenced in the courtroom,  
beginning at 8:45 a.m.)

THE COURT: All right. I appreciate your  
patience, appreciate the conversation I had with counsel in  
chambers.

I think the one thing that counsel and I agreed  
on was that this case could have benefited from a summary  
judgment practice because the issues that you all have  
presented the Court would have been better served by being  
addressed in a more fulsome manner than in Daubert motions  
and in my motion in limine practice at the very end of the  
case.

I can't do anything about that now. I think the  
record for appeal, and this case obviously will be appealed,  
will be clearer if I stick to the lines I've drawn, and if  
it comes back, it comes back. But I think if I start  
changing the lines now, it just muddies the water.

So with respect to the obviousness issue and  
what is prior art, consistent with my legal conclusion,  
right or wrong, I did make it, that the Drinkware case  
was the better description of the requirements. And the  
fact that the defendant went forward with its obviousness

1 defense knowing that its expert did not satisfy those  
2 requirements, I am, to be consistent, I will grant Amgen's  
3 motion for judgment as a matter of law on obviousness. That  
4 will not go to the jury. I understand that defendants have  
5 a good argument the other way, but it will be made to the  
6 Federal Circuit, not to the jury.

7 I think jurors, I'm not confident are as curious  
8 as you all think they are. I think generally, the fewer  
9 issues they have to decide, the better. It will simply be  
10 stated in the jury instructions that the issue of  
11 obviousness has been resolved. They don't need to know how  
12 or by whom or for what reason.

13 Having said that, all the other papers you've  
14 given me since 5:00 o'clock yesterday, because I was here  
15 until 5:00 o'clock yesterday, have been, I believe, a  
16 regurgitation of all of the issues that we have so painfully  
17 gone through, and to some extent, have made the two-hour  
18 charge conference we had on Friday a waste of everyone's  
19 time.

20 So I decline to let all of this evidence in that  
21 I declined on let in initially, and it is not clear to me  
22 what jury instruction issues there are for us to resolve,  
23 because you threw so much at me. And so what I propose to  
24 do at this point is go back to what I gave you on Friday,  
25 and we'll go from there.

# **EXHIBIT N**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

AMGEN INC.; AMGEN	)	
MANUFACTURING, LIMITED; AMGEN	)	
USA INC.,	)	
Plaintiff,	)	
v.	)	C.A. No. 14-1317-SLR
	)	(CONSOLIDATED)
SANOFI, SANOFI-AVENTIS U.S. LLC,	)	"
AVENTISUB LLC, f/d/b/a AVENTIS	)	<b><i>PUBLIC VERSION</i></b>
PHARMACEUTICALS INC., and	)	<hr/>
REGENERON PHARMACEUTICALS, INC.,	)	
	)	
Defendants.	)	

**PROFFER OF DONALD SIEGEL, M.D., Ph.D.**

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Dated: March 10, 2016

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Pursuant to the Court’s rulings on the parties’ respective *Daubert* motions (D.I. 226, Memorandum Order February 18, 2016; D.I. 249, Memorandum Order March 2, 2016), Defendants were precluded from submitting expert testimony relating to certain post-priority date evidence and argument concerning its impact on the invalidity of the asserted claims for failure to satisfy the written description requirement of 35 U.S.C. § 112, ¶ 1. Had the district court not excluded this evidence, Defendants’ expert Dr. Donald Siegel would have provided additional testimony concerning his opinions that the asserted claims are invalid for failure to satisfy the written description requirement. In particular, Dr. Siegel would have testified, as follows, consistent with the opinions set forth in his Opening and Supplemental Reports:

**Opening Expert Report**

1. The asserted patents provide arginine/glutamic acid scanning results for five antibodies – 31H4, 21B12, 31A4, 12H11, 3C4. Ex. 15, 165 Patent at 113:60-122:56, Example 39. The asserted patents explain that the arginine/glutamic acid scanning technique “determines if a residue is part of the structural epitope, meaning those residues in the antigen [PCSK9] which contact *or are buried* by the antibody.” Ex. 15, 165 Patent at 114:3-5 (emphasis added); *see* Ex. 29, Mehlin Tr. at 20:6-21:3, 23:19-23; Ex. 30, Ketchem Tr. at 92:9-93:24. The asserted patents also explain “[a]rginine and glutamic acid side chains are charged and bulky and can disrupt antibody binding *even if the mutated residue is not directly involved in antibody binding.*” Ex. 15, 165 Patent at 114:5-8 (*emphasis added*); *see* Ex. 29, Mehlin Tr. at 23:19-25:18.

2. For purposes of this technique, a bead-based multiplex assay was used to measure antibody binding to wild-type and mutant PCSK9 simultaneously. Ex. 15, 165 Patent at 115:12-45; *see also* Ex. 31, Carabeo Tr. at 30:2-37:20. Residues were considered part of the structural epitope (a “hit”) when mutating it to arginine or glutamic acid caused either a shift in the EC50

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(EC50 shift) or a reduction of maximum signal (B-max drop) compared to antibody binding to wild-type. Ex. 15, 165 Patent at 117:24-28; *see also* Ex. 31, Carabeo Tr. at 86:14-87:4, 89:11-20. The asserted patents explain that “[a]s will be appreciated by one of skill in the art, while the B-max drop and EC50 shift hits can be considered manifestations of the same phenomenon, strictly speaking, a B-max drop alone *does not reflect a loss of affinity per se* but, rather, the *destruction of some percentage of the epitope of an antibody.*” Ex. 15, 165 Patent at 121:53-58 (*emphasis added*); *see also* Ex. 31, Carabeo Tr. at 200:22-205:2; Ex. 29, Mehlin Tr. at 105:5-108:3, 109:19-110:19. A summary of the hits for the antibodies tested is shown in Table 39.5. Ex. 15, 165 Patent at 120:30-42.

3. Binning experiments were conducted on panels of antibodies in order to identify antibodies that compete with each other for binding to PCSK9. Ex. 15, 165 Patent at 88:30-89:37, 112:1-113:30, Examples 10 and 37; *see also* Ex. 31, Carabeo Tr. at 104:5-105:18; Ex. 29, Mehlin Tr. at 68:8-17; Ex. 30, Ketchem Tr. at 81:1-21. The asserted patents describe two different types of antibody binning experiments. One type of experiment used an ELISA-based method to determine whether two antibodies compete for binding (*see* Ex. 15, 165 Patent at 88:30-89:37, Example 10), whereas another experiment used a multiplex approach (*see* Ex. 15, 165 Patent at 112:1-113:30, Example 37). *See* Ex. 30, Ketchem Tr. at 86:4-87:15. The results of those experiments are shown in Table 8.3 and Table 37.1. Ex. 15, 165 Patent at 88:52-89:19, 112:50-113:6. The asserted patents explain that antibodies in bin 1 compete with 21B12, while antibodies in bin 3 compete with 31H4; however, bins 1 and 3 are mutually exclusive of each other. Ex. 15, 165 Patent at 113:7-14; *see also* Ex. 31, Carabeo Tr. at 177:3-21. Antibodies in bin 2 compete with both bin 1 and bin 3 antibodies. Ex. 15, 165 Patent at 113:7-9; *see* Ex. 25, Jackson Tr. at 259:23-260:6. According to the patents, “[a]s will be appreciated by one of skill in

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the art, [antigen binding proteins] in the same bin...likely bind to *overlapping sites* on the target protein. As such, the above epitopes and relevant residues can generally be extended to all such [antigen binding proteins] in the same bin.” Ex. 15, 165 Patent at 121:62-67 (*emphasis added*); Ex. 20, Walker Tr. at 99:11-100:16; Ex. 29, Mehlin Tr. at 70:9-17, 89:4-16; Ex. 25, Jackson Tr. at 219:2-8; Ex. 30, Ketchem Tr. at 83:5-10. As set forth below, these experiments do not actually indicate that antibodies in the same bin will bind to all of the same amino acid residues on PCSK9. Furthermore, the asserted patents explain that antibodies in different bins “are representative of *different types of epitope locations* on PCSK9...” Ex. 15, 165 Patent at 113:12-13 (*emphasis added*); *see also* Ex. 31, Carabeo Tr. at 144:11-24

4. [REDACTED]

5. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**CONTAINS CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER**

[REDACTED]

6. [REDACTED]

[REDACTED]

7. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

8. [REDACTED]

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9. [REDACTED]

**CONTAINS CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER**

[REDACTED]

10. [REDACTED]

[REDACTED]

11. [REDACTED]

[REDACTED]

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[REDACTED]

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12. [REDACTED]

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13. [REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

I reviewed the expert report of Dr. Michael Eck, including but not limited to his opinions related to x-ray crystal structures. Dr. Eck considered [REDACTED]

[REDACTED]

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14. Alirocumab is a recombinant antibody to human PCSK9 that was generated using Regeneron's VelocImmune® technology. The VelocImmune® mouse was created by removing genomic sequences bearing the germline variable regions of the mouse immunoglobulin loci (virtually all of the heavy chain V, D, and J segments, and all of the kappa light chain V and J segments) and precisely replacing them with human genomic fragments bearing human immunoglobulin germline variable sequences. Ex. 45, Murphy at REGN02794489. The flanking mouse sequences, including all mouse constant chain regions and transcriptional control elements, remain intact and functional within the hybrid loci. Ex. 45, Murphy at REGN0274490-492. The resulting mice produce "reverse chimeric" antibodies with fully human variable regions and mouse constant regions. Ex. 45, Murphy at REGN0274490. The immune system of these mice is indistinguishable from wild type mice using a variety of measures. For example,

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B-cell number and maturation, variable region gene usage, and somatic hypermutation are all normal. Ex. 46, REGN01386678 at 682; Ex. 47, REGN01423592 at 602.

15. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

16. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

17. I understand that [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**CONTAINS CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER**

[REDACTED]

18. [REDACTED]

[REDACTED]

I understand that an Amgen PCT application that discloses antibodies to PCSK9 published on February 26, 2009. Ex. 58, WO 2009/026558 at REGN00100345. [REDACTED]

[REDACTED]

I understand that REGN727 (alirocumab) was ultimately selected and is the active antibody ingredient in Praluent®.

19. [REDACTED]

[REDACTED]

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20. I understand that other companies (hereinafter, collectively referred to as “third parties”) developed antibodies that bind to PCSK9 and neutralize its activity.

21. Investigators at Merck Research Laboratories (“Merck”) panned the Morphosys HuCAL Gold phage display library against recombinant PCSK9 protein to identify antibodies capable of binding to PCSK9. Ex. 61, Ni at REGN02449916. Through this process, they identified a human Fab clone called 1D05 that was converted into a full-length IgG2 antibody. Ex. 61, Ni at REGN02449914. 1D05 was shown to bind to several PCSK9 species with nanomolar affinities. Ex. 61, Ni at REGN02449915, Table 1. 1D05 was also shown to block the binding of PCSK9 to the LDLR, as well as neutralize PCSK9-mediated inhibition of cellular LDL uptake in several cell lines. Ex. 61, Ni at REGN02449916, Fig. 1A-C.

22. The investigators determined the x-ray structure of the 1D05-Fab in complex with PCSK9. Ex. 61, Ni at REGN02449916-917, Fig. 2. Using this structure, they identified residues in the catalytic domain of PCSK9 that are bound by 1D05. Ex. 61, Ni at REGN02449916. The investigators concluded that extensive contacts were formed between the 1D05 heavy chain CDR H3 and the catalytic domain of PCSK9. Ex. 61, Ni at REGN02449916-917. Interestingly, the investigators found that the CDR H2 and CDR H3 regions of 1D05 adopt a structure that structurally mimics the EGFa domain of LDLR. Ex. 61, Ni at REGN02449916-917, Fig. 3. I understand that the x-ray structure of the 1D05-Fab/PCSK9 complex was made publicly available through the Protein Database (PDB) website.

23. Using phage display, investigators at Merck identified another human anti-PCSK9 antibody that they called AX132. This antibody was identified by panning a synthetic human Fab library against human PCSK9. Ex. 62, REGN01565029 at 080, Example 1. AX132 was shown to block the interaction between PCSK9 and LDLR using a TR-FRET assay. Ex. 62,

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REGN01565029 at 087, Example 15, Fig. 10. AX132 also neutralized PCSK9-mediated inhibition of cellular LDL uptake. Ex. 62, REGN01565029 at 087, Example 16, Tables 11-12, Fig. 11D-F. The investigators solved the x-ray structure of the AX132-Fab in complex with PCSK9. Ex. 62, REGN01565029 at 084, Example 10, Figure 8. I understand that the coordinates for the x-ray structure are disclosed in Table 14 of U.S. Publication 2012/0213794. Ex. 62, REGN01565029 at 090-190.

24. Investigators at Pfizer Inc. (“Pfizer”) also developed antibodies that bind and neutralize PCSK9. The investigators immunized wild-type and PCSK9 knockout mice with recombinant human PCSK9 and generated hybridomas. Ex. 63, REGN02449904 at 905. Clones were screened for the ability to bind human PCSK9 and block PCSK9-mediated down-regulation of LDLR levels. Ex. 63, REGN02449904 at 905. One of the antibodies identified in this screen, J10, was shown to completely rescue LDLR levels in cells treated with exogenous PCSK9 and completely block binding of PCSK9 to LDLR. Ex. 63, REGN02449904 at 906-907, Fig. 2A-B.

25. I understand that J10 was humanized and affinity matured. Ex. 63, REGN02449904 at 905. The resulting antibody, J16, was shown to bind to human PCSK9 with an affinity ( $K_D$ ) of approximately 5 pM. Ex. 63, REGN02449904 at 906. J16 was also shown to block human and mouse PCSK9 binding to the LDLR and reverse PCSK9-mediated down-regulation of LDLR levels in cells. Ex. 63, REGN02449904 at 906.

26. The investigators determined the co-crystal structure of J16 in complex with PCSK9. Ex. 63, REGN02449904 at 907, Fig. 2A. They concluded that J16 binds to a “nonlinear, three-dimensional epitope that almost perfectly overlaps with the LDLR EGFA domain binding site on PCSK9.” Ex. 63, REGN02449904 at 907, Fig. 2B. I understand that the x-ray structure of the J16-Fab/PCSK9 complex was made publicly available through the Protein

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Database (PDB) website. *In vivo* testing demonstrated that J16 reduces cholesterol in cynomolgus monkeys. Ex. 63, REGN02449904 at 908-909, Figs. 3-4.

27. I understand that Amgen has asserted that 12H11 falls within the scope of claims 2 and 19 of the 165 patent and claim 24 of the 914 patent. *See* Ex. 65, Amgen’s Suppl. Resp. and Obj. to Def. Interrogatories at p. 16-17. In my opinion, one of ordinary skill reading the specifications would not conclude that 12H11 meets the binding requirements of those claims. The asserted patents do not provide an x-ray structure for 12H11, nor do they provide any other information that is sufficient to show that 12H11 “binds to” any selected residue. Therefore, one skilled in the art reading the specification would not conclude that 12H11 binds to (*i.e.*, forms a non-covalent bond with) any of the selected residues of the 165 and 914 patent claims.

28. I understand that Amgen’s assertion that 12H11 meets the binding limitations recited in the claims is based, at least in part, on the results of arginine/glutamic acid-scanning experiments. *See* Ex. 15, 165 Patent at Example 39, Table 39.5. In my opinion, the arginine/glutamic acid-scanning method does not provide sufficient information to determine whether an antibody forms a non-covalent bond with a residue. This method also fails to show that a residue “contributes to the affinity of the PCSK9-antibody interaction” as required under the Court’s construction of “binds to”.

29. The asserted patents instruct that arginine/glutamic acid-scanning identifies residues that are part of the “structural epitope”, meaning the residues on the antigen “which contact *or are buried* by the antibody.” Ex. 15, 165 Patent at 114:2-5 (*emphasis added*). The patents further explain that, because arginine and glutamic acid side chains are “charged and bulky,” they can “disrupt binding *even if the mutated residue is not directly involved in antibody binding.*” Ex. 15, 165 Patent at 114:5-8 (*emphasis added*). A person of ordinary skill

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reading the patents would not conclude based on arginine/glutamic acid-scanning results that an antibody “binds to” (*i.e.*, forms a non-covalent bond with) a residue on the antigen.

30. [REDACTED]

31. Therefore, in my opinion, the arginine/glutamic acid-scanning results disclosed in the patents are insufficient to show that 12H11 “binds to [a residue]” as required by the asserted claims of the 165 and 941 Patents. For at least that reason, 12H11 is not encompassed by those claims and cannot provide written description support. As discussed below, even if the arginine/glutamic acid-scanning results somehow demonstrated that 12H11 meets the binding requirements of the 165 and 914 Patents – which they do not – the patents fail to demonstrate that 12H11 meets the neutralization requirements of the asserted claims.

32. In my opinion, a variety of techniques could be used to determine whether an antibody “binds an epitope” that includes residues R237 or D238, as required by claim 7 of the 741 Patent. As one non-limiting example, Dr. Eck explained that one skilled in the art could analyze the x-ray structure of the antibody/PCSK9 co-complex to determine whether the selected residues were either bound or buried by the antibody. Eck Rpt. at ¶¶28-30. However,

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arginine/glutamic acid-scanning, which does not distinguish residues that are contacted from those that are buried (Ex. 15, 165 Patent at 114:2-5; Ex. 30, Ketchem Tr. at 93:12-24), does not provide sufficient information to demonstrate that a residue is part of an antibody’s functional epitope.

33. I understand that the asserted patents provide arginine/glutamic acid-scanning results for a few of the disclosed antibodies – including 21B12, 31H4, and 12H11. *See* Ex. 15, 165 Patent at Example 39. I reviewed the arginine/glutamic acid-scanning results provided in Table 39.5 of the patents. I understand that R237 and D238 were identified as epitope “hits” for 21B12 in that assay. I understand that Amgen does not contend that 31H4 or 12H11 are encompassed by any asserted claim of the 741 patent. *See* Ex. 65, Amgen’s Suppl. Resp. and Obj. to Def. Interrogatories at p. 16-17. This is consistent with the results presented in Table 39.5, which show that R237 and D238 are not part of the structural epitope for 31H4 or 12H11. For at least those reasons, the asserted patents only teach that 21B12 meets the binding limitation of any asserted claim of the 741 Patent.

34. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**CONTAINS CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER**

[REDACTED] I understand there is a legal issue as to whether this extrinsic information, which is not within the four corners of the Amgen patents, may be considered for purposes of determining whether disclosed antibodies have the properties required by the patent claims.

35. Even assuming that Amgen may rely on evidence extrinsic to the patents, this evidence is at best sufficient to show that a few additional antibodies might be potentially capable of meeting the binding requirement of any asserted claim. As discussed above, an antibody must form a non-covalent bond with the recited residue(s) in order to meet the binding requirements of the asserted 165, 741 and 914 Patent claims. Amgen has only provided [REDACTED]

[REDACTED] For the remaining antibodies, Amgen has not provided information sufficient to show that they “bind to” (*i.e.*, form a non-covalent bond with) any of the residues recited in the 165, 741 or 914 Patents. For at least that reason, Amgen’s extrinsic evidence only shows that at most a few additional antibodies potentially meet the binding requirements of any asserted claim.

36. I understand that human V<sub>H</sub> genes not present in the XenoMouse® strains used by Amgen are capable of encoding anti-PCSK9 antibodies having the claimed properties. I considered a research article titled “From XenoMouse technology to panitumumab, the first fully human antibody product from transgenic mice,” which describes the series of genetic manipulations used to create the XenoMouse® mice. *See* Ex. 82, REGN02794479 at 479-487. Figure 1(c) of the article provides a list of the human V<sub>H</sub> genes that were successfully incorporated into the XenoMouse® mice. *See* Ex. 82, REGN02794479 at 480. Importantly, this figure shows that the human V<sub>H</sub> 1-69 gene was not present in the mice that Amgen used. *See* Ex.

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82, REGN02794479 at 480, Figure 1(c). [REDACTED]

[REDACTED]

[REDACTED]

37. As described below, I understand that 1D05 – a third party anti-PCSK9 antibody that falls within the claimed genus – is encoded by the V<sub>H</sub> 1-69 gene. As described in more detail below, the primary structure (*i.e.*, amino acid sequence) of 1D05 differs from the antibodies in the asserted patents that Amgen contends fall within the scope of the claims. Moreover, 1D05 binds to PCSK9 at a different epitope location and through different binding mechanisms than the antibodies in the asserted patents. In my opinion, the lack of complete genetic diversity of the XenoMouse® mice precluded Amgen from isolating the full diversity of antibody structures covered by the asserted claims, including antibodies having structures similar to 1D05.

38. I understand that, except for claim 29 of the 165 Patent, the asserted claims place no numerical limitation on the extent of receptor blocking (*i.e.*, they cover antibodies that block to any degree). In my opinion, the decision to characterize only the top blockers likely contributed to Amgen’s failure to identify the full diversity of antibody structures that meet the functional criteria of the asserted claims. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

***CONTAINS CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER***

39. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

40. As mentioned above, the genus of antibodies encompassed by the asserted claims is not limited in any way to antibodies having a certain structure. In contrast to the structurally-related families of antibodies that are described in the specification, the asserted claims cover a variable class of structurally-unrelated antibodies by using functional descriptions of what the antibodies do. As shown below, a broad class of structurally-unrelated antibodies is, or is alleged to be, encompassed by the claims.

41. The size of the genus of antibodies encompassed by any of the claims cannot be predicted. The variability of the genus of antibodies encompassed by the claims can, however, be exemplified by reference to other antibodies that are markedly different in structure from the antibodies described in the patent specification but have the functional features set forth in the patent claims. For example, to the extent that alirocumab is encompassed by any claim, it represents an example of an antibody having a markedly different structure from the antibodies described in the asserted patents. Furthermore, other antibodies not disclosed in the patents having the claimed functional features, including other antibodies developed by third parties, represent additional examples of the diversity of structures encompassed by the asserted claims.

42. Several other anti-PCSK9 antibodies not disclosed in the asserted patents also possess the claimed functional properties and, therefore, may be used for purposes of considering

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the breadth of structures encompassed by the claimed genus. Specifically, other antibodies developed by third parties (1D05, AX132, J16) – possess the functional requirements of the asserted claims. As part of my analysis, I considered information showing that each of those antibodies meets the receptor blocking and neutralization limitations of the asserted claims. Moreover, I rely on Dr. Eck’s analyses of the x-ray structures of those antibodies in complex with PCSK9 to determine whether they meet the binding requirements of each asserted claim. Eck Rpt. at ¶70, Appendix A; *see also* Eck Rpt. at ¶¶59-70.

43. Disclosure in the article by Ni and colleagues shows that 1D05 meets the functional limitations of the asserted claims. Ex. 61, Ni at REGN02449913-921. I understand that 1D05 was generated by panning human combinatorial phage display libraries using recombinant murine PCSK9 protein. Ex. 61, Ni at REGN02449914. BIACore experiments show that 1D05 is capable of binding to PCSK9 protein from several species. Ex. 61, Ni at REGN02449916, Table 1. I understand that Dr. Eck analyzed the x-ray structure of the 1D05-Fab/PCSK9 co-complex that was solved by Ni and colleagues and made publicly available through the Protein Database (PDB) website. Ex. 61, Ni at REGN02449916; Eck at ¶¶60-61. Having considered the details of the structures, Dr. Eck concludes the 1D05 binds to at least D238, I369, and V380 of PCSK9. Eck Rpt. at ¶¶61-62. According to Dr. Eck, the non-covalent bonds formed with these amino acids contribute to the affinity of binding to PCSK9. Eck Rpt. at ¶62. Dr. Eck’s analysis is consistent with the PCSK9 residues identified by Ni and colleagues as making contacts with 1D05. Ex. 61, Ni at REGN02449916; Eck Rpt. at ¶¶61-62.

44. Using a TR-FRET assay, Ni and colleagues showed that 1D05 dose-dependently blocks the binding of PCSK9 to the LDLR with an IC<sub>50</sub> of 3.7 nM. Ex. 61, Ni at REGN02449916, Fig. 1A. 1D05 also neutralized PCSK9’s ability to inhibit cellular LDL uptake

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in cell lines (Ex. 61, Ni at REGN02449916, Fig. 1B-C) and reduced circulating levels of LDL in mice and non-human primates. Ex. 61, Ni at REGN02449917-918, Figs. 4 and 6. I understand that sequence information for the heavy and light chain variable regions of 1D05 is disclosed on the PDB website at accession number 2XTJ and also in U.S. Pat. No. 8,188,234. *See* Ex. 74, 234 Patent.

45. AX132 also meets the functional limitations recited in the asserted claims. AX132 was isolated using phage display by panning a synthetic human Fab library against human PCSK9. Ex. 62, REGN01565029 at 080. AX132 was shown to bind to human PCSK9 protein using a BIACore assay. Ex. 62, REGN01565029 at 086, Example 14, Table 7 and 8. I understand that the coordinates for the x-ray structure of AX132 in complex with PCSK9 are disclosed in Example 21 and Table 14 of U.S. Pat. Pub. 2012/0213794. Ex. 62, REGN01565029 at 090-190. I understand that Dr. Eck analyzed the AX132/PCSK9 x-ray structure. Eck Rpt. at ¶¶36, 59. Having considered the details of the structures, Dr. Eck concludes the AX132 binds to at least S153, D238, I369, and R194 of PCSK9. Eck Rpt. at ¶¶64-65. According to Dr. Eck, the non-covalent bonds formed with these amino acids contribute to the affinity of binding to PCSK9. Eck Rpt. at ¶65.

46. AX132 was shown to “inhibit the PCSK9-LDLR interaction *fully*” using a TR-FRET assay. Ex. 62, REGN01565029 at 087, Example 15, Fig. 10 (*emphasis added*). AX132 also neutralized PCSK9-mediated inhibition of cellular LDL uptake in cells (Ex. 62, REGN01565029 at 087, Example 16, Tables 11-12, Fig. 11D-F) and in rhesus monkeys. Ex. 62, REGN01565029 at Example 19, Fig. 17. I understand that sequence information for the heavy and light chain variable regions of AX132 is disclosed in U.S. Pat. Pub. 2012/0213794 at SEQ ID NOS: 360 and 511, respectively. *See* Ex. 62, REGN01565029 at 056.

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47. J16 is a humanized antibody that meets the functional limitations of the asserted claims. Ex. 63, REGN02449904 at 905-906. Liang and colleagues solved the x-ray structure of J16 in complex with PCSK9. Ex. 63, REGN02449904 at 907, Fig. 2. I understand that Dr. Eck analyzed that structure, which was publicly available through the PDB website. Eck Rpt. at ¶¶36, 59. Having considered the details of the structures, Dr. Eck concludes the J16 binds to at least S153, D238, I369, R194, and F379 of PCSK9. Eck Rpt. at ¶¶67-68. According to Dr. Eck, the non-covalent bonds formed with these amino acids contribute to the affinity of binding to PCSK9. Eck Rpt. at ¶68.

48. Liang and colleagues demonstrated that J16 “completely and dose-dependently block[s]” binding of PCSK9 to the LDLR and reverses PCSK9-mediated downregulation of LDLR levels in cells. Ex. 63, REGN02449904 at 906. J16 also reduced LDL-C and total cholesterol levels in cynomolgus monkeys. Ex. 63, REGN02449904 at 908. I understand that sequence information for the heavy and light chain variable regions of J16 is disclosed on the PDB website at accession number 3SQQ. *See also*, Ex. 63, REGN02449904 at 906.

49. Table 2 below references the relevant binding and neutralization information for each of the additional third party antibodies mentioned above and also provides a list of the asserted claims that each antibody falls into.

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<b>Antibody</b>	<b>Type</b>	<b>"binds to [residues]"</b>	<b>Receptor Blocking</b>	<b>Neutralization</b>	<b>Asserted Claims</b>
<b>1D05</b>	Human	238 369 380	See Ex. 61, REGN02449913 (Ni, et al., J. Lipid Res. (2011) 52:78-86) at Fig. 1A (TR-FRET LDLR blocking assay)	See Ex. 61, REGN02449913 (Ni, et al., J. Lipid Res. (2011) 52:78-86) at Figs. 1B-C (LDL uptake assay), and 4, 6 (LDL-c levels in mice and non-human primates)	<b>165 Patent</b> <b>Claims:</b> 7, 9, 15, 19, 29; <b>741 Patent Claim:</b> 7
<b>AX132</b>	Human	153 194 238 369	See Ex. 62, REGN01565029 (US Pub. 2012/0213794) at Example 15, Fig. 10 (TR-FRET LDLR blocking assay)	See Ex. 62, REGN01565029 (US Pub. 2012/0213794) at Example 16, Tables 11-12, Figs. 11D-F (LDL uptake assay) and Example 19, Fig. 17 (LDL-c levels in non-human primates)	<b>165 Patent</b> <b>Claims:</b> 2, 7, 9, 19, 29; <b>741 Patent Claim:</b> 7
<b>J16</b>	Humanized	153 194 238 369 379	See Ex. 63, REGN02449904 (Liang, et al., J. Pharm. Exp. Ther. (2012) 340:228-236) at REGN02449906	See Ex. 63, REGN02449904 (Liang, et al., J. Pharm. Exp. Ther. (2012) 340:228-236) at REGN02449908, Fig. 3	<b>165 Patent</b> <b>Claims:</b> 2, 7, 9, 19, 29; <b>741 Patent Claim:</b> 7

**Table 2:** Summary of relevant functional information for third party antibodies that meet the recited limitations of the asserted claims.

50. In conclusion, 1D05 is encompassed by claims 7, 9, 15, 19, and 29 of the 165 Patent and claim 7 of the 741 Patent. AX132 is encompassed by claims 2, 7, 9, 19, and 29 of the 165 Patent and claim 7 of the 741 Patent. J16 is encompassed by claims 2, 7, 9, 19 and 29 of the 165 Patent and claim 7 of the 741 Patent.

51. For purposes of considering whether the antibody examples disclosed in Amgen's patents are representative of alirocumab, I compared the primary structures of the heavy and light chain variable region sequences of antibodies that fall within any of the claims to the heavy and light chain variable sequences of alirocumab. I made two types of comparisons: in one comparison, I compared the sequence of alirocumab to the sequence(s) of 21B12 and 31H4 – the only antibodies that the patents teach that may fall within the scope of any asserted claim. In another type of comparison, I compared the sequence of alirocumab to the sequence(s) of all of

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the antibody(ies) identified by Amgen as being within the scope of any asserted claim (plus 16F12), even though I disagree that the data in the patent, or extrinsic to the patent, support Amgen's contention in this regard.

52. Heavy and light chain variable region sequence alignments that include alirocumab are shown in Exs. X2A and X2B, respectively. Sequence alignments were performed as described above for the analysis of the Amgen antibodies alone except that all Amgen antibodies are compared with alirocumab (316P) placed at the top. Amino acid differences between any given antibody and alirocumab included not only non-identical amino acids at a particular position in a heavy or light chain, but also the absence of an amino acid in a given antibody where there are gaps in the antibody due to CDRs in alirocumab being longer than the corresponding CDR in the given antibody. Percent identities were calculated by dividing the number of amino acid differences for a given alirocumab/antibody pair by the total length of the alirocumab chain (118 amino acids for heavy chain and 113 amino acids for light chain), subtracting from 1, and expressing as a percent identity. Ex. X2A and Ex. X2B. As in the example above when just comparing Amgen antibodies, percent identities for alirocumab and each Amgen antibody were calculated for heavy and light chains together and using the total length of alirocumab heavy chain plus light as the reference. Ex. X2C. A similar analysis was performed for just the CDRs in heavy chains, light chains, and heavy plus light chains, as also indicated in Exs. X2A-C.

53. A comparison between the heavy and light chain variable regions of alirocumab to 21B12 and 31H4 shows that there are significant structural differences between those antibodies. The heavy chain of alirocumab is 50% and 72% identical to 21B12 and 31H4, respectively, whereas the light chain of alirocumab is 46% and 49% identical to those antibodies. Ex. X2A-B.

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Taking both chains into account, alirocumab is 48% identical to the variable region of 21B12 and 61% identical to the variable region of 31H4. Ex. X2C.

54. Considering only the CDRs, which are the regions of an antibody that are usually most directly involved in antigen binding, shows that the heavy chain CDRs of alirocumab are 31% and 39% identical to 21B12 and 31H4, respectively, whereas the light chain CDRs of alirocumab are 21% identical to both 21B12 and 31H4. Ex. X2A-B. Overall, the CDRs of alirocumab share 26% and 30% sequence identity with 21B12 and 31H4, respectively. Ex. X2C. I note that there are differences in CDR length between the antibodies. As one example, the heavy chain CDR H3 of alirocumab is 9 amino acids in length, which is 3 amino acids longer than 21B12 (6 amino acids) and 5 amino acids shorter than 31H4 (14 amino acids). Ex. X2A. As another example, the light chain CDR L1 of alirocumab (17 amino acids) is three amino acids longer than both 21B12 and 31H4 (14 amino acids). Ex. X2B.

55. [REDACTED]

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56. Even assuming that [REDACTED] do meet the recited limitations – which, as described above, they do not – these comparisons show that there are significant differences in primary structure between the disclosed antibodies and other antibodies encompassed by the claims, including alirocumab.

57. There are significant differences in structure between alirocumab and Family 1. The heavy chain variable region of alirocumab shares between 49-52% sequence identity with the members of that family, whereas the light chain variable region of alirocumab shares between 43-46% identity. Ex. X2A-B. Taking into consideration both heavy and light chains, alirocumab shares at most 49% (26H5, 27E7) sequence identity with the antibodies in that family. Ex. X2C. There are significant differences in the CDR regions. The heavy chain CDRs of alirocumab are between 31-36% identical to the members of that family, whereas the light chain CDRs of alirocumab are between 18-21% identical. Ex. X2A-B. There are also differences in the lengths of the CDRs. Ex. X2A-B. As one example, the heavy chain CDR H3 of alirocumab is 3 amino acids longer than any member of that family. Ex. X2A. As another example, the light chain CDR L1 of alirocumab is 3 amino acids longer than any member. Ex. X2B.

58. There are significant differences in structure between alirocumab and Family 2. The heavy chain variable region of alirocumab shares between 74-76% sequence identity with the members of that family, whereas the light chain variable region of alirocumab shares between 46-48% identity. Ex. X2A-B. Taking into consideration both heavy and light chains, alirocumab shares at most 62% (9H6) sequence identity with the antibodies in that family. Ex.

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X2C. The CDR regions of alirocumab are only 30-33% identical to the members of that family, with the light chain CDRs being only between 9-15% identical. Ex. X2A-C.

59. There are significant differences in structure between alirocumab and Family 3. The heavy chain variable region of alirocumab shares between 66-67% sequence identity with the members of that family, whereas the light chain variable region of alirocumab shares between 67-69% identity. Ex. X2A-B. Taking into consideration both heavy and light chains, alirocumab shares at most 68% sequence identity with the antibodies in that family. Ex. X2C. The heavy chain CDRs of alirocumab are between 19-22% identical to the members of that family. Ex. X2A. The heavy chain CDR H3 of alirocumab is 9 amino acids shorter than the members of that family. Ex. X2A.

60. There are significant differences in structure between alirocumab and Family 5. The heavy chain variable region of alirocumab shares between 81-82% sequence identity with the members of that family, whereas the light chain variable region of alirocumab shares 65% identity. Ex. X2A-B. The heavy chain CDRs of alirocumab are between 56-58% identical to 23B5 or 25G4, whereas the light chain CDRs of alirocumab are between 30-33% identical. Ex. X2A-B. There are also differences in CDR length. For example, the heavy chain CDR H3 of alirocumab is 3 amino acids shorter than 23B5 or 25G4, whereas the light chain CDR L1 of alirocumab is 6 amino acids longer than 23B5 or 25G4. Ex. X2A-B.

61. There are significant differences in structure between alirocumab and 12H11. The heavy chain variable region of alirocumab is 74% identical to 12H11, whereas the light chain variable region of alirocumab is 92% identical to 12H11. Ex. X2A-B. Taking into consideration both heavy and light chains, alirocumab is 83% identical to 12H11. The heavy chain CDRs of alirocumab share 42% sequence identity with 12H11, whereas the light chain

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CDRs share 79% identity. Ex. X2A-B. The heavy chain CDR H3 of alirocumab is 4 amino acids longer than the CDR H3 of 12H11. Ex. X2A.

62. There are significant differences in structure between alirocumab and Family 7. The heavy chain variable region of alirocumab is 69% identical to the members of that family, whereas the light chain variable region of alirocumab is 45% identical. Ex. X2A-B. The heavy chain CDRs of alirocumab are between 31-33% identical to the members of that family, whereas the light chain CDRs of alirocumab are 21% identical. Ex. X2A-B. Overall, the CDR regions of alirocumab are between 26-28% identical to the members of that family. Ex. X2C. There are also differences in the lengths of the CDRs. As one example, the heavy chain CDR H3 of alirocumab is 4 amino acids shorter than any member of that family. Ex. X2A. As another example, the light chain CDR L1 of alirocumab is 4 amino acids longer than any member. Ex. X2B.

63. There are significant differences in structure between alirocumab and 31G11. The heavy and light chain variable regions of alirocumab share 71% and 46% sequence identity with 31G11, respectively. Ex. X2A-B. Taking into consideration both heavy and light chains, alirocumab shares 59% sequence identity with 31G11. Ex. X2C. There are significant differences in the CDR regions. The heavy chain CDRs of alirocumab are 36% identical to 31G11, whereas the light chain CDRs of alirocumab are 21% identical. Ex. X2A-B. Overall, the CDRs of alirocumab are 29% identical to 31G11 and they differ in length in the CDR H3 and CDR L1 regions. Ex. X2A-C.

64. To put into perspective the significance of the structural differences observed between the disclosed antibodies and alirocumab, I compared the sequence of one of the disclosed antibodies – 12H11 – to antibodies that bind antigens completely unrelated to PCSK9.

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The antibodies included in this analysis were identified in a Pubmed BLAST search for antibodies having significant sequence homology with the heavy and light chain variable regions of 12H11. The results of those alignments are shown in Exs. X2A and X2B.

65. Those comparisons show that antibodies that bind to unrelated antigens – *i.e.*, anti-influenza A antibody (Ex. 80, PDB Accession No. 3ZTJ, REGN02799024), anti-rabies virus antibody (clone sc4117 in Ex. 84, Kramer, REGN02798999) – are closer in sequence to the disclosed antibody than alirocumab is. In addition, the anti-influenza and anti-rabies were compared to alirocumab (along with the 30 Amgen antibodies). This comparison showed that they are 79% and 87% identical to the variable region of alirocumab, respectively. Ex. X2C. This analysis also illustrates that antibodies having identical or nearly identical framework sequences can bind to completely unrelated antigens. I note that this is consistent with the teachings of the asserted patents, which instruct that *unrelated* antibodies can “share a common germline framework heritage.” Ex. 15, 165 Patent at 97:61-67 (emphasis added).

66. I reviewed the expert report and accompanying exhibits of Dr. Federico Mingozi. Dr. Mingozi performed an in vitro binding assay to test whether the antibody referred to as [REDACTED] Mingozi Rpt. at ¶¶7-9. I understand that the [REDACTED]  
[REDACTED]  
[REDACTED] As expected,  
[REDACTED] Mingozi Rpt. at ¶9. In my opinion, this analysis illustrates that the differences in primary structure observed between alirocumab and the antibodies disclosed in the asserted patents – including 12H11 – mean that one cannot predict, visualize, or recognize whether alirocumab would be within the genus of antibodies having the claimed features. Indeed, one could not predict whether an antibody with

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these levels of differences would bind to PCSK9, because antibodies with fewer differences bind to the flu or rabies viruses.

67. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

68. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

69. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

70. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

71. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

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72. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

73. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

74. [REDACTED]

[REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like alirocumab.

75. I compared the primary structures of 1D05, AX132, J16 and 300N against 21B12 and 31H4 – the only antibodies that the patent teaches fall within the scope of any asserted claim.

I also compared the structures of the third party and Regeneron antibodies [REDACTED]

[REDACTED]

Heavy and light chain variable region sequence alignments are shown in Exs. X3A-C, X4A-C, X5A-C, and X7A-C.

76. There are significant structural differences between 1D05 and the only antibodies shown by the patent to fall within the claims – 21B12 and 31H4. The heavy chain of 1D05 is 67% and 47% identical to 21B12 and 31H4, respectively, whereas the light chain of 1D05 is 45% and 47% identical to those antibodies. Ex. X3A-B. Taking both chains into account, 1D05 is

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57% identical to the variable region of 21B12 and 47% identical to the variable region of 31H4.

Ex. X3C.

77. Considering only the CDRs, the heavy chain CDRs of 1D05 are 29% and 20% identical to 21B12 and 31H4, respectively, whereas the differences in light chain CDRs between 21B12 and 31H4 are difficult to quantify because the number of differences is greater than or equal to the total length of 1D05 light chain CDRs. Ex. X3A-B. For example, for 21B12, the number of differences with 1D05 light chain CDRs is 27, but the total number of CDR residues for 1D05 is 26 due to differences in CDR lengths. Ex. X3B. Therefore, the ratio of differences to 1D05 CDR length is >1 leading to a “negative” percent identity. Overall, the CDRs of 1D05 share only 17% and 13% sequence identity with 21B12 and 31H4, respectively. Ex. X3C. I note that there are significant differences in CDR length between the antibodies. The heavy chain CDR H3 of 1D05 is 22 amino acids in length – which is 16 amino acids longer than 21B12 and 8 amino acids longer than 31H4. Ex. X3A. As described in detail below, the CDR H3 region of 1D05 is involved in making important contacts with PCSK9.

78. Even assuming that [REDACTED] do possess the functional limitations, there are significant structural differences between 1D05 and each of the antibodies in the families identified in Exs. X3A-C. The heavy chain variable region of 1D05 shares at most between 66-69% identity (*see* Family 1) and at a minimum approximately 44% identity with antibodies that Amgen contends fall within the claims. Ex. X3A-B. The light chain variable region of 1D05 shares at most 83% identity (Family 5 - 23B5, 25G4) and at minimum approximately 42% identity (*see* Family 1). Ex. X3B. Taking into consideration both heavy and light chains, 1D05 shares at most 63-64% identity

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(Family 5 - 23B5, 25G4) with antibodies that Amgen contends meet the recited limitations. Ex. X3C.

79. There are also significant differences in the CDR regions. The heavy chain CDRs of 1D05 are at most between 29-31% identical (*see* Family 1) and at a minimum are approximately 14% identical to the antibodies that Amgen contends fall within the scope of any asserted claim. Ex. X3A. The light chain CDRs of 1D05 are at most between 46-54% identical (Family 5 - 23B5, 25G4) and at a minimum 0% identical to the antibodies that Amgen contends meet the claims. Ex. X3B. There are also differences in the lengths of the CDRs. For example the heavy chain CDR H3 of 1D05 is 4 amino acids longer than the longest CDR H3 of the disclosed antibodies (*see* Family 3) and is 17 amino acids longer than the shortest CDR H3 of the disclosed antibodies (12H11). Ex. X3A.

80. Notably, antibodies that bind to antigens unrelated to PCSK9 are closer in sequence to 1D05 than the antibodies disclosed in the asserted patents are. Thrombotic thrombocytopenic purpura (TTP) is a disease that is caused by autoantibodies to an autoantigen called ADAMTS13. As shown in Exs. X3A and X3B, these antibodies (denoted as TTP-A9, TTP-A10, and TTP-A27; Genbank heavy/light chain sequences DQ021405, DQ021406, DQ021407, DQ021408, DQ225093, and DQ225094, respectively), have heavy chain variable regions that share 76% identity with 1D05 and light chain variable regions that share between 81-83% identity. Overall, these antibodies are between 78-79% identical to 1D05. Ex. X3C. In my opinion, this analysis illustrates that the differences in primary structure observed between 1D05 and the antibodies disclosed in the asserted patents mean that one cannot predict, visualize, or recognize whether 1D05 would be within the genus of antibodies having the claimed features.

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Indeed, one could not predict whether an antibody with these levels of differences would bind to PCSK9, because antibodies with fewer differences bind to ADAMTS13.

81. There are also significant differences in structure between AX132 and the only antibodies shown by the patent to fall within the claims – 21B12 and 31H4. The heavy chain of AX132 is 55% and 67% identical to 21B12 and 31H4, respectively, whereas the light chain of AX132 is 46% and 51% identical to those antibodies. Ex. X4A-B. Taking both chains into account, AX132 is 51% identical to the variable region of 21B12 and 59% identical to the variable region of 31H4. Ex. X4C.

82. Considering only the CDRs, the heavy chain CDRs of AX132 are 36% and 22% identical to 21B12 and 31H4, respectively, whereas the light chain CDRs of AX132 are 11% identical to 21B12 and 21% identical to 31H4. Ex. X4A-B. Overall, the CDRs of AX132 share only 25% and 22% sequence identity with 21B12 and 31H4, respectively. Ex. X4C. I note that the heavy chain CDR H3 of AX132 is 9 amino acids in length, which is 3 amino acids longer than the CDR H3 of 21B12 and 5 amino acids shorter than the CDR H3 of 31H4. Ex. X4A.

83. Even assuming that [REDACTED] do possess the functional limitations, there are significant structural differences between AX132 and each of the antibodies in the families identified in Exs. X4A-C. The heavy chain variable region of AX132 shares at most between 74-75% identity (Family 5 - 23B5, 25G4) and at a minimum approximately 54-57% identity (*see* Family 1) with antibodies that Amgen contends fall within the claims. Ex. X4A. The light chain variable region of AX132 shares at most 68-69% identity (Family 5 - 23B5, 25G4) and at minimum approximately 44-46% identity (*see* Family 1). Ex. X4B. Taking into consideration both heavy and light chains,

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AX132 shares at most 71% identity (Family 5 - 23B5, 25G4) with antibodies that Amgen contends meet the recited limitations. Ex. X4C.

84. There are also significant differences in the CDR regions. The heavy chain CDRs of AX132 are at most between 36-44% identical (*see* Family 1) and at a minimum are approximately 6-8% identical (*see* Family 3) to the antibodies that Amgen contends fall within the scope of any asserted claim. Ex. X4A. The light chain CDRs of AX132 are at most between 39-50% identical (Family 5 - 23B5, 25G4) and at a minimum between 7-18% identical (*see* Family 1) to the antibodies that Amgen contends meet the claims. Ex. X4B. There are also differences in the lengths of the CDRs. I note that the heavy chain CDR H3 of AX132 is 9 amino acids in length, which differs in length from the CDR H3 of any disclosed antibody that Amgen contends meets the recited limitations. Ex. X4A.

85. There are also significant differences in structure between J16 and the only antibodies shown by the patent to fall within the claims – 21B12 and 31H4. The heavy chain of J16 is 75% and 49% identical to 21B12 and 31H4, respectively, whereas the light chain of J16 is 47% and 48% identical to those antibodies. Ex. X5A-B. Taking both chains into account, J16 is 62% identical to the variable region of 21B12 and 48% identical to the variable region of 31H4. Ex. X5C.

86. Considering only the CDRs, the heavy chain CDRs of J16 are 36% and 17% identical to 21B12 and 31H4, respectively, whereas the light chain CDRs of J16 are 4% identical to 21B12 and 4% identical to 31H4. Ex. X5A-B. Overall, the CDRs of J16 share only 22% and 11% sequence identity with 21B12 and 31H4, respectively. Ex. X5C. I note that the heavy chain CDR H3 of J16 is 9 amino acids in length, which is 3 amino acids longer than the CDR H3 of 21B12 and 5 amino acids shorter than the CDR H3 of 31H4. Ex. X5A. Moreover, the light

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chain CDR L1 of J16 is 11 amino acids long, which is 3 amino acids shorter than the CDR L1 of 21B12 and 31H4. Ex. X5B.

87. Even assuming that [REDACTED] do possess the functional limitations, there are significant structural differences between J16 and each of the antibodies in the families identified in Exs. X5A-C. The heavy chain variable region of J16 shares at most between 75-79% identity (*see* Family 1) and at a minimum approximately 45-47% identity (*see* Family 3) with antibodies that Amgen contends fall within the claims. Ex. X5A. The light chain variable region of J16 shares at most 83% identity (Family 5 - 23B5, 25G4) and at minimum approximately 43-44% identity (*see* Family 7). Ex. X5B. Taking into consideration both heavy and light chains, J16 shares at most 68% identity (Family 5 - 23B5, 25G4) with antibodies that Amgen contends meet the recited limitations. Ex. X5C.

88. There are also significant differences in the CDR regions. The heavy chain CDRs of J16 are at most between 36-42% identical (*see* Family 1) and at a minimum are approximately 6-8% identical (*see* Family 3) to the antibodies that Amgen contends fall within the scope of any asserted claim. Ex. X5A. The light chain CDRs of J16 are at most between 48-56% identical (Family 5 - 23B5, 25G4) and at a minimum are difficult to quantify (“-4%”) to the antibodies that Amgen contends meet the claims. Ex. X5B. There are also differences in the lengths of the CDRs. I note that the heavy chain CDR H3 of J16 is 9 amino acids in length, which differs in length from the CDR H3 of any disclosed antibody that Amgen contends meets the recited limitations. Ex. X5A.

89. Although 300N shares sequence homology with antibodies in Family 3 (see Ex. X7A-C), I note that these antibodies are all close in sequence to the germline gene from which

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they were derived. Ex. X7A-C. In fact, the germline gene sequence is closer to the sequence of 300N than the sequence of 8A3 is to 300N. [REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

90. [REDACTED]

[REDACTED]. For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

91. I understand that [REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

92. I understand that [REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

93. I understand that [REDACTED]

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[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

94. I understand that [REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

95. I understand that [REDACTED]

[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

96. I understand that [REDACTED]

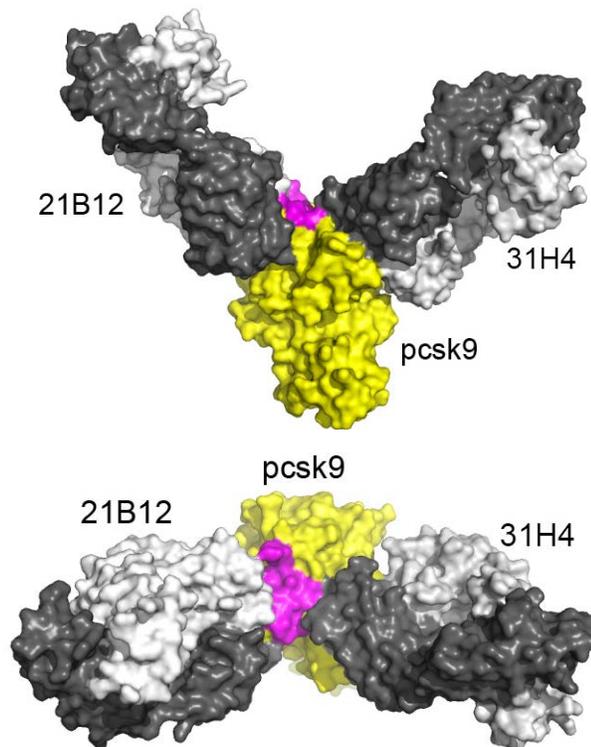
[REDACTED] For at least the reasons stated above, those antibodies are not representative of an antibody having a structure like 1D05, or an antibody having a structure like AX132, or an antibody having a structure like J16.

97. I considered Dr. Eck's analysis of the binding characteristics of the other anti-PCSK9 antibodies not disclosed in the asserted patents, but that fall within the genus, including alirocumab. *See* Eck Rpt. at ¶¶45-58. As described in Dr. Eck's report, those antibodies interact with PCSK9 at different epitope locations and through a variety of diverse mechanisms, which differ from those of the antibodies disclosed in the patent. Eck Rpt. at ¶¶47-57. Because an

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antibody's binding characteristics, including its epitope location and mechanisms of binding (*i.e.*, location and types of non-covalent bonds), are determined by its structure, differences in binding characteristics reflect differences in structures between antibodies.

98. As described by Dr. Eck, 21B12 and 31H4 each contact PCSK9 at regions that are on either side of, and not directly on top of, the area contacted by the EGF $\alpha$  domain (again colored in magenta). Eck Rpt. at ¶¶42-43. (In the picture, the heavy chains of the 21B12 and 31H4 antibodies are colored dark gray and the light chains are colored light gray).



99. I understand that Dr. Eck's opinions are consistent with the teachings of the asserted patents. For example, the patents instruct that the binding sites for 21B12 and 31H4 only "partially overlap with the position of the EGF $\alpha$  domain of LDLR." *See* Ex. 15, 165 Patent at 103:14-16; *see also* Fig. 20A. *See* Eck, ¶¶42-43. Table 12 of the patents provides a list of residues on PCSK9 that are bound by both EGF $\alpha$  and the antibodies. Of the 15 core residues on PCSK9 that interact with EGF $\alpha$ , only 3 are within 5 angstroms of 31H4 while only 6 are within 5

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angstroms of 21B12. *See* Ex. 15, 165 Patent at Table 12. Moreover, I understand that Dr. Eck's opinion that the epitope for 12H11 only partially overlaps with the EGFA binding site is consistent with the arginine-scanning results which show that only 2 of the 15 residues on PCSK9 that interact with EGFA are part of the epitope for 12H11. *See* Ex. 15, 165 Patent at Fig. 27D, Table 39.5; *see* Eck Rpt. at ¶79.

100. [REDACTED]

[REDACTED]

[REDACTED] In comparison, Dr. Eck explained that other antibodies not disclosed in the asserted patents – including alirocumab, 1D05, AX132, and J16 – bind to a different epitope location than any of the disclosed antibodies that more completely overlaps with the EGFA binding site. *See* Eck Rpt. at ¶¶62-70.

101. [REDACTED]

[REDACTED]

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102. Dr. Eck has considered the details of the crystal structures of 21B12, 31H4, and alirocumab. Eck Rpt. at ¶¶42, 45, 58. [REDACTED]

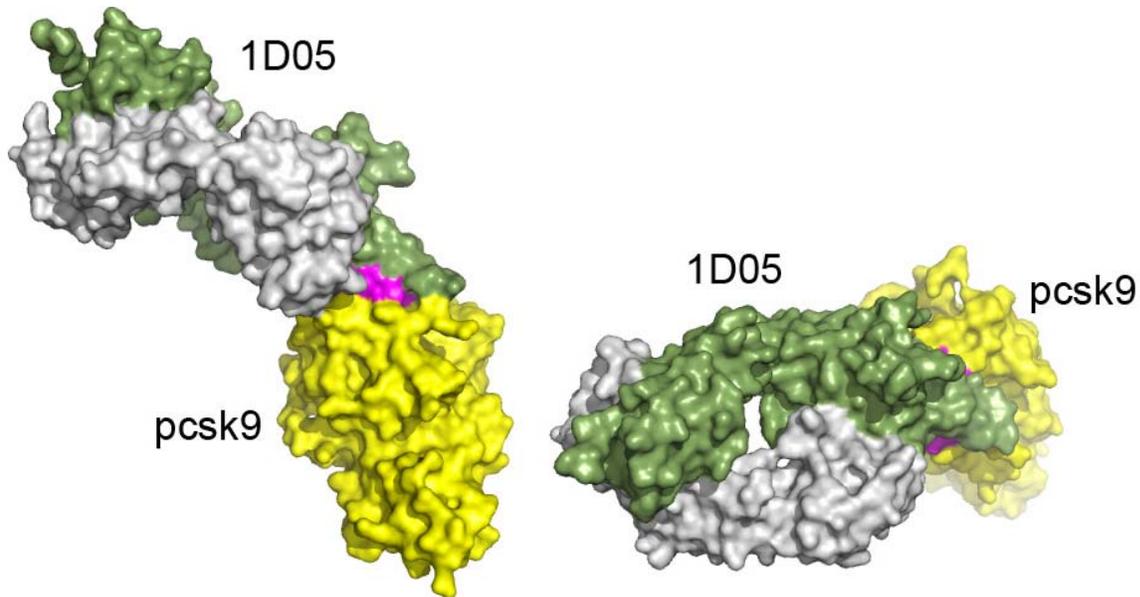


103. I understand that Regeneron conducted arginine-scanning experiments in order to assess the interaction between alirocumab and PCSK9. Ex. 56, 371 Patent at Example 16. 21B12 and 31H4 were also included in these experiments. Control III in Table 27 is defined in the 371 Patent as “anti-hPCSK(mAbs SEQ ID NO:49/23 (WO 2009/026558),” which I

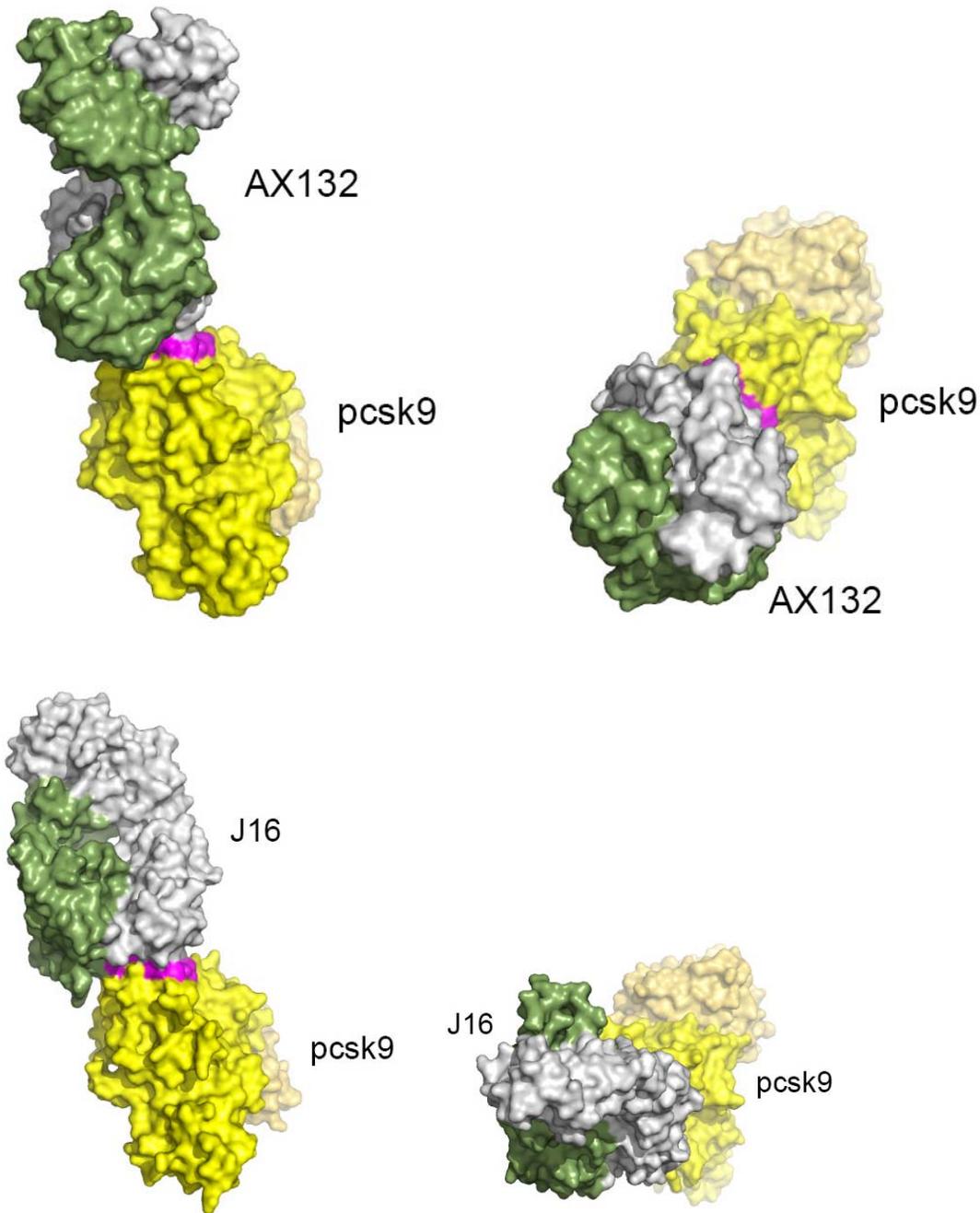
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understand to be Amgen’s 21B12 antibody disclosed in Amgen’s PCT patent application. Ex. 56, 371 Patent at 28:3-4; *see* Ex. 58, WO 2009/026558. Control II in Table 27 is defined in the 371 Patent as “anti-hPCSK9 mAbs SEQ ID NO:67/12 (WO 2009/026558),” which I understand to be Amgen’s 31H4 antibody disclosed in Amgen’s PCT patent application. Ex. 56, 371 Patent at 26:39-40; *see* Ex. 58, WO 2009/026558. *See also* Ex. 81, MacDonald Tr. at 108:5-110:5. The results of these experiments showed that mutating residue D238 to arginine dramatically affects the ability of alirocumab to interact with PCSK9. Ex. 56, 371 Patent at 39:62-67, Table 27. However, the D238 mutation did not affect the interaction between PCSK9 and either 21B12 or 31H4. Ex. 56, 371 Patent at 39:62-67, Table 27. In my opinion, these results show that the binding site of alirocumab differs from the binding site of 21B12 and 31H4.

104. As Dr. Eck describes, the complexes of 1D05, AX132, and J16 each show that the antibody binds on top of the EGFA site. Eck Rpt. at ¶¶60-61, 64-65, 67-68.



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105. Dr. Eck has considered the details of the crystal structures of 21B12, 31H4, 1D05, AX132, and J16. Eck Rpt. at ¶¶45, 59. Again, there are many differences in the ways that these antibodies contact PCSK9 at the level of individual amino acids. According to Dr. Eck, 1D05, AX132, and J16 do not make a single interaction with PCSK9 that is structurally equivalent to an interaction made by 21B12 or 31H4. Eck Rpt. at ¶¶63, 66, 69, Tables 1-5. And the different

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structures of these antibodies lead to completely different binding modes and interactions. The differences lead to 1D05, AX132, and J16 interacting centrally with the EGF $\alpha$  domain site, while 21B12 and 31H4 bind on either side.

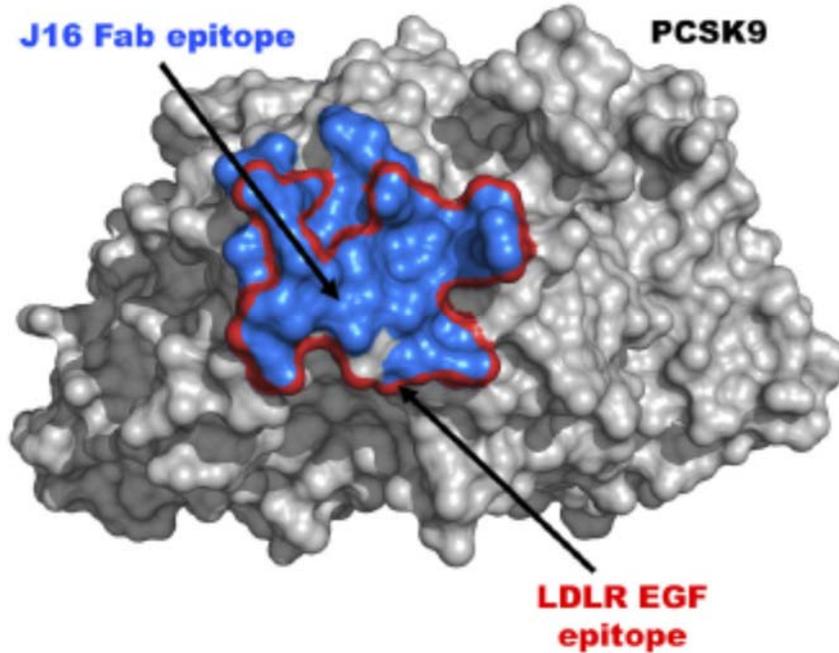
106. I understand that Dr. Eck's opinions are consistent with descriptions of the binding locations of 1D05 and J16 in the published literature. The x-ray structure of 1D05 in complex with PCSK9 was reported by Ni and colleagues. *See* Ex. 61, Ni at REGN02449913. The article explains that "with the exception of Ser153 and Ile154, which are disordered in the PCSK9 $\Delta$ C/1D05 complex, all the amino acids of PCSK9 that contact EGF(A) also interact with 1D05." Ex. 61, Ni at REGN02449917. Moreover, I note that [REDACTED]

[REDACTED] While not proof that 1D05 "binds to" selected residues on PCSK9 as that term has been construed by the Court, these descriptions are consistent with Dr. Eck's opinion that 1D05 contacts PCSK9 on top of the EGF $\alpha$  binding site. Eck Rpt. at ¶¶60-62.

107. A research article by Liang and colleagues titled "Proprotein Convertase Subtilisin/Kexin Type 9 Antagonism Reduces Low-Density Lipoprotein Cholesterol in Statin-Treated Hypercholesterolemic Nonhuman Primates" describes the x-ray structure of J16 in complex with PCSK9. Ex. 63, *J. Pharmacol. and Exp. Therap.* (2012) 340:228-236. The article explains that "J16 binds to a nonlinear, three-dimensional epitope that almost *perfectly overlaps* with the LDLR EGF-A domain binding site on PCSK9." Ex. 63, REGN02449904 at 907 (emphasis added). Figure 2B of the article, reproduced below as Figure 13, provides a comparison of the residues buried upon J16 binding to the residues that are buried by the EGF $\alpha$  domain of LDLR. Again, while not proof that J16 "binds to" specific residues according to the

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Court's construction of that term, the description in Liang is consistent with Dr. Eck's opinion that J16 contacts PCSK9 on top of the EGFa binding site. Eck Rpt. at ¶¶67-68.



**Figure 13:** Epitope residues for J16 and LDLR EGFa on PCSK9.

108. Because where an antibody binds is dictated by its structure, differences in epitope locations between antibodies reflect differences in antibody structures. In my opinion, this shows that the antibody structures described in the asserted patents are not representative of the diversity of structures encompassed within a genus that also includes alirocumab, 1D05, or J16.

109. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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110. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The asserted patents explain that antibodies in different bins “are representative of *different types of epitope locations* on PCSK9...” Ex. 15, 165 Patent at 113:12-13 (*emphasis added*). In my opinion, one skilled in the art reading the patents would understand that the bin 1 and/or bin 3 antibodies are not representative of a genus that includes bin 2 antibodies, such as alirocumab or 1D05.

111. The fact that 12H11 is characterized as a bin 2 antibody according to the asserted patents does not show that it binds to the same epitope location as alirocumab, 1D05 or J16.

[REDACTED]

[REDACTED] In my opinion, as described above, the epitopes for alirocumab, 1D05, and J16 differ significantly from 12H11, with the epitopes for alirocumab, 1D05, and J16 overlapping more completely with the EGFA binding site on PCSK9. As discussed in more detail below, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

112. As described above, the epitopes of the disclosed examples in the Amgen patent are not like those of alirocumab and are not like those of the third party PCSK9 antibodies

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discussed. That is further evidence that the Amgen examples are not representative of alirocumab or of those other third party antibodies.

113. In addition to epitope location, I also considered Dr. Eck's comparisons of the binding mechanisms between the antibodies disclosed in the asserted patents and the other anti-PCSK9 antibodies that fall within the claimed genus, including alirocumab. Eck Rpt. at ¶¶53, 54, 56, 63, 66, 69, Tables 1-5. As Dr. Eck explained, there are significant differences in the mechanisms through which those antibodies interact with PCSK9. Eck Rpt. at ¶¶53, 54, 56, 63, 66, 69, Tables 1-5.

114. Dr. Eck has considered the details of the crystal structures of 21B12, 31H4, and alirocumab. Eck Rpt. at ¶58, Appendix A. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

115. Dr. Eck has considered the details of the crystal structures of 21B12, 31H4, 1D05, AX132, and J16. Eck Rpt. at ¶59. Again, there are many differences in the ways that these antibodies contact PCSK9 at the level of individual amino acids. Eck Rpt. at ¶¶62-63, 65-66, 68-69. According to Dr. Eck, 1D05, AX132, and J16 do not make a single interaction with PCSK9 that is structurally equivalent to an interaction made by 21B12 or 31H4. Eck Rpt. at ¶¶63, 66, 69, Tables 3-5. And the different structures of these antibodies lead to completely different binding modes and interactions. Eck Rpt. at ¶¶62-63, 65-66, 68-69. The differences lead to

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1D05, AX132, and J16 interacting centrally with the EGF $\alpha$  domain site, while 21B12 and 31H4 bind on either side. Eck Rpt. at ¶¶60-62, 64-65, 67-68.

116. The asserted patents do not provide an x-ray structure for 12H11 – or for any other bin 2 antibody disclosed in the patents. I understand that Amgen is relying, at least in part, on the results of arginine/glutamic acid-scanning experiments as evidence that 12H11 meets the binding requirements of the asserted claims. Using this approach, Amgen mutated amino acids on PCSK9 in order to identify “residues in the antigen which contact or are buried by the antibody.” Ex. 15, 165 Patent at 114:2-5. While this technique provides information about which residues on the *antigen* are part of an antibody’s structural epitope, it fails to provide any information about the structure of the *antibody* itself, including the mechanisms (*i.e.*, antibody chains involved, types of non-covalent bonds) through which the antibody interacts with an antigen. For at least that reason, the asserted patents fail to demonstrate that the binding mechanisms of 12H11 are representative of the variety of mechanisms through which other antibodies not disclosed in the asserted patents interact with PCSK9. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

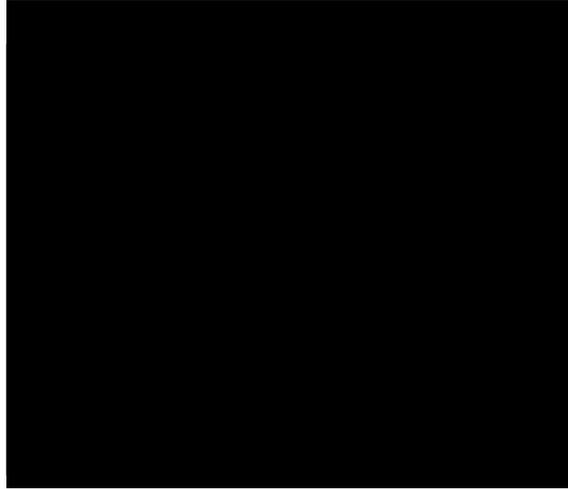
117. Dr. Eck looked at the amino acids identified by Amgen in its arginine scanning experiment for 12H11. Eck Rpt. at ¶78. He concludes that, taking that experiment at face value, 12H11 antibody contacts an area on PCSK9 that is to the side of, and not directly on, the area contacted by the EGF $\alpha$  domain. Eck Rpt. at ¶¶79-80, 85. In the picture, the residues listed by Amgen from its arginine scanning experiment for 12H11 are colored in red and orange (red if the

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residue was listed as affecting the EC50 of antibody binding and orange if the residue was listed as affecting the Bmax of antibody binding). [REDACTED]

[REDACTED]

That contact area for 12H11 is different from that contacted by alirocumab, 1D05, AX132, and J16.



118. I also understand that Amgen is relying, at least in part, on the results of binning experiments to show that some of the disclosed antibodies meet the binding requirements of the asserted claims. I understand that binning experiments can be used to determine whether antibodies have overlapping epitopes on PCSK9. However, like arginine/glutamic acid-scanning experiments, binning results do not provide information about the structure of the *antibody* or the mechanisms by which the antibody interacts with PCSK9.

119. Importantly, as Dr. Eck explained, antibodies having different structures can bind to identical or overlapping epitopes through completely different mechanisms. Eck Rpt. at ¶92. This shows that antibodies having different structures are capable of binding to the same residues or epitope. I note that [REDACTED]

[REDACTED]



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[REDACTED]

[REDACTED]

123. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

124. [REDACTED]

125. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

126. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

127. Significantly, not all bin 2 antibodies are neutralizing. The asserted patents teach that one of the bin 2 antibodies – 25A7.1 – is non-neutralizing. Ex. 15, 165 Patent at 81:21-25. [REDACTED]

[REDACTED]

[REDACTED] An antibody that almost completely overlaps with the EGFa binding site (*i.e.*, [REDACTED]) would be expected to strongly block the binding of PCSK9 to the LDLR. In my opinion, these results are further evidence [REDACTED]

[REDACTED]

128. In my opinion, [REDACTED]

[REDACTED]

[REDACTED] As Dr. Eck explained, the epitope for 12H11 only partially overlaps with the EGFa binding site on PCSK9. Eck Rpt. at ¶79. This is consistent with the arginine/glutamic acid-scanning results described in the asserted patents, which show that the epitope for 12H11 only overlaps with 3 of the 15 residues that are bound by EGFa. Ex. 15, 165 Patent at Example 39, Table 39.5.

129. The asserted patents do not provide any evidence that 12H11 blocks binding of PCSK9 to the LDLR. Therefore, one skilled in the art reading the specifications would not understand that 12H11 meets this functional limitation. I [REDACTED]

[REDACTED] While not all antibodies that block receptor binding strongly qualify as an [REDACTED] –

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which binds an epitope that almost completely overlaps with the EGFA binding region – to strongly block receptor binding. This is further evidence that 12H11 is not an [REDACTED]

130. I understand that through its screening process [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

131. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED].<sup>1</sup>

132. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

<u>Antibody</u>	<u>Type</u>	<u>"binds to [residues]"</u>	<u>Receptor Blocking</u>	<u>Asserted Claims</u>
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**Table 3**

133. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].<sup>2</sup>

\_\_\_\_\_

<sup>1</sup> [REDACTED]

<sup>2</sup> [REDACTED]

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134. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

135. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

136. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

137. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

138. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

139. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

140. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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141. [REDACTED]

[REDACTED]

142. [REDACTED]

[REDACTED]

143. [REDACTED]

[REDACTED]

144. [REDACTED]

[REDACTED]

145. [REDACTED]

[REDACTED]

146. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

147. [REDACTED]

[REDACTED]

[REDACTED]

148. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] alirocumab “completely blocked” the binding of PCSK9 to either LDLR or LDLR-EGFa. Ex. 56, 371 Patent at 32:33-35, Example 8. [REDACTED]

[REDACTED]

149. In my opinion, two other third party antibodies – 1D05 and J16 – are also [REDACTED]

[REDACTED]

[REDACTED] The article by Ni and colleagues,

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which discloses the structure of 1D05 bound to PCSK9, is titled “A PCSK9-binding antibody that *structurally mimics the EGF(A) domain* of LDL-receptor reduces LDL cholesterol in vivo.” Ex. 61, Ni at REGN02449913. The article explains that the epitope of 1D05 includes “the entire LDLr EGF(A) binding site” on PCSK9. *See* Ex. 61, Ni at REGN02449913. Moreover, the article describes that the CDR-H2 and CDR-H3 loops of 1D05 adopt a secondary structure that mimics the EGFa domain of the LDLR. The article states that:

Strikingly, superposition of the PCSK9/1D05 and PCSK9/EGF(A) structures reveals that the 1D05 CDR-H3 adopts a hairpin structure that *structurally mimics* two  $\beta$ -strands of EGF(A)...Thus, together with two  $\beta$ -strands of PCSK9 (residues 378-382 and 368-371), CDR-H3 forms an equivalent antiparallel four-stranded  $\beta$ -sheet...In addition, the tip of the CDR-H2 loop, composed of residues Gly50-Gly56, *structurally mimics* a helical turn in EGF(A) (residues Gly293-Asp299).

*See* Ex. 61, Ni at REGN02449917 (*emphasis added*).

150. The article also teaches that 1D05 strongly blocks the binding of PCSK9 to the LDLR with an IC<sub>50</sub> of 3.7 nM. *See* Ex. 61, Ni at REGN02449916, Fig. 1A.

151. In my opinion, J16 is another [REDACTED]

[REDACTED] Moreover, Liang and colleagues solved the x-ray structure of J16 in complex with PCSK9 and concluded that “J16 binds to a non-linear, three dimensional epitope that *almost perfectly overlaps with the LDLR EGFa domain binding site* on PCSK9.” Ex. 63, REGN02449904 at 907 (*emphasis added*). It was also shown that J16 “completely and dose-dependently block[s]” human and mouse PCSK9 binding to the LDLR. Ex. 63, REGN02449904 at 906.

152. The fact that, [REDACTED]

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[REDACTED]

153. [REDACTED]

[REDACTED]

154. [REDACTED]

[REDACTED]

155. In conclusion, there are multiple independent reasons why it is my opinion that the examples disclosed in the asserted patents are not representative of the structural variability of antibodies encompassed within the functionally claimed genus. The first independent reason is that the examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – are not representative of an antibody having a structure like alirocumab. The second independent

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reason is that the examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – are not representative of an antibody having a structure like 1D05. The third independent reason is that the examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – are not representative of an antibody having a structure like AX132. The fourth independent reason is that the examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – are not representative of an antibody having a structure like J16.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The sixth independent reason is that the examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – are all human antibodies and are, therefore, not representative of the structural diversity of a genus that includes other types of antibodies, such as mouse, chimeric, and humanized antibodies, as well as other non-human antibodies.

156. I also conclude that, because of the unpredictability and wide variability of antibody structures that possess the recited functional limitations, one skilled in the art cannot visualize or recognize other members of the genus based on the examples disclosed in the asserted patents. As described in detail above, there are significant differences in structure between alirocumab, the third party antibodies, and the examples disclosed in the asserted

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patents. One skilled in the art would not know, from the patent disclosure, that these structurally diverse antibodies would fall within the claimed genera.

157. Alirocumab has a substantially different amino acid sequence, particularly in the CDR regions, binds to a different epitope location, and interacts with PCSK9 using different binding mechanisms (*i.e.*, non-covalent bonds) as compared to 21B12 and 31H4 – the only antibodies shown by the specifications to meet the recited limitations of any asserted claim – as well as any other antibody that Amgen contends falls within the scope of any asserted claim. The specification does not suggest that the inventors were in possession of or had described an invention that encompasses the broad genus of antibodies covered by the claims.

158. Other anti-PCSK9 antibodies developed by third parties (1D05, AX132, J16), [REDACTED] have substantially different amino acid sequences, including CDR composition and length, and bind to different epitope locations using different binding mechanisms as compared to the antibody structures described in the asserted patents. For example, as described above, 1D05 binds to a unique epitope, is derived from a different heavy chain gene ( $V_H$  1-69), and has a CDR H3 that differs significantly in length from any antibody disclosed in the asserted patents. Thus, the structural features of the antibodies described in the asserted patents are not common to the broad genus of antibodies encompassed by the claims.

159. I note that not all of the antibodies included in the analysis were used to define the consensus sequences. The asserted patents explain that only antibodies having “similar groups of sequence” – defined as having fewer than 15 substitutions per 100 residues – in both the light and heavy chains were placed into one of the four groups that were used to define the CDR consensus sequences. *See* Ex. 15, 165 Patent at 98:17-26; Figure 13E.

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160. In my opinion, the antibodies that Amgen used to define the consensus sequences are clonally related. This is illustrated by the high degree of sequence homology observed between the members of a group, particularly in the CDR regions, notably CDR3. Clonally related antibodies are derived from the same B cell clone and, therefore, originate from the same set of gene re-arrangement events. As described in detail below, the common structural features identified in each consensus group are not found in other antibodies that fall within the scope of the asserted claims, including alirocumab.

161. To determine whether the consensus sequences identified by this analysis are common to other antibodies that fall within the claimed genus, I compared the consensus sequences for each of the four groups to the CDRs of the other members of the genus, including alirocumab. The patents describe 2 ways they derived their four consensus sequences. In Figs. 13F-13G, Amgen aligns groups of antibodies and derives consensus sequences for CDRs using “a hybrid combination of the Chothia method ..... and the Kabat method....” Ex. 15, 165 Patent at 47: 2-10. In Figs. 13H and 13I, the consensus CDRs were obtained “by the Kabat method alone.” Ex. 15, 165 Patent at 47:13-14. In Figs. 13F-13G, Amgen indicates residues that are common among all members of a group with an asterisk in a consensus sequence as an indication that those amino acids should be conserved. Residue positions that vary among members of a group are positions that can likely be altered and indicated with a gap in consensus sequence. Ex. 15, 165 Patent at 98:27-33. In Figs. 13H and 13I, Amgen provides a second set of consensus sequences without any gaps. They appear to have chosen consensus sequences that represent the most common CDR sequence found in their cohort of antibodies within each of their 4 groups. In 13H and 13I, they also use a shorter heavy chain CDR1 designation. In Exhibit X8, I combine both of their consensus sequence derivations in one figure. I reproduce the 6 CDRs for each of

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the 4 groups as depicted in Figs. 13H and 13I and indicate with a grey background those residue positions that were given asterisks in Figs. 13F and 13G. Beneath each of the 4 consensus sequences, I aligned the CDRs of the other antibodies not included in the patents, including alirocumab.

162. These comparisons show that the common structural features identified in Amgen's consensus analysis are not found in other antibodies that fall within the claimed genus, including alirocumab. As shown in Exhibit X8, there are significant differences between the consensus sequences for each of the groups and the other antibodies that fall within the genus including the amino acid positions that Amgen says should be conserved. As one non-limiting example, there are significant differences in sequence between the heavy chain CDR H3 consensus sequences and the other members of the genus. There are differences in length between the CDR H3 consensus sequences and the other members of the genus. As one example, the CDR H3 of alirocumab has a different length than any of the four consensus sequences. As another example, the CDR H3 of 1D05 differs in length from any of the four consensus sequences. As another example, there are significant structural differences between the light chain CDR L1 consensus sequences and the other members of the genus. Notably, the CDR L1 region of alirocumab is, at a minimum, 3 amino acids longer than any of the four consensus sequences.

163. In my opinion, the common structural features Amgen attempts to identify in Amgen's consensus analysis are not present in all members of a genus that includes an antibody like alirocumab. These structural features are also not found in all members of a genus that includes other third party antibodies (1D05, AX132, J16) and [REDACTED]

[REDACTED]

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164. In conclusion, there are multiple independent reasons why it is my opinion that there are no common structural features between the antibodies disclosed in the asserted patents and other members encompassed within the functionally claimed genus. The first independent reason is that there are no common structural features between examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – and an antibody having a structure like alirocumab. The second independent reason is that there are no common structural features between examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – and an antibody having a structure like 1D05. The third independent reason is that there are no common structural features between examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – and an antibody having a structure like AX132. The fourth independent reason is that there are no common structural features between examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – and an antibody having a structure like J16. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The sixth independent reason is that there are no common structural features between examples disclosed in the asserted patents – whether they include only 21B12 and 31H4 or whether they include additional antibodies that Amgen contends fall within the claims – which are all human antibodies and other types of antibodies

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that fall within the functionally claimed genus, such as mouse, chimeric, and humanized antibodies, as well as other non-human antibodies.

165. Looking at everything included in the patent descriptions, and considering that information from the perspective of a person of ordinary skill in the art at the relevant time, the patents do not provide a description that shows that the inventors possessed an invention that was broad enough to encompass a group of antibodies that includes alirocumab, other third party antibodies (1D05, AX132, J16), [REDACTED] [REDACTED] or any other antibodies structurally diverse from the disclosed species. The asserted patents fail to provide examples that are representative of the variability of antibody structures that possess the functional properties recited in the asserted claims. And the structural features identified in the patents are not common to the group of antibodies having the functional features recited in the asserted claims. The patents therefore fail to describe structural features common to the genus or a representative number of antibodies to correspond to the variable genus of antibodies allegedly encompassed by the claims. In my opinion, each of the asserted claims fails to meet the written description requirement and is, therefore, invalid.

166. To the extent that Amgen contends that 16F12 does not meet the recited limitations of the asserted claims, but that other antibodies in Family 7 fall within the claimed genus, I note that this shows the unpredictability of making even small changes in structure will have on an antibody's function. *See Ex. 1A-C.*

167. The asserted patents provide variable region sequences for the antibodies disclosed in the specification. Moreover, the patent specification directs the person of ordinary skill in the art to make antibodies close in structure to the disclosed antibodies. The specification provides insufficient teaching to one of ordinary skill in the art to make antibodies like

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alirocumab, which Amgen now asserts is encompassed by the asserted claims. The specification also provides insufficient teaching to one of ordinary skill in the art to make other antibodies encompassed by the claims, including third party antibodies, [REDACTED]

168. As one non-limiting example, the light chain CDR L1 consensus sequences for the four consensus groups only indicate that a few residues in the light chain CDR L1 are amenable to substitution. For example, all six members of consensus group 2 have identical light chain CDR L1 sequences and, therefore, the CDR L1 consensus sequence derived from those members does not teach that substitutions can be made at any of those residues. Moreover, the three members of consensus group 3 only differ at a single residue in the light chain CDR L1 region. In my opinion, this analysis teaches one skilled in the art to make antibodies having light chain CDR L1 structures that are similar to the disclosed antibodies. It also fails to teach one skilled in the art how to make changes to the consensus sequence to arrive at different structures that still have the desired functional properties. As shown in Exhibit X8, the light chain CDR L1 of other antibodies that fall within the genus, including alirocumab and other PCSK9 antibodies shown in the chart, differ in structure from the consensus sequences. The specification does not teach one skilled in the art that substitutions could be made to the disclosed antibodies to arrive at diverse structures, like alirocumab, that fall within the asserted claims.

169. As another non-limiting example, the consensus sequences for the heavy chain CDR H2 only teach that a few residues are amenable to substitution. The eleven members that made up consensus group 1 only differed at 4 of the 17 CDR H2 residues, while the three members of consensus group 3 only differed at 1 of the 17 CDR H2 residues. In my opinion, this analysis teaches one skilled in the art to make antibodies having heavy chain CDR H2

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structures that are similar to the disclosed antibodies. It also fails to teach one skilled in the art how to make changes to the consensus sequence to arrive at different structures that still have the desired functional properties. As shown in Exhibit X8, there are significant differences in the heavy chain CDR H2 sequences of alirocumab and other anti-PCSK9 antibodies as compared to the consensus sequences. This analysis fails to inform one skilled in the art how to make changes to the CDRs of the disclosed antibodies to arrive at antibodies having diverse structures, such as alirocumab.

170. I also note that the consensus analysis directs one of skill to make antibodies having CDRs that are the same length as the disclosed antibodies. However, as shown in Exhibit X8, other antibodies that fall within the scope of the asserted claims have CDRs that differ in length from the consensus groups. This analysis fails to teach one skilled in the art to make additions or deletions to the existing CDRs in order to generate antibodies having different CDR lengths. In my opinion, this would guide a person of ordinary skill to make antibodies having CDR sequences that are highly related to the antibodies disclosed in the asserted patents and, therefore, away from other antibodies falling within the genus that have diverse structures, such as alirocumab.

171. In my opinion, each of the asserted claims is invalid since the patent specifications do not provide an enabling disclosure that is commensurate in scope with each of those claims. A person of ordinary skill in the art could not use the disclosed antibodies as a starting point and make modifications to them to arrive at antibodies that are unrelated in structure but still fall within the scope of the asserted claims, including alirocumab. Furthermore, a person of ordinary skill could not use the disclosed antibodies as a starting point and make modifications to them to arrive at antibodies having structures like the third party

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antibodies (1D05, AX132, J16) and [REDACTED] discussed above.

There is also insufficient teaching in the Amgen specifications for a person of ordinary skill in the art to be able to make and use the full scope of the asserted claims – *i.e.*, antibodies that bind to particular residues as identified in the asserted claims – by virtue of simply having a desired residue or residues that the antibodies are intended to bind to.

172. [REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED] One of ordinary skill would have to test through trial and error experimentation to determine whether any amino acid changes affect the antibody’s function. In my opinion, the amount of experimentation necessary to modify the antibodies disclosed in the asserted patents to arrive at structures like alirocumab, or like the other anti-PCSK9 antibodies that fall within the genus but that were not disclosed in the asserted patents, is undue.

173. For example, the asserted patents do not teach adding additional residues in the CDRs beyond the examples disclosed. Moreover, the asserted patents do not suggest making an antibody having a heavy chain CDR H3 that is the length of the CDR H3 of 1D05. [REDACTED]

[REDACTED]  
[REDACTED].<sup>3</sup> Ex. X3A.

Because one cannot predict the effect that adding even a single amino acid in the CDRs would have on an antibody’s function, the amount of testing required to modify the existing antibodies to arrive at an antibody having a structure like 1D05 is undue.

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<sup>3</sup> [REDACTED]  
[REDACTED]

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174. In carrying out this process, the skilled artisan would have to test each of the antibodies, through trial and error experimentation, to determine whether they possess the desired functional characteristics. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] In my opinion, the amount of

experimentation necessary to make and identify such antibodies is undue in view of the limited teaching and guidance provided by the specification, and the asserted claims are invalid on that basis.

175. The amount of experimentation is even more undue to the extent one of ordinary skill in the art seeks to perform x-ray crystallography to determine whether any antibody that may be produced actually “binds to” a particular residue as identified in the asserted claims. If x-ray crystallography is necessary to determine the presence of binding between an antibody and a particular amino acid residue, one of ordinary skill in the art faces a nearly insurmountable, if not entirely impossible, task in attempting to make and use the full scope of the claimed invention in view of the limited teachings of the Amgen specifications. As discussed above,

[REDACTED]

[REDACTED]

[REDACTED]

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176. For example, [REDACTED]

177. It is my opinion that the patent specifications do not provide an enabling disclosure that is commensurate in scope with the claims. The patent specifications do not provide sufficient teaching, even when combined with the knowledge of a person of ordinary skill in the art at the time, to make and use antibodies that are not related to the disclosed antibodies without undue experimentation. It would require undue experimentation to do so because the patent provides no specific guidance or direction for how to make such an antibody other than those that are disclosed. As such, and as discussed above, the patent claims are invalid for lack of enablement for at least four independent reasons. First, it would require undue experimentation to modify the antibodies disclosed in the asserted patents to arrive at antibodies

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having diverse structures that still that meet the recited functional limitations of the asserted claims, such as alirocumab. Second, it would also require undue experimentation to modify the existing antibodies to arrive at any one of the antibodies having a structure like the third party antibodies (1D05, AX132, J16) or [REDACTED]

[REDACTED] Third, the patent specifications fail to provide sufficient teachings to one of ordinary skill in the art regarding how to make antibodies, other than those disclosed, that will bind to any of the particular residues identified in the asserted claims. Short of an extensive and undue experimental process, one of ordinary skill in the art cannot make and use the full scope of the varied antibodies encompassed by the full scope of the asserted claims. Lastly, if practicing the full scope of the asserted claims requires the completion of x-ray crystallography to seek to identify which particular residues are bound by an individual antibody, the amount of experimentation goes from undue to nearly, if not, impossible, and the asserted claims are invalid for lack of enablement for this independent reason as well.

**Supplemental Expert Report<sup>4</sup>**

178. Dr. Rees and Dr. Petsko both opine that the Asserted Patents teach many more antibody sequences beyond the sequences explicitly disclosed. However, in giving their opinions, they fail to consider whether the specific teachings of the patents – including CDR swapping or amino acid substitutions – direct a skilled person to make other antibodies that fall within the scope of the claims, as opposed to simply making other sequences that one would need to screen for the desired functional properties. This oversight is a fundamental flaw in their analyses. Tellingly, neither Dr. Rees nor Dr. Petsko ever states that a skilled person could use the

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<sup>4</sup> Citations in this section are to the Supplemental Report of Donald Siegel, M.D., Ph.D. which was served on December 30, 2015.

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teachings of the patents to get to the full diversity of structures covered by the claims – including structures like alirocumab and the Third Party Antibodies.

179. Neither Dr. Rees nor Dr. Petsko conducts the correct analysis for whether the Amgen patents provide written description support for the Asserted Claims. Neither of them states that the antibody examples in the Amgen patents are representative of the variability of the amino acid structures of the antibodies encompassed by each Asserted Claim. Neither of them states that the antibody examples in the Amgen patents are representative of the amino acid structure of alirocumab, or of the amino acid structures of any of the Third Party Antibodies. Neither of them states that there are structural features disclosed in the Amgen patents that are common to the antibodies encompassed by the Asserted Claims and that distinguish the claimed antibodies from unclaimed antibodies. Instead of responding directly to these points raised in my Opening Report, Drs. Petsko and Rees try to change the question, but, as indicated herein, the questions they choose to answer fail to address in any way whether the Amgen patent disclosure evidences that the Amgen inventors were in possession of the full scope of their claims or whether that disclosure enables one skilled in the art to visualize or recognize the full scope of those claims.

180. For example, Dr. Petsko compares the epitopes of various anti-PCSK9 antibodies. Petsko Rebuttal Rpt. at ¶¶351-366, 376-405. As described in my Opening Report and the Opening Report of Michael Eck, the epitopes for these antibodies are different from each other. But rather than appreciating the differences in epitopes (and the differences in antibody structure that allow the various antibodies to bind to these epitopes), Dr. Petsko attempts to “add up” the different binding regions to form a conglomerate area on PCSK9. Because the invention is to the antibodies rather than to any portion of PCSK9 itself, this analysis is exactly backwards.

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[REDACTED]

181. At paragraph 346 of the Petsko Report, Dr. Petsko states that “Amgen has defined the boundaries of the LDLR interface through 21B12 and 31H4” and further opines that “the only reasonable inference is that the space in between has also been defined.” Petsko Rebuttal Rpt. at ¶346. Again, Dr. Petsko improperly focuses on the structure of the antigen, rather than the antibodies. The problem is that Amgen is not claiming the “space” on PCSK9. [REDACTED]

[REDACTED]

[REDACTED] They have only invented and disclosed antibodies that bind at the edge of the EGFA interface.

182. Dr. Petsko’s focus on the antigen rather than the antibody leads him to ignore important differences in the way that an antibody binds to PCSK9. As described by Dr. Eck in his Opening Report (¶¶93, 95-96) and his Supplemental Report (¶¶10, 12, 23, 24), the way that an antibody binds to a particular amino acid on PCSK9 is different for different antibodies, and that shows that those skilled in the art cannot predict what the structure of the antibody will be from the fact that it binds to a particular PCSK9 amino acid. [REDACTED]

[REDACTED]

[REDACTED] That is because

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their structures are different. See Eck Opening Rpt. at ¶¶91-93; Eck Supplemental Rpt. at ¶¶23, 24.

183. In Figure 7 of the Petsko Report, Dr. Petsko presents [REDACTED]

[REDACTED]

184. Again, Dr. Petsko is not looking at individual antibodies. Rather, he is adding up the epitopes of several antibodies in an attempt to show that Amgen invented antibodies that cover the entire EGFA interface. This analysis misses the mark. Dr. Petsko focuses on the EGFA interface, but ignores the fact that Amgen did not describe in its patents any antibody that binds to that complete interface. [REDACTED]

[REDACTED]

[REDACTED] Dr. Petsko is forced to add up epitopes from different antibodies in an attempt to show that, as a group, they cover a significant portion of the EGFA interface because Amgen does not have a single antibody that, by itself, binds to that epitope location. In my opinion, Dr. Petsko's analysis fails to show that Amgen invented antibodies that bind to the same epitope location as alirocumab or the Third Party Antibodies. And that underscores that, even though alirocumab or any of the Third Party Antibodies might happen to bind to a single PCSK9 residue shared by one of the Amgen antibodies, Amgen did not possess or invent the full scope of

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antibodies that bind to that residue. This is because, as I explained in my Opening Report,

[REDACTED]

[REDACTED]

[REDACTED] Thus, the Asserted Patents fail to describe species that are representative of antibodies that are structurally similar to alirocumab or the Third Party Antibodies.

185. I also note that, strikingly, even when Dr. Petsko combines three different Amgen antibodies, the combination of those antibodies still does not completely cover the EGFA interface. Dr. Petsko only contends that [REDACTED]

[REDACTED] Petsko Rebuttal Rpt. at ¶358 (emphasis added). Figure 7 of the Petsko Report demonstrates that, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

186. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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187. This argument misses the point. The issue is not whether the epitopes simply “overlap with” 21B12 or 31H4, as Dr. Petsko suggests. The point is that alirocumab and the Third Party Antibodies bind to a different epitope location on PCSK9 as compared to 21B12 and 31H4. [REDACTED]

[REDACTED]

[REDACTED] Moreover, the fact that Dr. Petsko considers both 21B12 and 31H4 in combination in his analysis shows that, once again, he is improperly “adding up” the properties of different Amgen antibodies in an effort to demonstrate that Amgen invented an antibody like alirocumab or like the Third Party Antibodies. This is a fundamental flaw.

188. Dr. Petsko also relies on the purported fact that [REDACTED] [REDACTED] in concluding that 21B12 covers an epitope space that is representative of alirocumab or an antibody like alirocumab. Petsko Rebuttal Rpt. at ¶381. This analysis is insufficient and incorrect. [REDACTED]

[REDACTED] Moreover, the Asserted Patents teach that antibodies in each of the bins are representative of “different types of epitope locations on PCSK9.” Ex. 15, 165 Patent at 113:11-14. [REDACTED]

[REDACTED]

189. At paragraph 382 of the Petsko Report, [REDACTED] [REDACTED]

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<sup>5</sup> [REDACTED]

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[REDACTED]

[REDACTED] These differences are due to differences in the structures of the antibodies.

190. [REDACTED]

[REDACTED]

[REDACTED] I disagree that an epitope location is “fully representative” of another epitope location simply because there is some degree of overlap between the epitopes. As shown in Dr. Eck’s Opening Report, there are significant differences in contacts made between these antibodies and PCSK9. *See* Eck Opening Rpt. at Tables 1, 3-7, 9. [REDACTED]

[REDACTED]

[REDACTED] Therefore, Dr.

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<sup>6</sup> I understand that Amgen cannot rely on these post-filing date x-ray structures as written description support for any of the Asserted Claims because the question is what invention a person of skill in the art would have understood the inventors to have possessed based on the content of the patent specification. But even if it were determined that Amgen can rely on these post-filing date x-ray structures, my opinion that the patents lack adequate written description is unchanged, as explained in my Opening Report.

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Petsko's conclusion that the epitope space of the Amgen antibodies is representative of alirocumab and the Third Party Antibodies is incorrect.

191. At paragraph 292 and Figure 4 of the Petsko Report, Dr. Petsko shows a figure of the arginine-scanning hits for 12H11 mapped onto the PCSK9 crystal structure. Petsko Rebuttal Rpt. at ¶292. Dr. Petsko concludes from this analysis that [REDACTED] [REDACTED] Petsko Rebuttal Rpt. at ¶292. I am puzzled by this conclusion. In my view, Figure 4 prepared by Dr. Petsko does not show that 12H11 is [REDACTED] – if anything, it clearly shows that 12H11 is interacting with PCSK9 at a spot that is located below the 21B12 and 31H4 binding sites. *See* Petsko Rebuttal Rpt. at ¶292, Figure 4.

192. First, as I stated in my Opening Report, arginine scanning results do not show that an antibody “binds to” a particular residue on PCSK9. Siegel Opening Rpt. at ¶120. Dr. Petsko again mischaracterizes my analysis when he argues that these experiments do show binding. Petsko Rebuttal Rpt. at ¶384. At best, arginine scanning can indicate whether an amino acid is within the structural epitope of an antibody. *See* Ex. 15, 165 Patent at 114:2-5 (“By way of background, this method [arginine-scanning] determines if the residue is part of the structural epitope, meaning those residues in the antigen which contact or are buried by the antibody.”)

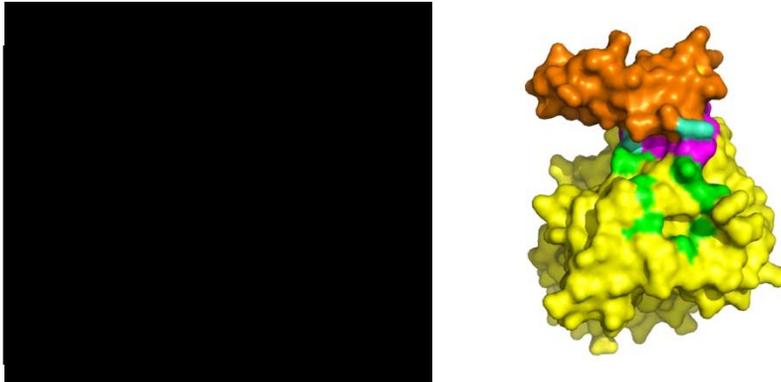
193. Another problem with Dr. Petsko's analysis is that, while he opines that [REDACTED] [REDACTED], he fails to identify the location of the EGFA interface in his figure. Petsko Rebuttal Rpt. at ¶292, Figure 4. [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]

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[REDACTED]

The figure on the right (below) from the Eck Supplemental Report shows the EGFa domain (orange) bound to PCSK9.



In the comparison of 12H11 to the EGFa interaction region, the residues that Petsko says are part of the EGFa binding region are in magenta, the 12H11 arginine scanning hits are green, and the two amino acids that are part of both groups (S153 and S381) are cyan (*see* Eck Supplemental Rpt. at ¶37). The area covered by 12H11 is different from that covered by the EGFa domain.

194. From his analysis of the 12H11 arginine-scanning hits, Dr. Petsko also concludes that [REDACTED]

[REDACTED] Petsko Rebuttal Rpt. at ¶292. I note that the Asserted Patents do not disclose any receptor blocking results for 12H11.

In addition, Dr. Petsko has not cited to any results which show that [REDACTED]

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[REDACTED]

[REDACTED] This directly contradicts Dr. Petsko’s assertion that a [REDACTED]

[REDACTED] Petsko Rebuttal

Rpt. at ¶292. In my view, [REDACTED]

[REDACTED]

[REDACTED]

195. In conclusion, for the reasons stated above, Dr. Petsko’s epitope analysis fails to show that Amgen’s antibodies are representative of the genus of antibodies encompassed within the Asserted Claims, including alirocumab and the Third Party Antibodies.

196. Dr. Rees explains that Amgen’s antibodies bind to PCSK9 at locations that are [REDACTED] the alleged pharmacophore. Rees Rebuttal Rpt. at ¶207. At Figure Z of the Rees Report, Dr. Rees displays the residues within the pharmacophore that are contacted by Amgen’s antibodies. Rees Rebuttal Rpt. at ¶207, Figure Z. [REDACTED]

[REDACTED]

[REDACTED] Dr. Rees concludes that Amgen’s antibodies and the Third Party Antibodies exhibit “[REDACTED]”. Rees Rebuttal Rpt. at Section Heading VI(B)(4); ¶208.

197. I disagree. First, I note that these figures only show *where* the antibodies bind and, thus, ignore the actual binding mechanisms through which the different antibodies contact the individual residues on PCSK9. In my view, it is insufficient to conclude that antibodies exhibit “common modes of binding” based simply on the fact that they bind to overlapping sites on PCSK9. Dr. Rees’ opinion ignores the well accepted principle that antibodies can bind to the same epitope through a wide variety of diverse and unpredictable binding mechanisms. A skilled

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person would understand that different antibodies can use amino acids at different positions to make contacts with a particular residue on PCSK9. In fact, different antibodies can contact a particular residue using amino acids located in different antibody chains (heavy or light). A skilled person would appreciate these well-established principles and would understand that Amgen has not invented antibodies that represent the multitude of diverse binding mechanisms that are encompassed by the claims.

198. I also note that, in his pharmacophore analysis, Dr. Rees “adds up” the contact residues of Amgen’s antibodies in an effort to show that Amgen invented antibodies that cover the entire surface of the alleged PCSK9 pharmacophore. Rees Rebuttal Rpt. at ¶207, Figure Z. This is improper. [REDACTED]

[REDACTED] As I explained above, and as demonstrated by Dr. Rees’ figures, none of the antibodies disclosed in the Asserted Patents binds to a spot that is located centrally on top of the PCSK9 pharmacophore. See Rees Rebuttal Rpt. at Figure Z. [REDACTED]

[REDACTED]

199. [REDACTED]

[REDACTED]

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[REDACTED]

200. [REDACTED]

[REDACTED]

201. [REDACTED]

[REDACTED]

202. [REDACTED]

[REDACTED]

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[REDACTED]

203. [REDACTED]

[REDACTED]

204. [REDACTED]

[REDACTED]

205. At paragraph 259 of the Rees Report, Dr. Rees discusses the genetic diversity of antibodies that can be obtained from the XenoMouse mice. Rees Rebuttal Rpt. at ¶259. [REDACTED]

[REDACTED]

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<sup>7</sup> [REDACTED]

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206. This statement mischaracterizes the opinion provided in my Opening Report and misses the point. As I explained above, the presence or absence of specific germline genes – in and of itself – is insufficient to demonstrate that the disclosed antibodies are representative of the claimed genus. On the other hand, as I explained in my Opening Report, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Focusing on epitope location or binding region improperly ignores the antibody structure. As I discussed in my Opening Report, none of the antibodies the Amgen disclosed have an amino acid sequence representative of 1D05. Siegel Opening Rpt. at ¶¶208-211, 236-238.

207. In conclusion, Dr. Rees’ germline gene analysis fails to provide evidence that Amgen’s antibodies are representative of antibody structures encompassed by the claimed genus, including antibody structures like alirocumab and the Third Party Antibodies. Dr. Rees’ analysis is fundamentally flawed because it includes antibodies disclosed in the specification that fall outside the scope of the Asserted Claims and also because it analyzes a structural feature that is common to many antibodies that bind to a whole host of unrelated antigens.

208. Dr. Rees goes on to compare the canonical structures of antibodies disclosed in the Asserted Patents to alirocumab and the Third Party Antibodies (1D05, AX132, and J16). Rees Rebuttal Rpt. at ¶¶343-361. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

209. Dr. Rees notes that “the third party antibodies 1D05, AX132, and J16, adopt the same canonical structures as the Amgen antibodies 23B5 and 25G4: 2-1 for L1 and L2”. Rees Rebuttal Rpt. at ¶352. However, a multitude of other antibodies whose antigens have no relationship to PCSK9 also adopt canonical structures 2-1 for L1 and L2. Dr. Rees even explains that L1 canonical structure 2, 3, 4, and 6 are adopted by the vast majority of human kappa light chains and that there is only one canonical structure defined for kappa L2. Rees Rebuttal Rpt. at ¶¶118, 123.

210. At paragraph 353 of the Rees Report, Dr. Rees shows the following comparison of light chain CDR L1 amino acids and positions of “key residues” for canonical class 2 for L1:

**Comparison of the Class 2 L1 amino acids**

	25	29	33
1D05	RASQGI	RSAIN	
J16	RASQGI	SSALA	
AX132	RASQYV	GSYLN	
23B5	RASQSI	SSYLN	
25G4	RASQSI	SIYLN	

Blue = key residues for canonical class 2 for L1. For the same backbone conformation, CDR position 25 is always A, position 29 can be V, I or L and position 33 can be L or M.

Focusing first on these anti-PCSK9 antibodies, it is important to note that the light chain CDR1 residues do not interact with PCSK9 in the same way for the different antibodies. For 1D05,

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<sup>8</sup> Dr. Rees fails to provide a kappa L3 canonical structure for AX132 in Table 12 of the Rees Report.

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CDR L1 comes within 5 Å of residue 192 of PCSK9. Eck Opening Rpt. at Table 3. For AX132, CDR L1 comes within 5 Å of residues 153, 155, 194-195, 237-239, 369, 377 and 379. Eck Opening Rpt. at Table 4. For J16, CDR L1 comes within 5 Å of residues 372, 374-375, and 377-379. Eck Opening Rpt. at Table 5.

211. In the following figure, I reproduce this alignment and add the CDR L1 amino acid residues from 3 human anti-ADAMTS13 antibodies described in my Opening Report. Siegel Opening Rpt. at ¶212.<sup>9</sup> ADAMTS13 is metalloprotease involved in the processing of von Willebrand Factor, a protein involved in platelet adhesion.

		25				29				33	
1D05	R	A	S	Q	G	I	R	S	A	L	N
J16	R	A	S	Q	G	I	S	S	A	L	A
AX132	R	A	S	Q	Y	V	G	S	Y	L	N
23B5	R	A	S	Q	S	I	S	S	Y	L	N
25G4	R	A	S	Q	S	I	S	I	Y	L	N
TTP-A09	R	A	S	Q	S	V	S	N	W	L	A
TTP-A10	R	A	S	Q	S	I	S	S	W	L	A
TTP-A27	R	A	S	Q	S	I	S	S	W	L	A

**Figure 2:** Amino acid sequence alignment of CDR L1 regions from Third Party Antibodies (1D05, J16, AX132), Amgen antibodies (23B5, 25G4), and anti-ADAMTS13 antibodies (TTP-A09, TTP-A10, TTP-A27).

212. As shown in Figure 2 above, anti-ADAMTS13 antibodies TTP-A09, TTP-A10, and TTP-A27 are among a multitude of human antibodies whose kappa light chains have the same backbone conformation as the other antibodies in the group, consistent with the antibodies adopting the same canonical structure 2.

<sup>9</sup> Nucleotide and amino acid sequences, germline genes used, and canonical structures displayed by these and other non-PCSK9 antibodies are listed in Appendix A, which is attached to this report.

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213. In paragraph 354 of the Rees Report, Dr. Rees notes that, “(b)ecause the Amgen antibodies 23B5 and 25G4 also adopt canonical structure class 2 for CDR1 of the light chain, the skilled artisan would expect that 23B5 and 25G4 would adopt backbone conformations similar to those [of 1D05 L1-2, AX132 L1-2, J16 L1-2] shown below [Figure RR].” Rees Rebuttal Rpt. at ¶354. If so, it then follows that the skilled artisan would expect TTP-A09, TTP-A10, and TTP-A27 to also adopt backbone conformations similar 1D05 L1-2, AX132 L1-2, and J16 L1-2.

214. In paragraph 355 of the Rees Report, Dr. Rees notes that, “[i]n addition to having the same backbone conformation, there is a high degree of similarity in L1 sequences of the third party antibodies and the Amgen antibodies 23B5 and 25G4.” Rees Rebuttal Rpt. at ¶355. He notes:

1D05:23B5	8/11 = 73%
J16:23B5	8/11 = 73%
AX132:23B5	8/11 = 73%

215. However, as shown below, the anti-ADAMTS13 antibodies share the following percent sequence identity with 23B5:

TTP-A09:23B5	7/11 = 64%
TTP-A10:23B5	9/11 = 82%
TTP-A27:23B5	9/11 = 82%

216. If one applies the rules for conservative amino acid substitutions described in the Asserted Patents (*see* Ex. 15, 165 Patent at Table 1) where one is starting with 23B5:

1D05:23B5	8/11 = 73% (similarity does not change)
J16:23B5	8/11 = 73% (similarity does not change)
AX132:23B5	9/11 = 82% (similarity increases due to I/V)
TTP-A09:23B5	9/11 = 82% (similarity increases due to I/V, Y/W)
TTP-A10:23B5	10/11 = 91% (similarity increases due to Y/W)
TTP-A27:23B5	10/11 = 91% (similarity increases due to Y/W)

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217. Therefore, neither L1 canonical structure nor even L1 sequence similarity to Amgen antibodies allows one to distinguish whether or not an antibody is a member of the claimed genus.

218. Although Dr. Rees notes that the Third Party Antibodies 1D05, AX132, and J16, along with Amgen antibodies 23B5 and 25G4 share the same L2 canonical structure (1) (*see* Rees Rebuttal Rpt. at ¶352), he does not compare their amino acid sequences as he does for L1.

219. As shown in Figure 3 below, I compared the L2 sequences of these antibodies along with the same set of ADAMTS13 antibodies mentioned above.

	50	51	52	53	54	55	56
1D05	N	G	S	T	L	Q	S
J16	S	A	S	Y	R	Y	T
AX132	D	A	S	N	R	A	T
23B5	A	A	S	S	L	Q	S
25G4	A	A	A	S	L	Q	S
TTP-A09	G	A	T	T	L	Q	S
TTP-A10	A	A	S	S	L	Q	S
TTP-A27	A	A	S	S	L	Q	S

**Figure 3:** Amino acid sequence alignment of CDR L2 regions from Third Party Antibodies (1D05, J16, AX132), Amgen antibodies (23B5, 25G4), and anti-ADAMTS13 antibodies (TTP-A09, TTP-A10, TTP-A27).

220. Applying the same sequence analysis approach Dr. Rees applied to L1 sequences:

1D05:23B5	4/7 = 57%
J16:23B5	2/7 = 29%
AX132:23B5	2/7 = 29%
TTP-A09:23B5	4/7 = 57%
TTP-A10:23B5	7/7 = 100%
TTP-A27:23B5	7/7 = 100%

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221. If one applies the rules for conservative amino acid substitutions described in the Asserted Patents (*see* Ex. 15, 165 Patent at Table 1) where one is starting with 23B5:

1D05:23B5	5/7 = 71% (similarity increases due to S/T)
J16:23B5	3/7 = 43% (similarity increases due to S/T)
AX132:23B5	3/7 = 43% (similarity increases due to S/T)
TTP-A09:23B5	5/7 = 71% (similarity increases due to S/T)
TTP-A10:23B5	7/7 = 100% (similarity cannot increase since already identical)
TTP-A27:23B5	7/7 = 100% (similarity cannot increase since already identical)

222. Therefore, as illustrated by this set of antibody light chains, neither L2 canonical structure nor L2 sequence similarity to Amgen antibodies allows one to distinguish whether or not an antibody is a member of the claimed genus.

223. In paragraph 356 of the Rees Report, Dr. Rees notes that, “[t]he third party antibodies 1D05, J16, and AX132 adopt the same canonical structure class (1) for the L2 loop as the Amgen antibodies,” as though there was some significance carried along with this fact. Rees Rebuttal Rpt. at ¶356. However, all kappa L2 loops fall into just one canonical class. Rees Rebuttal Rpt. at ¶123.

224. [REDACTED]

Following Dr. Rees’ logic above for CDR1 structures of 23B5 and 25G4, the skilled artisan would expect TTP-A09, TTP-A10, and TTP-A27 to also adopt backbone conformations similar to 1D05 L2-1, AX132 L2-1, and J16 L2-1.

225. In paragraph 357 of the Rees Report, Dr. Rees notes that the “third party antibody J16 adopts the same canonical structure for L3 (class 1) as the Amgen antibodies 23B5, 25G4, 30A4, 8A3, 8A1, 11F1 and 12H11.” Rees Rebuttal Rpt. at ¶357. [REDACTED]

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[REDACTED]

226. In paragraph 358 of the Rees Report, Dr. Rees compares CDR3 canonical class 1 amino acid sequences of Third Party Antibody J16 with Amgen antibodies. Rees Rebuttal Rpt. at ¶358. I have reproduced his chart below with the addition of CDR3 canonical class 1 amino acid sequences of anti-influenza virus and anti-rabies virus antibodies described in my Opening Report. I have also crossed out 30A4 because Amgen does not contend that it is covered by any of the Asserted Claims. The blue highlighted residues show “[c]anonical residues are position 90 (Q, N or H) and position 95 (P)”, as described by Dr. Rees in the Rees Report. Rees Rebuttal Rpt. at ¶358. He also notes that J16 does not have a P at position 95, though in paragraph 126 of his report he states, “L3 loops that form canonical structure 1 have a proline at position 95.” Rees Rebuttal Rpt. at ¶126. However, anti-influenza virus and anti-rabies virus antibodies have a P at position 95.

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		90					95		
23B5	Q	Q	S	Y	S	S	P	I	T
25G4	Q	Q	S	Y	S	A	P	I	T
12H11	Q	Q	Y	Y	S	T	P	W	T
<del>30A4</del>	<del>M</del>	<del>Q</del>	<del>V</del>	<del>L</del>	<del>Q</del>	<del>T</del>	<del>P</del>	<del>L</del>	<del>T</del>
8A1	M	Q	A	L	Q	T	P	L	T
8A3.1	M	Q	A	L	Q	T	P	L	T
11F1	M	Q	A	L	Q	T	P	L	T
J16	Q	Q	R	Y	S	L	W	R	T
flu	Q	Q	H	Y	R	T	P	P	T
rabies	Q	Q	Y	D	S	N	P	Y	T

**Figure 4:** Amino acid sequence alignment of CDR L3 regions from Third Party Antibody J16, Amgen antibodies (23B5, 25G4, 12H11, 8A1, 8A3.1, 11F1), anti-flu and anti-rabies antibodies.

227. I note that there is a high degree of similarity between amino acid sequences of 30A4 to those of 8A1 and 8A3.1, two antibodies Amgen believes are members of the covered genus. After making conservative amino acid substitutions per Table 1 of the Asserted Patents (V/A; F/L), the CDR-L3 of antibody 30A4 becomes identical to the other two, indicating that identical canonical structures and even identical amino acid sequences for light chain CDR3 cannot reliably provide structural information to distinguish whether an antibody is a member of the genus or not.

228. In paragraph 361, Dr. Rees concludes, “[f]or all the reasons recited above, the Amgen antibodies are representative of the third party antibodies 1D05, J16, and AX132.” Rees Rebuttal Rpt. at ¶361. I disagree. Rather, a person of ordinary skill in the art would conclude that, for all of Dr. Rees’ reasons he recites, the Amgen antibodies are just as representative of numerous antibodies not covered by the Asserted Claims of the patents.

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229. I note that, even *if* canonical structures provided evidence that the disclosed antibodies are representative of the structural diversity of the claimed genus – which, as I explained above, they do not – Amgen did not disclose any antibodies having the same canonical pattern as 1D05. Dr. Rees’ analysis shows that the heavy and light chains of 1D05 have the canonical structure 1-2, 2-1-3, respectively. Rees Rebuttal Rpt. at ¶¶344, 347, Tables 8-12. None of the antibodies that Amgen contends fall within the scope of at least one Asserted Claim have the same canonical structure as 1D05 for both the heavy and light chains. Rees Rebuttal Rpt. at Tables 5, 6. As I explained above, it is improper to “mix and match” structural features from different antibodies disclosed in the Asserted Patents to show that Amgen invented antibodies that are representative of the structure of 1D05, alirocumab, or the other Third Party Antibodies.

230. For the reasons stated above, Dr. Rees erred when he relied on an analysis of canonical structures in reaching his opinion that the disclosed antibodies are representative of the claimed genus, which includes antibodies having structures like alirocumab or the Third Party Antibodies. Rather than looking at structural features of the antibodies that are found in many antibodies that bind to a wide range of different antigens, a person skilled in the art would look to the structural features that distinguish antibodies that fall inside the claimed genus from those that fall outside and, therefore, define the claimed genus. As I discuss below in Section V(A)(6), a skilled person would understand that the primary amino acid sequence of an antibody is a structural feature that distinguishes the antibodies that fall within the claims from the multitude of antibodies that do not. Therefore, a skilled person would look at amino acid sequences in order to determine whether Amgen’s antibodies are representative of the antibody structures that are covered by the claimed genus.



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antibodies, including any differences in amino acids at specific residue locations and any differences in CDR length.

233. In paragraphs 363 and 364 of the Rees Report, Dr. Rees states that alirocumab and 12H11 light chains are both derived from the Vk4-1 germline gene. Rees Rebuttal Rpt. at ¶¶363-364. Numerous other antibodies described throughout the immunology literature that do not fall within the scope of the Asserted Claims are also derived from the Vk4-1 gene including the anti-rabies and anti-influenza antibodies. Dr. Rees states that alirocumab is derived from the JK2 gene. Rees Rebuttal Rpt. at ¶363. Numerous antibodies described in the immunology literature that do not fall within the scope of the Asserted Claims are also derived from the JK2 gene including the anti-rabies and anti-influenza antibodies. 12H11 is derived from the JK1 gene, not JK2. Rees Rebuttal Rpt. at ¶¶367, 369; Tables 1, 2, 6.

234. As a first step in his analysis, Dr. Rees compares the amino acid sequence of the 12H11 light chain to alirocumab. Rees Rebuttal Rpt. at ¶¶363-377. Dr. Rees opines that the “sequences of CDR1 and CDR2 of alirocumab and 12H11 are remarkably similar.” Rees Rebuttal Rpt. at ¶367. Dr. Rees states that the light chain “CDR3 sequence of alirocumab and 12H11 . . . is also remarkably similar.” Rees Rebuttal Rpt. at ¶369.

235. I have reviewed Dr. Rees’ analysis. As I explain below, his analysis fails to show that 12H11 is representative of alirocumab or an antibody having a structure like alirocumab.

236. In paragraph 367 of the Rees Report, Dr. Rees aligns the amino acid sequences of the light chain CDRs and framework 4 regions of 12H11 with what he contends are the corresponding regions of alirocumab (“AL”). Rees Rebuttal Rpt. at ¶367. For comparison, he also includes the Vk4-1 germline sequence and what he contends are the germline sequences for

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JK1 and JK2. Rees Rebuttal Rpt. at ¶367. His alignments and legend are copied and pasted below:

	CDR1	CDR2	CDR3	FW4	
AL	KSSQSVLYRSNNRNLFLG	WASTRES	QQYYSTPYT	FGQGTKLEIK	VK4-1/JK2
12H11	KSSQSVLYSSNSKNYL <del>V</del>	WASTRES	QQYYSTPWT	FGQGTKVEIK	VK4-1/JK1
VK4GL	KSSQSVLYSSNNKNYLA	WASTRES	QQYYSTPYT	FGQGTKLEIK	VK4-1/JK1
VK4GL	KSSQSVLYSSNNKNYLA	WASTRES	QQYYSTPLT	FGGGTKVEIK	VK4-1/JK2

For CDR1, residue differences between the germline sequence and the antibody CDRs are marked in red and must have arisen by somatic mutation during the antigen driven affinity maturation (or by protein engineering in the laboratory although no evidence of that is known).

237. Dr. Rees makes several errors in his alignment figure and in his analysis that follows.

238. First, Dr. Rees states that, “[t]he sequence identity between alirocumab and 12H11 with respect to L1 is 13/17=76%, rising to 82% if the conservative R<>K substitution (both positively charged) at position 30F is included.” Rees Rebuttal Rpt. at ¶368. This is incorrect. As shown in Dr. Rees’ own figure above, there are 5, not 4, differences between the L1 of alirocumab and 12H11 (R<>S, N<>S, R<>K, F<>Y, and G<>V). Therefore, a person of ordinary skill in the art would calculate the sequence identity as 12/17=71% and 76% (13/17) if the R<>K substitution is made.

239. In the figure below, I reproduce Dr. Rees’ figure again but where I have corrected additional errors made by Dr. Rees in red.

	CDR1	CDR2	CDR3	FW4	
AL	K S S Q S V L Y R S N N R N F L G	W A S T R E S	Q Q Y Y <del>T</del> T P Y T	F G Q G T K L E I K	VK4-1/JK2
12H11	K S S Q S V L Y S S N S K N Y L V	W A S T R E S	Q Q Y Y S T P W T	F G Q G T K V E I K	VK4-1/JK1
VK4GL	K S S Q S V L Y S S N N K N Y L A	W A S T R E S	Q Q Y Y S T P <del>W</del> T	F G Q G T K <del>V</del> E I K	VK4-1/JK1
VK4GL	K S S Q S V L Y S S N N K N Y L A	W A S T R E S	Q Q Y Y S T P <del>Y</del> T	F G <del>Q</del> G T K <del>L</del> E I K	VK4-1/JK2

**Figure 5:** Corrected alignment of alirocumab (“AL”), 12H11, and VK4-1/JK1 or JK2 light chain CDR and framework 4 sequences.

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240. The CDR3 sequence of alirocumab is “QQYY**T**TPYT” not “QQYY**S**TPTYT”. Therefore, Dr. Rees is incorrect when he states that, “8 of the 9 amino acids are identical” when comparing CDR3 regions of alirocumab and 12H11. Rees Rebuttal Rpt. at ¶369. When working with the correct sequences, a person of ordinary skill in the art would determine that 7, not 8, of the 9 amino acids are identical.

241. Furthermore, it is difficult to understand Dr. Rees’ statement, “[t]he remaining two amino acids, YT in alirocumab and WT in 12H11 are also similar despite being encoded by JK2 and JK1 genes” (*see* Rees Rebuttal Rpt. at ¶369) when his figure shows corresponding residues of “LT” and “YT” for germline JK2 and JK1 genes, respectively. A person of ordinary skill in the art would recognize that the germline sequence he labels as “JK1” has 2 errors in it, and the germline sequence he labels as “JK2” has 3 errors in it including the substitution of a G for a Q.

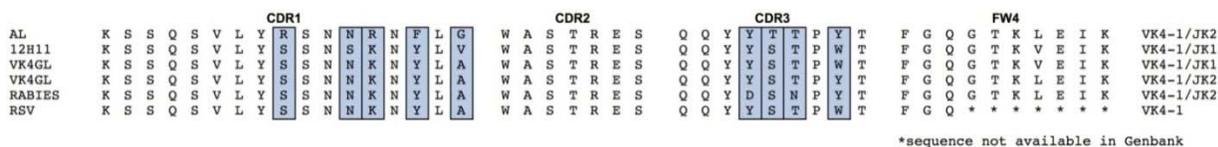
242. In addition, it is not clear why Dr. Rees has put in the germline gene sequence for JK4 (*see* Rees Rebuttal Rpt. at ¶369) when he states that 12H11 is encoded by the JK1 gene. He further states in footnote 154, “[w]hat is also clear is that antibody 12H11 has undergone a somatic mutation (no N addition is seen at the junction) at the first J position (L=>W).” Since the germline JK1 sequence begins “**WT**” not “LT”, it is difficult to follow his logic. According to his earlier erroneous figure in paragraph 367, I would have expected him to have erroneously stated that the somatic mutation 12H11 had undergone at the first position was “Y=>W”, not the erroneous statement “L=>W”. Of course, a person of ordinary skill in the art would recognize that 12H11 had not undergone any somatic mutation at its first J position (“W=W”).

243. Numerous errors notwithstanding, the idea that genetic origin or amino acid sequence similarities between 12H11 and alirocumab light chains teaches us how to distinguish

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an antibody that falls within the genus of antibodies covered by the scope of the Asserted Claims from an antibody that does not, is not supported if one considers the genetic and amino acid sequence correlations between 12H11 and antibodies that are not members of the genus.

244. This is illustrated below where I have again reproduced Dr. Rees’ alignment (with his 6 errors corrected), but I added the light chain CDR and Framework 4 sequences for the anti-rabies antibody as well as an example of a human anti-respiratory syncytial (RSV) virus antibody (RSV28, Genbank FJ385457). This anti-RSV antibody is also encoded by the Vk4-1 gene and has the same heavy and light chain canonical CDR structures as alirocumab, 12H11, and the anti-rabies antibody (1-3, 3-1-1).



**Figure 6:** Sequence alignment of alirocumab (“AL”), 12H11, VK4-1/JK1 or JK2 germline genes, anti-rabies antibody, and anti-RSV antibody light chain CDR and framework 4 regions.

245. I have highlighted in blue the positions that differ among the 4 antibodies and Vk/Jk germline genes within the CDR1, CDR2, and CDR3 regions. Below I summarize the results of an analysis using Dr. Rees’ method of analysis that counts numbers of residue identities, calculates a % identity, and adjusts for conservative substitutions. *See* Rees Rebuttal Rpt. at ¶368.

CDR1 region:

AL:12H11 12/17 = 71% (or 14/17 = 82% if consider K<>R and Y<>F)  
 Rabies:12H11 15/17 = 88% (or 16/17 = 94% if consider V<>A)  
 RSV:12H11 15/17 = 88% (or 16/17 = 94% if consider V<>A)

CDR2 region:

AL:12H11 7/7 = 100%  
 Rabies:12H11 7/7 = 100%

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RSV:12H11 7/7 = 100%

CDR3 region:

AL:12H11 7/9 = 78% (or 9/9 = 100% if consider S<>T and W<>Y)

Rabies:12H11 6/9 = 67% (or 7/9 = 78% if consider W<>Y)

RSV:12H11 9/9 = 100% without any conservative substitutions

246. In paragraph 370 of the Rees Report, Dr. Rees concludes from his analysis that there is some meaningful significance vis-à-vis common genetic origin and CDR sequence relationship between alirocumab and 12H11 that helps one to visualize why they both may fall within the scope of the Asserted Claims. Rees Rebuttal Rpt. at ¶370. Though he does not clearly explain the origin of the numerator and denominator in his calculation (“31/32 = 97%”), it is clear from the above analysis, that 12H11 is as close, if not closer, in light chain CDR sequence to antibodies outside the scope of the Asserted Claims than to alirocumab.

247. [REDACTED]

[REDACTED]

Rees Rebuttal Rpt. at ¶371. However, since numerous antibodies including the rabies and RSV antibodies described above also share 3-1-1 light chain CDR structures, a person of ordinary skill in the art would not rely on these structural features to determine whether Amgen’s antibodies are representative of other structures encompassed within the claimed genus.

248. [REDACTED]

[REDACTED]

[REDACTED] The insertion sequence is always at position 30. For these two antibodies 6 residues are inserted marked 30A(Y) to 30F(R).” Rees Rebuttal Rpt. at ¶372. I would note that the 6-residue insertions for these two antibodies are not both 30A(Y) to 30F(R). It is 30A(Y) to 30F(R) for alirocumab and 30A(Y) to 30F(K) for 12H11.

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249. I have reproduced Dr. Rees’ figure below, corrected his error in the labeling of amino acid position 33, and have added the L1 sequences of the rabies and RSV antibodies. As one of ordinary skill in the art would appreciate, rabies and RSV antibodies also have an S at position 25, also have a V at position 29, also have an L at position 33, and also have 6-residue insertions at position 30. Like 12H11, but unlike alirocumab, rabies and RSV antibodies have a K at position 30F.

		25				29	30	30A				30F	31		33	
AL	K	S	S	Q	S	V	L	[Y R S N N R]	N	F	L	G				
12H11	K	S	S	Q	S	V	L	[Y S S N S K]	N	Y	L	V				
RABIES	K	S	S	Q	S	V	L	[Y S S N N K]	N	Y	L	A				
RSV	K	S	S	Q	S	V	L	[Y S S N N K]	N	Y	L	A				

**Figure 7:** Sequence alignment of the CDR L1 regions of alirocumab (“AL”), 12H11, anti-rabies antibody, and anti-RSV antibody.

250. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

251. In paragraph 374, Dr. Rees compares the L3 CDR sequence of 23B5 with alirocumab stating, “CDR3 of 23B5 shows 67% identity with alirocumab if the conservative T<>S is included.” Rees Rebuttal Rpt. at ¶374. This is not true as Dr. Rees uses an incorrect sequence for the alirocumab L3 CDR sequence as already noted above. A person of ordinary skill in the art would recognize that the CDR3 of 23B5 shows 56% identity if conservative T<>S mutations are included. Dr. Rees continues, “[a]s the CDR region that is frequently ‘involved in antigen contact,’ the similarities between 23B5 and alirocumab are particularly relevant.” Rees

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Rebuttal Rpt. at ¶374. If the similarities between 23B5 and alirocumab to which Dr. Rees refers are also shared with antibodies that bind antigens other than PCSK9, then their relevance in terms of characterizing antibodies that are within the scope of the Asserted Claims would be questionable.

252. To examine this further, I reproduced Dr. Rees’ figure from paragraph 374 of the Rees Report but included the correct light chain CDR3 sequence for alirocumab. I also include the light chain CDR amino acid sequences for the rabies and RSV antibodies described above.

AL	K	S	S	Q	S	V	L	Y	R	S	N	N	R	N	F	L	G	W	A	S	T	R	E	S	Q	Q	Y	Y	T	P	Y	T	F	G	Q	G	T	K	L	E	I	K	VK4-1/JK2	
23B5							R	A	S	Q	S	I	S	S	Y	L	N	A	A	S	S	L	Q	S	Q	Q	S	Y	S	S	P	I	T	F	G	Q	G	T	R	L	E	I	K	VK1D39-1/JK5
VKD39-1GL							R	A	S	Q	S	I	S	S	Y	L	N	A	A	S	S	L	Q	S	Q	Q	S	Y	S	T	P	I	T	F	G	Q	G	T	R	L	E	I	K	
RABIES	K	S	S	Q	S	V	L	Y	S	S	N	N	K	N	Y	L	A	W	A	S	T	R	E	S	Q	Q	Y	D	S	N	P	Y	T	F	G	Q	G	T	K	L	E	I	K	VK4-1/JK2
RSV	K	S	S	Q	S	V	L	Y	S	S	N	N	K	N	Y	L	A	W	A	S	T	R	E	S	Q	Q	Y	Y	S	T	P	W	T	F	G	Q	*	*	*	*	*	*	*	VK4-1

\*sequence not available in Genbank

**Figure 8:** Sequence alignment of the light chain CDR and framework 4 regions of alirocumab (“AL”), 23B5, anti-rabies antibody, and anti-RSV antibody.

253. Using Dr. Rees’ approach for quantifying sequence similarities in CDRs:

AL:23B5      5/9 = 56% (or 7/9 = 78% if consider S<>T and S<>T)  
 Rabies:23B5   5/9 = 56%  
 RSV:23B5      6/9 = 67% (or 7/9 = 78% if consider S<>T)

254. Therefore, from comparing light chain CDR3 regions using Dr. Rees’ approach, one would conclude that 23B5 is as representative of alirocumab as it is of an antibody that binds to RSV. Furthermore, if one uses Dr. Rees’ approach to compare the light chain CDR3 regions of the RSV antibody and alirocumab, one would conclude that the RSV antibody is more representative of alirocumab than is 23B5.

AL:RSV      7/9 = 78% (or 9/9 = 100% if consider S<>T and W<>Y)

255. I note, also, that Dr. Rees fails to consider the dissimilarity in sequence between the CDR L1 and L2 regions. As shown in Figure 8 above, there are significant differences in

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sequence in the CDR L1 regions of alirocumab and 23B5, including a large gap in the 23B5 sequence compared to alirocumab. There are also significant differences in the CDR L2 region. Alirocumab and 23B5 differ at 4 out of 7 residues in the CDR L2 region and, therefore, share 43% sequence identity in that region. Dr. Rees' decision to ignore the CDR L1 and L2 regions is a fundamental flaw in his analysis.

256. [REDACTED]

257. In paragraph 379 of the Rees Report, Dr. Rees provides a list of Amgen antibodies that are derived from the V3 family. Rees Rebuttal Rpt. at ¶379. A person of ordinary skill in the art would also understand that a multitude of non-Amgen antibodies that do not fall within the scope of the Asserted Claims are also derived from the V3 family. Even three of the Amgen antibodies Dr. Rees provides in his list as being derived from the V3 family [REDACTED] are antibodies that Amgen does not contend are within the scope of the Asserted Claims.

258. In paragraph 380 of the Rees Report, Dr. Rees notes that 23B5 and 25G4 are derived from the V3-23 subfamily. Rees Rebuttal Rpt. at ¶380. A person of ordinary skill in the art would also understand that the V3-23 subfamily is one of the most commonly used VH germline genes. Similarly, in paragraphs 381 to 383, Dr. Rees describes how certain D families, D genes, or J genes are used by Amgen antibodies. Rees Rebuttal Rpt. at ¶¶381-383. A person of ordinary skill in the art would also understand that these families and genes are used to encode a multitude of antibodies that are not within the scope of the Asserted Claims. Therefore, none of

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these characteristics of Amgen antibodies noted by Dr. Rees can be used to visualize what makes an antibody a member of the genus covered by the Asserted Claims and what does not.

259. Following paragraph 385 of the Rees Report, Dr. Rees shows an alignment of the amino acid sequences of a portion of the heavy chain of alirocumab with those of 23B5 and the V3-23 germline gene. Rees Rebuttal Rpt. at ¶385. He notes, “Amgen antibody 23B5 shows close similarity to alirocumab between the first two heavy chain CDRs, 1 and 2.” Rees Rebuttal Rpt. at ¶386.

260. Below, I reproduce Dr. Rees’ alignment along with the addition of the corresponding portion of the heavy chain of the rabies antibody described in my Opening Report.

AL	G F T F <b>N N</b> Y	S G S G G <b>T</b>	<b>D S N W G N</b>	[F - - - <b>D L</b>	V3-23/D7-27/J2
23B5	G F T F S S Y	S G S G <b>D N</b>	K F V L M V	[Y A M L] D Y	V3-23/D2-08/J4
V3-23 GL	<b>G F T F S S Y</b>	<b>S G S G G S</b>	[L T G D Y W Y F D L]		
RABIES	G F T F S S Y	S G S G G <b>N</b>	R Y Y G G G	D Y	V3-23/D2-21/J4

**Figure 9:** Sequence alignment of the heavy chain CDR regions of alirocumab (“AL”), 23B5, the VH3-23 germline gene, and the anti-rabies antibody.

261. Using Dr. Rees’ approach for quantifying sequence similarities in CDRs:

CDR1:

AL:23B5      5/7 = 71%  
 Rabies:23B5   7/7 = 100%

CDR2:

AL:23B5      4/6 = 67%  
 Rabies:23B5   5/6 = 83%

262. [REDACTED]

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263. I note that Dr. Rees never contends that the heavy chain CDR H3 region of 23B5 is structurally similar to alirocumab in any way. As shown in Figure 9 above, the CDR H3 regions of alirocumab and 23B5 differ at 11 out of 12 positions, in part because they also differ in length. They also differ in length.

264. In paragraph 388 of the Rees Report, Dr. Rees states that, “Amgen antibody 9C9 also has a closely similar CDR1 sequence to that of alirocumab, although the two antibodies are derived from different gene families.” Rees Rebuttal Rpt. at ¶388. He then provides an alignment figure which I cut and paste below:

	<b>CDR1</b>	<b>CDR2</b>	<b>CDR3</b>	
AL	GFTF <b>N</b> NY	SGSG <b>G</b> T	DSNWGN[F--- DL	V3-23/D7-27/J2 13
9C9	GLTFSS <b>F</b>	KQDGSE	ESNWGF[AF]--DI	V3-07/D7-27/J3 13
V3-07	GL <b>GFTFSSY</b>	<b>KQDGSE</b>		

265. Again, Dr. Rees has made an error in his analysis as the line that starts off “9C9” is not the sequence of Amgen antibody 9C9. The CDR1 of 9C9 is “G**F**TFSS**Y**”, not “GLTFSS**F**”.

266. Below, I have reproduced his alignment, but I use the correct sequence for 9C9. I also properly align the V3-07 germline gene and add the heavy chain CDR regions of the rabies antibody described in my Opening Report. 

 The rabies antibody also shares the same VH gene (V3-23) with alirocumab.

	<b>CDR1</b>	<b>CDR2</b>	<b>CDR3</b>	
AL	G F T F N N Y	S G S G G T	D S N W G N [ F - - - D L	V3-23/D7-27/J2
9C9	G F T F S S Y	K Q D G S E	E S N W G F [ A F ] - - D I	V3-07/D7-27/J3
V3-07 (GL)	G F T F S S Y	K Q D G S E		
RABIES	G F T F S S Y	S G S G G N	R Y Y G G G	D Y V3-23/D7-21/J4

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**Figure 10:** Sequence alignment of the heavy chain CDR regions of alirocumab (“AL”), 9C9, the VH3-07 germline gene, and the anti-rabies antibody.

267. Using Dr. Rees’ approach for quantifying sequence similarity for CDRs:

CDR1:

AL:9C9	5/7 = 71%
Rabies:9C9	7/7 = 100%
AL:Rabies	5/7 = 71%

CDR2:

AL:9C9	1/6 = 17%
Rabies:9C9	1/6 = 17%
AL:Rabies	5/6 = 83%

268. Therefore, based on heavy chain CDR1 and CDR2, 9C9 is more representative of a rabies antibody than it is of alirocumab. Also, based on heavy chain CDR1 and CDR2, a rabies antibody is more representative of alirocumab than is 9C9.

269. The similarities between amino acid positions in CDR3 also do not reflect a similarity in the structural interaction with PCSK9. As I showed in my Opening Report, the 9C9 antibody is a variant of 1A12, so close that it can be considered a minor variation of 1A12.

Siegel Opening Rpt. at ¶¶165, 166. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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270. Based on his analysis and comparison of CDR sequences, Dr. Rees concludes that the antibodies disclosed in the Asserted Patents are representative of the sequence of alirocumab. Rees Rebuttal Rpt. at ¶¶362, 398.

271. For all the reasons stated above, I disagree. Moreover, I note that in reaching his conclusion, Dr. Rees improperly combines parts of structures and/or sequences from different antibodies in order to (purportedly) show that Amgen invented antibodies that are representative of the diversity of structures encompassed within the claimed genus.

272. [REDACTED]

[REDACTED] As another example, Dr. Rees never says that the light chain of 9C9 is representative of alirocumab's light chain. It is not. In fact, Dr. Rees never points to a single *antibody* that is representative of the variable region of alirocumab, which consists of heavy and light chains that harbor six different CDR regions.

273. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Dr. Rees' failure to compare antibody structures as a whole while, instead, adding up isolated parts of certain antibodies to support his opinion, and ignoring other parts, is a fundamental flaw in his analysis.

274. At paragraphs 399-408 of the Rees Report, Dr. Rees provides his opinions that the antibodies disclosed in the Asserted Patents are structurally representative of the Third Party

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Antibodies (1D05, AX132, and J16) and of antibodies developed by Amgen years after filing its patent application [REDACTED] Rees Rebuttal Rpt. at ¶¶399-408.

275. I note that, rather than comparing the primary amino acid structures of the framework or CDR regions to determine whether the disclosed antibodies are representative of the Third Party Antibodies or [REDACTED], Dr. Rees bases his opinion solely on an analysis of canonical structures and CDR lengths. Rees Rebuttal Rpt. at ¶¶401, 402, 406-407. As I explained in detail above, canonical loop structures are not a structural feature that distinguishes antibodies falling within the claimed genus from those falling out. Neither is CDR length. Dr. Rees' failure to analyze the amino acid sequences of the Third Party Antibodies and [REDACTED] is error.

276. At paragraph 400 of the Rees Report, Dr. Rees states that it is improper to compare the amino acid sequence of Amgen's antibodies to J16 "because the J16 antibody was obtained through an affinity maturation process in which various residues in the CDR regions were mutated." Rees Rebuttal Rpt. at ¶400. Dr. Rees further opines that because "we have only the final sequence . . . and we also have no indication of which mutations were made . . . it is simply not possible to draw any conclusion based on sequence similarity data involving J16." Rees Rebuttal Rpt. at ¶400.

277. I disagree. Contrary to Dr. Rees' assertion, a skilled person would be able to draw conclusions based on sequence similarity to J16 even if they only have the "final sequence". In fact, it is exactly the final sequence that a skilled person would use in a comparison to determine the structural similarity between Amgen's antibodies and J16. Furthermore, I am puzzled by Dr. Rees' suggestion that it's improper to analyze the amino acid sequence of J16 because it was "obtained through an affinity maturation process in which various residues in the CDR regions

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were mutated.” Rees Rebuttal Rpt. at ¶400. In my view, it’s proper to consider the CDR residues that were mutated when comparing primary structures of different antibodies.

278. As I showed in my Opening Report, there are significant differences in the primary structure of J16 as compared to Amgen’s antibodies. Siegel Opening Rpt. at ¶217-220, Ex. X5A, X5B, X5C. Again, Dr. Rees criticizes my sequence analysis as “based solely on percent sequence identity.” Rees Rebuttal Rpt. at ¶400. His criticism is baseless. As I explained above, and as a skilled person would readily appreciate, my analysis provides a wealth of information beyond mere overall percent sequence identity. It reports the specific differences in primary structure between J16 and Amgen’s antibodies, including the exact location of those differences and the specific type of amino acid differences at those locations. My analysis also shows the location and types of amino acid differences in the CDR regions, including any differences in CDR length. In my opinion, Dr. Rees erred when he chose not to consider the amino acid sequence of J16 in his analysis.

279. Rather than comparing the amino acid sequence of Amgen’s antibodies to 1D05, Dr. Rees only compares the *length* of the 1D05 CDR H3 to the “distribution of commonly observed H3 length in humans and mouse antibodies.” Rees Rebuttal Rpt. at ¶404. He concludes that “1D05 is an outlier in that its H3 loop contains 22 amino acid residues.” Rees Rebuttal Rpt. at ¶403. In my view, Dr. Rees erred when he failed to consider the amino acid sequence of 1D05 in his analysis. His analysis, which only considers CDR H3 length, is wholly insufficient to show that Amgen’s antibodies are representative of an antibody having a structure like 1D05.

280. In my Opening Report, I explained that there are significant differences in primary structure between 1D05 and Amgen’s antibodies. Siegel Opening Rpt. at ¶¶208-212, Ex. X3A, X3B, X3C. These include significant differences in CDR sequence and length.

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281. At paragraphs 406-409, Dr. Rees opines that the Amgen antibodies are representative of [REDACTED]. Rees Rebuttal Rpt. at ¶¶406-409. Again, rather than comparing the amino acid sequences of Amgen's antibodies to [REDACTED], Dr. Rees only looks at canonical structures. For the reasons stated above, this is wholly insufficient to show that Amgen's antibodies are representative of an antibody having a structure like [REDACTED]

282. I note that, even *if* canonical structures provided evidence that Amgen's antibodies are representative of other structures encompassed by the claimed genus – which they do not – none of the antibodies disclosed in the Asserted Patents have the same canonical structure as [REDACTED] in both the heavy and light chains (1-2, 1-1-2).

283. As described above, there are significant differences in primary structure between Amgen's antibodies and [REDACTED] Siegel Opening Rpt. at ¶¶265-269, Ex. X6A, X6B, X6C.

284. For the reasons stated above, Dr. Rees' analysis fails to show that Amgen's antibodies are representative of antibody structures that are encompassed within the claimed genus, including antibodies having structures like 1D05, AX132, J16, and [REDACTED]. It is still my opinion that the Asserted Claims are invalid for failing to satisfy the written description requirement.

285. Even assuming, however, that conservative changes could be made to the framework regions, one of ordinary skill would understand that these residues are normally not directly involved in antigen binding and, therefore, generally do not dictate antibody binding specificity. Therefore, a skilled person would not expect these changes to affect the epitope location or binding specificity of the disclosed antibodies. [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

286. This misses the point. Again, as I stated above, it's not simply a numbers game. Dr. Rees fails to consider whether the diversity of sequences that may be obtained following the teachings of the patent are representative of antibody structures encompassed within the claimed genus, including alirocumab and the Third Party Antibodies.

287. But, more fundamentally, Dr. Rees again fails to consider whether a skilled person would understand from the teachings of the patents that the antibodies made according to the substitution process would fall within the scope of the Asserted Claims. There is no indication in the Asserted Patents that the specific residues listed in the algorithm were selected based on antibodies that meet the recited claim limitations, as opposed to the disclosed antibodies that fall outside of the claims. Therefore, a skilled person would not consider these general teachings as directing someone to make additional antibodies that specifically possess the claimed functional characteristics. I note that Amgen's experts have not argued that these amino acid substitutions are a way forward to generate antibodies as diverse as those that Amgen is now trying to encompass in its claims – antibodies with structures as diverse as alirocumab, 1D05, AX1 32, or J16, for example. In my opinion, the disclosure in the specification does not show that Amgen was in possession of additional antibodies that fall within the scope of the claims and are representative of the claimed genus. Again, the patents only provide an invitation for further research.

288. At paragraphs 295 to 297 of the Rees Report, Dr. Rees walks through “an example of how either swapping out a CDR or making substitutions within the CDR occurs and demonstrates that the inventors were in possession of far more sequences than just the sequences

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disclosed in the Patents expressly.” Rees Rebuttal Rpt. at ¶¶295-297. Using the Amgen antibody 31H4, Dr. Rees first explains that the heavy chain CDR H2 of 31H4 is not involved in making any contacts with the claimed residues and, therefore, selects this CDR as a potential region to be swapped. Thus, Dr. Rees explains that a skilled person would be directed to making changes in the regions of the antibody that are not directly involved in antigen binding. Changes to these regions would likely have no effect on the binding properties, including epitope location, of the antibody variant as compared to the parent molecule. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

289. Dr. Petsko also explains that the substitution process that is taught by the Asserted Patents would [REDACTED]

[REDACTED] Petsko Rebuttal Rpt. at ¶314 (emphasis added). In my opinion, one skilled in the art would understand that making even a single conservative change in the CDR regions of an antibody can have unpredictable consequences on an antibody’s binding properties. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

290. Significantly, I note that neither Dr. Rees nor Dr. Petsko opines that a skilled person would understand that the Asserted Patents teach making substitutions to the disclosed antibodies to arrive at an antibody having a structure like alirocumab, or like the Third Party Antibodies.

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291. This analysis further shows that Amgen was not in possession of antibodies having a structure like alirocumab or like the Third Party Antibodies (1D05, AX132, J16) at the time that it filed its patent application.

292. Given that a plethora of antibodies to different antigens can be produced from a relatively limited set of heavy and light chain germline immunoglobulin genes, when one is trying to describe structural features that characterize a particular genus of antibodies, one needs to describe structural features that enable one to distinguish what makes an antibody a member of the genus from not being a member of the genus. Clearly, being encoded by particular immunoglobulin genes (which confer basic amino acid sequence as well canonical loop structures) is not a specific enough way to distinguish structural features that determine what's "in" from what's "out". To say that the structural features that define members of a genus is that they simply bind to the same antigen, to a particular region of an antigen, or even to one or more of a collection of amino acid residues on an antigen is really not describing the detailed structure of an antibody nor is it particularly productive since it doesn't allow you to visualize their tertiary structures, much less the primary structures required to actually make the antibodies. Being able to make conservative amino acid changes to antibodies you already have, or mixing and matching pieces of antibodies you already have, would not be expected to create additional members of the genus that differ significantly in the way they may satisfy the boundaries of the genus. Tellingly, neither Drs. Rees nor Petsko have argued that the patents teach a way forward to generate antibodies having structures as diverse as alirocumab or the Third Party Antibodies.

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# **EXHIBIT O**

No. 2017-\_\_\_\_

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**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

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SANOFI, SANOFI-AVENTIS U.S. LLC, AVENTISUB LLC, f/d/b/a AVENTIS  
PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC.,

*Defendants-Appellants,*

v.

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; and AMGEN USA INC.,

*Plaintiffs-Appellees.*

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On Appeal from the United States District Court for the District of Delaware,  
No. 14-1317-SLR

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**DECLARATION OF ROBERT H. ECKEL, M.D.**

I, Robert H. Eckel, hereby declare and state as follows:

1. I am currently the Charles A. Boettcher II Endowed Chair in Atherosclerosis in the Department of Medicine at the University of Colorado Denver, Anschutz Medical Campus. From 2005-2006, I was the President of the American Heart Association. I am board certified in Internal Medicine and Endocrinology and Metabolism. I am a clinical practitioner where I act as a preventive cardiologist. I have an appointment in cardiology and also participate in a clinic in the Heart Center of the University of Colorado Hospital. My participation in the clinic is largely focused on preventive medicine, including looking at metabolic and lifestyle issues related to heart attack and stroke.

2. I testified at the injunction hearing held before the Court on March 23-24, 2016. I am submitting this declaration in support of the motion to stay the permanent injunction filed by Sanofi, sanofi-aventis U.S. LLC, Aventisub LLC, f/d/b/a Aventis Pharmaceuticals Inc., and Regeneron Pharmaceuticals, Inc. (“Defendants”). I am fully familiar with the facts discussed below.

3. For at least the reasons discussed herein, as well as the reasons discussed during my testimony at the injunction hearing, if the Court’s permanent injunction order is not stayed, doctors and patients will be harmed because they will be deprived of key medical benefits that PRALUENT® provides, which no other product offers. Thus, it is my opinion that an injunction should be stayed so long as the case is not final – *i.e.*, insofar as there remains a possibility that the permanent injunction decision may be overturned by a court.

4. I have prescribed PRALUENT® to a number of my patients since the product was first launched in the United States around August of 2015. At this point, I have multiple patients who are benefiting from PRALUENT® and, in my opinion, it is very important that these patients continue to have access to the product while this case is further considered by the courts.

5. Cardiovascular disease (CVD) is the number one cause of death worldwide.<sup>1</sup> CVD can be caused by a number of things, including high levels of “bad cholesterol,” also called “LDL-C” (which stands for low-density lipoprotein cholesterol). A number of drugs have been available over the years to try to control LDL-C in patients. The most commonly prescribed

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<sup>1</sup> Much of the background information that follows was discussed during my testimony at the injunction hearing. For the purpose of context for the opinions set out in this declaration, I am providing a brief recitation of some of the key background facts.

drug to control LDL-C is a statin. But there are a large number of patients who do not achieve sufficient LDL-C lowering while on statins. These patients remain at a very high risk of developing conditions leading to CVD and other life-threatening cardiovascular problems. For those patients, doctors now have the option to prescribe anti-PCSK9 antibodies such as PRALUENT® (alirocumab) or REPATHA® (evolocumab) in an attempt to lower LDL-C levels. But there are critical differences between PRALUENT® and REPATHA® and, thus, it is very important that doctors and patients continue to have uninterrupted access to both products, at least until this case is finally resolved.

6. One of the critical distinctions between PRALUENT® and REPATHA® is the availability of a “low dose” with PRALUENT®. PRALUENT® is approved in two doses – a 75 mg low-dose option and a 150 mg high-dose option, both taken every two weeks. REPATHA® is also approved in two doses, but there is no low dose option. Rather, there is a 140-mg-every-two-weeks dose and a 420-mg-every-four-weeks dose, which is just three injections of the 140 mg dose. Because each of these products comes in a pre-filled syringe or a pre-filled autoinjector, it is not possible for a doctor to measure out smaller doses of REPATHA® than what is provided in the syringe or autoinjector. Once started on a PCSK9 product, and assuming a clinical response is achieved and there are no adverse reactions, a patient will generally remain on the product in order to keep their LDL-C at appropriate levels.

7. In terms of percent LDL-C reduction, the 75 mg dose of PRALUENT® provides a reduction of approximately 45% in LDL-C level compared to baseline. The 140 mg dose of REPATHA® and the 150 mg dose of PRALUENT® each provide a reduction of approximately 60% in LDL-C levels. The 420 mg monthly dose of REPATHA® provides approximately the same 60% reduction in LDL-C as the 140 mg dose administered every two weeks.

8. Importantly, PRALUENT®'s low- and high-dose options provide physicians significant flexibility in tailoring a treatment regimen for each patient. In particular, PRALUENT®'s two doses allow physicians to (1) start patients on a low dose (75 mg) and then titrate to the higher dose (150 mg) if additional reduction is necessary; and (2) start with the high dose (150 mg) and then down titrate to the lower dose (75 mg) as needed. REPATHA® simply does not provide this flexibility, as its two different high doses provide the same 60% anticipated reduction in LDL-C.

9. PRALUENT® and its flexible titration options are very important to doctors and patients since the majority of doctors in this country treat a patient's LDL-C to a "target" – *i.e.*, a desired LDL-C value that is sought without going too far below that number. There is no particular LDL-C level that is widely accepted as being correct for patients. Instead, doctors evaluate patients on a case-by-case basis and, based on the available information and circumstances, identify a desired LDL-C level. Importantly, the majority of doctors (including me) do not treat a patient's LDL-C level to get it as low as it will go. This is because LDL-C levels that are "very low" (e.g., those under 25 mg/dL) are a concern for many doctors working in the cardiovascular area because it is unknown if there is an added benefit and/or any added safety risks to patients having such very low levels of LDL-C. Very low levels of LDL-C were a point of much discussion between the FDA and each of Regeneron/Sanofi and Amgen during the pre-approval advisory committee meetings for their respective products. In fact, the FDA-approved labels for both products state "the long-term effects of very low levels of LDL-C induced by [either product] are unknown."

10. My preference is to start a patient on the 75 mg dose of PRALUENT® to see if the target LDL-C can be achieved *prior to* increasing the dose and potentially going too low with

the patient's LDL-C level. Importantly, for many patients, the 75 mg dose is all that is necessary. That is, with the 75 mg dose, numerous PRALUENT® patients hit their LDL-C target number and don't go too low with their LDL-C. In fact, I currently have multiple patients who have achieved their LDL-C target on the 75 mg dose of PRALUENT®. In the event PRALUENT® is taken off the market, these patients would be required to (a) switch to 140 mg REPATHA®, which would lower their LDL-C levels by approximately 15% more, likely bringing LDL-C levels for at least some patients to very low levels; or (b) not take an anti-PCSK9 antibody. Neither of these options is medically sound. In my opinion, the best treatment option for patients achieving their target LDL-C goal on the low dose of PRALUENT® is to remain on that dose – and it is important that this option remains available during the time the courts review this case.

11. I understand that many doctors, like me, have a preference for the 75 mg low dose of PRALUENT®, approximately 85% of PRALUENT® prescriptions have been for the low dose. This is not surprising to me, as I understand that the majority of patients studied in the PRALUENT® clinical trial program achieved their LDL-lowering goals with the 75 mg dose. Thus, like many of my patients, I would expect that many current PRALUENT® patients that are on the 75 mg low dose would remain on that dose if the product were to remain available. Again, it is my opinion that the best treatment option for patients achieving their target LDL-C goal on the low dose of PRALUENT® is to remain on that dose.

12. It is important to understand what happens in terms of treatment options if PRALUENT® is removed from the market for an extended period of time. If PRALUENT® were to be discontinued but patients still required the amount of LDL-C lowering achieved with a PCSK9 inhibitor, low dose PRALUENT® patients would be forced to switch to REPATHA® which would be the only anti-PCSK9 antibody product available and which would reduce LDL-

C levels more than necessary. Thus, removal of PRALUENT® from the market, even if only for the time period that the case is on appeal, may result in at least some patients achieving concerning very low LDL-C levels. In other words, there are certainly patients who have near-low levels of LDL-C while on the 75 mg low dose of PRALUENT®. If that product is no longer available, those same patients will likely be forced to take the 140 mg dose of REPATHA® – which will almost certainly result in an *even lower and potentially concerning LDL-C level* for those patients. These are risks that patients should not be exposed to unless and until it is certain that an injunction is appropriate in this case.

13. In addition to potentially achieving unwanted very low levels of LDL-C, removal of PRALUENT® from the market at this point also means that many patients on the 75 mg dose of PRALUENT® will likely be forced to take what is essentially a double dose of medication – the 140 mg dose of REPATHA® (the lowest dose of that product that is available) – when it is not needed. This is counter to what doctors are taught as early as medical school which is to use as little medicine as possible to achieve the desired clinical result. Exposing these patients to larger dosages of medication than is necessary is a risk that should not be taken while this case is on appeal and the question of whether to permanently remove PRALUENT® from the market is finally resolved.

14. It is also my opinion that doctors and patients stand to be harmed if left with only one supplier of anti-PCSK9 antibody products. If PRALUENT® is unavailable going forward, REPATHA® is then the only PCSK9 product available. Obviously, should REPATHA® become unavailable for some reason, patients will be dramatically harmed by virtue of having no available anti-PCSK9 antibody product. There are a multitude of reasons that a product like REPATHA® could become unavailable. For example, any pharmaceutical company can have

manufacturing or supply issues caused by things like contamination or even a safety recall. In fact, numerous pharmaceutical products have been recalled because of later-identified safety issues, including the well-known cases of BAYCOL® and VIOXX®. Robust enough data on PRALUENT® and REPATHA® do not exist at this point, and it is in the best interests of patients for both products to remain available going forward.

15. In addition, it is my opinion that the Defendants stand to be substantially harmed if PRALUENT® is removed from the market now, only to be returned to the market in the event it is determined in the future that a permanent injunction is not appropriate. In terms of the pharmaceutical market, trust and confidence in both a medicine and its supplier are paramount. Doctors and patients must have complete trust not only in a medicine's efficacy, but also in its availability. Unfortunately, Defendants' hard-earned reputation for reliability will be irreparably harmed the moment PRALUENT® is pulled from the market. In my opinion, that immediate damage could not be undone if Defendants succeed on appeal, as the goodwill and trust in both Defendants and PRALUENT® will be permanently and irreparably harmed.

16. The flexibility provided by PRALUENT® and its two different dosage options is the best option for many of my patients. Removal of PRALUENT® from the market would cause significant disruption to my practice and require me to prescribe REPATHA® to my patients in need of an anti-PCSK9 antibody product when in my experienced clinical judgment that product may not be the best option for those particular patients. It is important to me and my patients that PRALUENT® remains an available PCSK9 inhibitor option, at least until this case is finally resolved.

17. Lastly, if the injunction were not stayed and then later reversed, I would have patients taken off of PRALUENT® that would have to be put back on the treatment. From my

perspective as a practitioner, such switching of treatments is not in patients' best interests, especially if it can be avoided.

I declare under penalty of perjury under the laws of the United States of America and the State of Colorado that the foregoing is true and correct and that this declaration was executed in Colorado on January 13, 2017.

A handwritten signature in cursive script, appearing to read "Robert H. Eckel".

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Robert H. Eckel, M.D.

# **EXHIBIT P**

No. 2017-\_\_\_\_

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**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

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SANOFI, SANOFI-AVENTIS U.S. LLC, AVENTISUB LLC, f/d/b/a AVENTIS  
PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC.,

*Defendants-Appellants,*

v.

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; and AMGEN USA INC.,

*Plaintiffs-Appellees.*

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On Appeal from the United States District Court for the District of Delaware,  
No. 14-1317-SLR

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**DECLARATION OF SHARON M. OSTER**

I, Sharon M. Oster, declare as follows:

I am the Frederick Wolfe Professor of Management and Entrepreneurship at the Yale School of Management. I received my undergraduate degree in Economics from Hofstra University in 1970 and my Ph.D. Degree in Economics from Harvard University in 1974. I have been a member of the faculty at Yale University since 1974 and served as the Dean of the Yale School of Management from 2008 to 2011.

1. On March 24, 2016, I testified before this Court with respect to my analysis of economic issues pertaining to Amgen's request for an injunction that would prohibit the sale of

Praluent in the U.S.<sup>1</sup> Prior to that, I submitted an expert report disclosing my opinions and the basis thereof on December 7, 2015.<sup>2</sup>

2. I understand that this Court issued a decision enjoining the sale of Praluent in the U.S. on January 1, 2017. I further understand that this decision will be appealed by Sanofi and Regeneron and that the foregoing decision can be reversed by an appellate court. As a result, from an economic perspective, it would be appropriate to stay the injunction pending the outcome of the appeal for the reasons described below.

Absent A Stay, Defendants Will Be Irreparably Harmed

3. Absent a stay, if the permanent injunction were to be reversed on appeal, Defendants would suffer significant and irreparable harm.

4. In the current complex healthcare environment, contracting with insurers is a key business function that affects physician and patient access to pharmaceutical products. If Praluent is enjoined while awaiting appeal, numerous contracts between Sanofi/Regeneron and payers, such as insurers and pharmacy benefit managers (PBMs), will likely be voided and Amgen would likely have the opportunity to negotiate new contracts related to Repatha without any competition.<sup>3</sup> In the event of a successful appeal, to the extent some payers were not contractually restricted from doing so based on those new contracts for Repatha, Sanofi/Regeneron would again have to negotiate contracts with payers related to Praluent.<sup>4</sup> This creates substantial uncertainty for both patients and physicians, and may impede access of some patients to this new and important cholesterol therapy.

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<sup>1</sup> Amgen Inc., v. Sanofi et al., Trial Transcript, Volume II, March 24, 2016 (“Trial Transcript, Vol. II”), at pp. 439-492.

<sup>2</sup> Expert Report of Sharon M. Oster, December 7, 2015 (“Oster Report”).

<sup>3</sup> Declaration of Robert Terifay in Support of a Stay, dated January 13, 2017 (“Terifay Declaration”), at pp. 4-5.

<sup>4</sup> Terifay Declaration, at pp. 4-5.

5. The withdrawal of Praluent from the market pending an appeal can lead potentially to long-term reputational harms for the Defendants. According to Regeneron and Sanofi personnel, in the pharmaceutical industry, a manufacturer's reputation for reliability and safety of supply is essential for the successful commercialization of a drug.<sup>5</sup> An interruption of that supply, as in the case of an injunction without stay, threatens both companies' reputations for reliability and undermines customer confidence in those companies.<sup>6</sup> This may be especially true for a completely new class of drugs such as the PCSK9 inhibitors.

6. An injunction would lead to substantial layoffs of Regeneron and Sanofi employees involved in the manufacture, marketing and sale of Praluent.<sup>7</sup> According to Regeneron personnel, withdrawal of Praluent from the U.S. market would require Regeneron to lay off "a large majority of the 450 employees working on Praluent."<sup>8</sup> Similarly, Sanofi would may eventually lay off "the vast majority of the 700 Praluent-related field and sales employees."<sup>9</sup> These employees are dedicated to Praluent and have specialized knowledge related to the drug.<sup>10</sup> Interruption of the job contract in an environment in which human capital is both specialized and key is problematic and highly inefficient. In the event that Praluent reenters the market at a later date, employees would need to be rehired and retrained, which is both time-consuming and costly.<sup>11</sup>

### The Public Interest Favors A Stay

7. A stay pending appeal will benefit the public interest.

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<sup>5</sup> Terifay Declaration, at pp. 3-6; Declaration of Victoria Carey in Support of Stay, January 13, 2017 ("Carey Declaration"), at p. 4.

<sup>6</sup> Terifay Declaration, at pp. 3-6; Carey Declaration, at pp. 3-4.

<sup>7</sup> Trial Transcript, Vol. II, at pp. 447, 480-481.

<sup>8</sup> Terifay Declaration, at pp. 5-6.

<sup>9</sup> Carey Declaration, at p. 3.

<sup>10</sup> Carey Declaration, at p. 3. See also Terifay Declaration, at pp. 5-6.

<sup>11</sup> Terifay Declaration, at pp. 5-6; Carey Declaration, at p. 3.

8. From an economic perspective, consumers benefit from a choice of differentiated products.<sup>12</sup> Here, Praluent provides patients and physicians with an important treatment option. It is a different molecule than Repatha, and unlike Repatha, it is available in a low dose form.<sup>13</sup> Economic evidence supports the value of this option given that the vast majority of sales of Praluent are of the low dose form of the drug.<sup>14</sup> Without a stay pending appeal, patients and physicians will be deprived of this important treatment option.

9. In addition, enjoining Praluent could lead to higher net prices of Repatha, which would harm the public interest. Without competition from Praluent, Repatha will be the only PCSK9 inhibitor on the market. As Amgen personnel testified, competition from Praluent has led to significant discounts to payers for PCSK9 inhibitors. An injunction would remove this downward price pressure resulting from competition, potentially leading to higher prescription drug costs for payers and patients.<sup>15</sup>

10. Finally, the public also benefits from having multiple manufacturers on the market due to an increase in the reliability of supply.<sup>16</sup> Absent a stay during the appeal process, the public would be deprived of an alternative anti-PCSK9 therapy, which could become very important in the event that Amgen were to experience manufacturing difficulties or contamination issues.

#### Amgen Will Not Be Irreparably Harmed By A Stay

11. Amgen will not be irreparably harmed by a stay. A temporary stay simply maintains the status quo.

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<sup>12</sup> Trial Transcript, Vol. II, at pp. 446, 448, 456-459.

<sup>13</sup> Oster Report, ¶51.

<sup>14</sup> Tr. 455:1-13.

<sup>15</sup> Tr. 466:1-467:16

<sup>16</sup> Tr. 459:7-461:2

12. A stay would not affect Amgen's ability to conduct research and development (R&D). Amgen is a large company with more than \$15 billion in revenues<sup>17</sup> and sixteen drugs currently on the market.<sup>18</sup> Even with Praluent on the market, Amgen has substantial financial resources from which to fund R&D. Amgen's strong financial position is evidenced by a series of recent share repurchases. In Q3 2015, Amgen's stock repurchases totaled \$0.7 billion and the buybacks are expected to continue into 2016.<sup>19</sup> According to a Q3 2015 Amgen earnings call presentation, Amgen is "[p]ositioned well for future sustainable growth."<sup>20</sup>

13. With respect to reputational harm, Amgen will not suffer from a stay. The alleged harms espoused by Amgen in the permanent injunction proceedings focused on injury to Amgen's reputation as an innovator.<sup>21</sup> My research indicates that Amgen's reputation as an innovator in the pharmaceutical industry is well-established and that there is no evidence of such injury absent an injunction.<sup>22</sup> Even accepting the potential for reputational harm, however, this would not be exacerbated if a stay were granted.

14. Finally, to the extent that Amgen suffers any losses, including those in the form of price erosion, lost market share or lost profits, they are financial in nature, quantifiable and compensable by money damages.<sup>23</sup> Damages experts routinely quantify such losses based on the sort of data available here, such as sales projections and rebate agreements.<sup>24</sup> For example, Amgen's own expert, Mr. Meyer, was able to calculate past damages in this case.<sup>25</sup> As I

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<sup>17</sup> Tr. 476:10-15

<sup>18</sup> Tr. 63:16-19 (Bradway direct)

<sup>19</sup> Tr. 476:2-478:4

<sup>20</sup> Tr. 477:13-20

<sup>21</sup> Tr. 229:20-230:16 (Berndt direct)

<sup>22</sup> Tr. 478:5-479:17

<sup>23</sup> Tr. 472:8-16

<sup>24</sup> Tr. 472:25-473:22

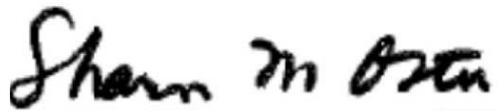
<sup>25</sup> Expert Report of Paul K. Meyer, November 6, 2015 ("Meyer Report"),

testified, the quantification of such financial injury is the “bread and butter of damages experts.”<sup>26</sup>

15. For the foregoing reasons, the permanent injunction should be stayed pending appeal.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on January 13, 2017

  
Sharon M. Oster

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<sup>26</sup> Tr. 472:25-473:9

# **EXHIBIT Q**

No. 2017-\_\_\_\_

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**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

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SANOFI, SANOFI-AVENTIS U.S. LLC, AVENTISUB LLC, f/d/b/a AVENTIS  
PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC.,

*Defendants-Appellants,*

v.

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; and AMGEN USA INC.,

*Plaintiffs-Appellees.*

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On Appeal from the United States District Court for the District of Delaware,  
No. 14-1317-SLR

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**DECLARATION OF VICTORIA CAREY IN SUPPORT OF A STAY**

I, Victoria Carey, declare as follows:

1. I am employed by sanofi-aventis U.S. LLC (“Sanofi”) as the Vice President and Business Lead for the Cardiovascular Unit. In this role, I am responsible for the commercial aspects of several Sanofi cardiovascular drug projects, including PRALUENT® (“Praluent”).

2. I testified at the injunction hearing held before the Court on March 23, 2016. I understand that this Court’s issued its permanent injunction decision on January 5, 2017. I also understand that that decision will be appealed by Sanofi and Regeneron (collectively, “Defendants”).

3. I submit this declaration in support of Defendants’ motion to stay the permanent injunction in the case.

**Praluent Is Significant to Sanofi**

4. Sanofi, a global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. It has core strengths in innovative drugs, including in diabetes solutions, cardiovascular health, and human vaccines.

5. Praluent is central to Sanofi's cardiovascular business in the United States. Praluent is projected to be one of the most significant therapies directed to patient cardiovascular health offered by Sanofi in the United States. As such, Sanofi has devoted significant resources to develop and support the delivery of Praluent to U.S. patients.

6. More than 700 Sanofi United States employees are dedicated to educating doctors and patients on Praluent in the United States. This includes sales representatives, nurse educators, and medical affairs specialists. There are also marketing employees, trade and access managers, operations people, and other employees dedicated to Praluent in the United States. Our Praluent employees are experienced in the cardiovascular disease state and have specific training related to Praluent.

7. Since 2009, Sanofi, in conjunction with Regeneron, has spent significant resources to develop Praluent and bring it to market. Significant resources were also spent on U.S. commercialization, which includes educational, marketing, and sales expenditures.

**Absent a Stay, the Injunction Would Irreparably Harm Sanofi**

8. Unless the injunction is stayed pending appeal, Sanofi will be irreparably harmed in ways that would be difficult to calculate and impossible to fully reimburse.

9. At the outset, if the injunction is not stayed pending appeal, Sanofi will no longer sell Praluent and lose the associated sales/profits.

10. Due to this fact, the majority of the 700 Praluent-related United States field and sales employees may eventually have to be laid off. These employees are dedicated to the Praluent project and have specialized knowledge related to the drug.

11. If Praluent had to be re-launched at a later date, Sanofi would have to attempt to rehire the employees it was forced to lay off to market and sell Praluent. In the interim, however, many employees would likely have found other jobs and even if they did not would likely be hesitant to come back to a company that just laid them off. With respect to new recruitment, Sanofi's ability to recruit talent would also be compromised due to reputational harm. Indeed, employees will likely be wary of joining a company that just had substantial layoffs.

12. Additionally, any qualified employees that Sanofi could hire would most likely need specialized training relating to Praluent. This training is a substantial undertaking that is time consuming and costly. If the injunction were reversed, one of the reasons why Praluent cannot be simply relaunched immediately after such a decision is the time involved in employee training.

13. Other efforts that Sanofi must take to respond to an injunction are immense. For example, Sanofi will have to modify and void contracts with payers (i.e., insurance companies and pharmacy benefit managers) relating to Praluent. Sanofi would have to undertake a complex and burdensome operation to stop the manufacture and distribution of Praluent, including

removing Praluent from all stages in the supply chain (e.g. manufacturing, packaging and distribution). This is a massive, complex and costly logistical undertaking. Sanofi also will have to modify and repurpose other employees and infrastructure that were dedicated to Praluent. This includes areas such as supply chain, patient support and research and development. This process is quite involved and will take many months. Similarly, if the foregoing had to be reinstated due to a re-launch of Praluent, it is not something that could be simply undone. A re-launch would be an even more costly and complex undertaking than a shut down. .

14. Absent a stay, Sanofi will suffer additional and serious harm to its reputation as a company and to that of Praluent. Customer confidence and brand reliability are critical to sales of Praluent, and removal of the drug from the market, for any period of time, would put a re-launch of Praluent at a severe disadvantage. This is particularly true in the case of a completely new drug class such as the PCSK9 inhibitors.

15. Insurers that reimburse patients who take and physicians that prescribe Sanofi's drugs, including Praluent, rely on Sanofi's reputation to reliably supply drugs. The injunction absent a stay will injure Sanofi's hard-earned reputation for reliability. It would also damage Sanofi's good will and injure its customer relationships. This reputational injury would not only affect Praluent, but pervade other Sanofi drugs.

16. With respect to Praluent itself, absent a stay, if it were re-launched, it would not be viewed the same way by some physicians and patients. For example, those unfamiliar with the present litigation may falsely perceive Praluent as having safety, efficacy or supply issues. Thus, the hard-earned reputation of Praluent will suffer absent a stay.

17. Indeed, the challenge involved in re-launching Praluent would be much more difficult than the initial launch of Praluent due to these reputational harms. Thus, it would be

difficult if not impossible for Sanofi to generate new sales and obtain the market share it once had.

18. Additionally, during the time that Sanofi was off the market, payer organizations (insurance companies) that originally listed Praluent would have renegotiated and listed Repatha. It would be difficult to persuade those insurance companies to list Praluent again due to potential contractual issues and concerns from insurance companies.

**The Public Will Be Harmed Absent a Stay**

19. Our market research shows that physicians have a strong preference for Praluent's dosing flexibility and the real world sales data have also shown a strong physician preference for Praluent's low dose form (75 mg). To date, about 85% of prescriptions and about 80% of sales have been for the low-dose form of Praluent.

20. Absent a stay, the large number patients on Praluent, the vast majority of whom are on the low dose, will have to be transitioned by practitioners to either Repatha or off of an anti-PSCK9 inhibitor altogether. Then if the injunction is reversed, the practitioner will have to decide whether to put these patients back on Praluent. This will be an undue burden on both practitioners and patients.

21. Absent a stay, even if an injunction were overturned, patients would be further delayed in receiving Praluent. As described above, multiple aspects of the Praluent project would be eliminated or repurposed after an injunction. Each of these aspects would have to be modified or recreated to support Praluent, which could take many months implement after an injunction was overturned.

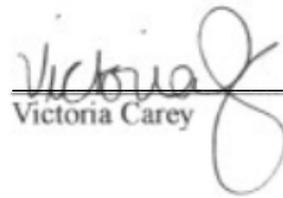
22. Additionally, removing Praluent from the market now would impose a significant administrative burden on the U.S. healthcare system and the parties because contracts between Sanofi and payers would likely have to be voided in light of an injunction (this in turn would create a situation where Amgen would have to negotiate contracts with, at least, payers that did not previously list Repatha).

23. Then, if the injunction were reversed, Sanofi would have to go through yet another negotiation process with payers. However, some payers may be contractually restricted from listing Praluent due to new contracts that would have been executed for Repatha while the injunction was in force.

24. These highly complex contracts can take months to draft/negotiate. Multiple rounds of negotiations can be avoided by a stay, and that would be a preferable course of action.

25. Even if the injunction were reversed and some payers were able to relist Praluent, such negotiations could delay getting Praluent to patients who need it.

I declare under penalty of perjury that the foregoing is true and correct on January 13, 2017.

  
Victoria Carey

# **EXHIBIT R**

No. 2017-\_\_\_\_

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**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

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SANOFI, SANOFI-AVENTIS U.S. LLC, AVENTISUB LLC, f/d/b/a AVENTIS  
PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC.,  
*Defendants-Appellants,*

v.

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; and AMGEN USA INC.,  
*Plaintiffs-Appellees.*

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On Appeal from the United States District Court for the District of Delaware,  
No. 14-1317-SLR

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**DECLARATION OF JAY M. EDELBERG, M.D., PH.D.**

I, Jay M. Edelberg, hereby declare and state as follows:

**Introduction**

1. I am employed by sanofi-aventis U.S. LLC (“Sanofi”) as the Head of Cardiovascular Development. My duties include leading programs being developed for cardiovascular disease or heart disease, including the PRALUENT® (“Praluent”) program. Praluent is a member of a brand new class of monoclonal antibody drugs that inhibit the enzyme PCSK9, a key regulator of cholesterol metabolism. These drugs are commonly referred to as “PCSK9 inhibitors.”

2. I testified on March 24, 2016 at the injunction hearing held before the United States District Court, District of Delaware on March 23-24, 2016. I understand that the district

court issued its permanent injunction decision on January 5, 2017. I also understand that the decision is being appealed by Sanofi and Regeneron (collectively, “Defendants”) to this Court.

3. I submit this declaration in support of Defendants’ motion to stay the permanent injunction.

**Absent a Stay, the Injunction Will Jeopardize the Completion of FDA-Mandated Outcomes Studies Designed to Study the Safety and Efficacy of Praluent and the PCSK9 Inhibitor Class Generally**

4. Unless the injunction is stayed, many patients will likely withdraw from ongoing FDA-mandated clinical trials, reasoning that there is no point in participating in trials for an innovator drug that will ultimately be unavailable to them. Specifically, those patients will likely withdraw from the “ODYSSEY Outcomes” study, which was required by the FDA, and is a multi-year study that analyzes safety and efficacy of Praluent, specifically and PCSK9 inhibitors in general, such as Amgen’s REPATHA®.

5. ODYSSEY Outcomes, which was initiated in 2012, involves approximately 18,600 patients enrolled in a double-blind, placebo-controlled, parallel-group, multi-year study. ODYSSEY Outcomes was designed to answer, among other things, two key questions regarding the safety and efficacy of PCSK9 inhibitors. First, it was designed to assess the safety and efficacy of Praluent in the highest of risk patients—those patients who have recently experienced an acute coronary syndrome event. Second, it was designed to address the safety and efficacy of treating patients to a specific LDL-C target (below 50 mg/dl), a question raised by the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Notably, the Outcomes study is the *only* PCSK9-related study designed to answer the foregoing questions—Amgen’s ongoing clinical trials of its PCSK9 inhibitor, REPATHA®, do not answer these questions.

6. Losing patients prior to completion of the study, particularly those patients who are on placebo, will have a devastating impact on the public interest. It will jeopardize the results of these studies, thereby leaving unanswered crucial questions concerning the safety and efficacy of Praluent, and PCSK9 inhibitors overall. More than four years of data gathering and analysis will be lost, not to mention several hundred million dollars in resources invested by Defendants to conduct this large-scale study.

**Absent a Stay, the Injunction May Adversely Affect the Enrollment of Patients in New Clinical Trials Involving Praluent**

7. Unless the injunction is stayed, many patients will likely decline to enroll in new clinical trials involving Praluent, again reasoning that there is no point in participating in trials for an innovative drug that will ultimately be unavailable to them.

8. These new clinical trials are designed to address other key aspects of the safety and efficacy of PCSK9 inhibitors. For instance, ODYSSEY KIDS, an FDA-mandated clinical trial, is an 8-week dose-finding study to evaluate the safety and efficacy of alirocumab in children and adolescents with the genetic condition heterozygous familial hypercholesterolemia, which causes dangerously high levels of cholesterol in such patients.

9. Without the necessary patients to enroll, studies like ODYSSEY KIDS will no longer be viable. This would deprive the public of additional knowledge concerning PCSK9 inhibitors and their ability to treat very high cholesterol in children.

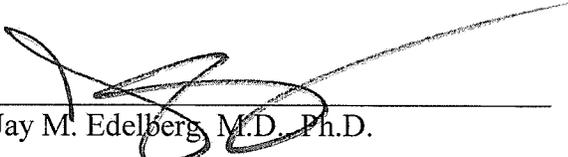
**Absent a Stay, the Injunction Will Jeopardize Clinical Trials in Certain Key U.S. Subpopulations**

10. If the injunction is not stayed, Defendants' U.S. studies with respect to U.S. subpopulations that are particularly affected by the health impact of high cholesterol will be jeopardized. As an example, there is a strong correlation between cardiovascular disease and diabetes (80% of patients with diabetes die of cardiovascular disease) and the Defendants have

ongoing clinical trials of a PCSK9 inhibitor have focused on a diabetic population. LPS14354, is one of those studies and is designed to specifically address the safety and efficacy of Praluent in patients with type 2 diabetes and mixed dyslipidemia. This critically important study could be jeopardized, based on drop out issues discussed above, if the injunction is not stayed.

11. For at least the foregoing reasons, absent a stay, the public will be harmed because they will be deprived of the important information that current and future clinical trials involving Praluent would provide, and which no other trials would provide.

I declare under penalty of perjury that the foregoing is true and correct on January 13, 2017.



Jay M. Edelberg, M.D., Ph.D.

# **EXHIBIT S**

No. 2017-\_\_\_\_\_

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**UNITED STATES COURT OF APPEALS  
FOR THE FEDERAL CIRCUIT**

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SANOFI, SANOFI-AVENTIS U.S. LLC, AVENTISUB LLC, f/d/b/a AVENTIS  
PHARMACEUTICALS INC., and REGENERON PHARMACEUTICALS, INC.,

*Defendants-Appellants,*

v.

AMGEN INC.; AMGEN MANUFACTURING, LIMITED; and AMGEN USA INC.,

*Plaintiffs-Appellees.*

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On Appeal from the United States District Court for the District of Delaware,  
No. 14-1317-SLR

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**DECLARATION OF ROBERT TERIFAY IN SUPPORT OF A STAY**

I, Robert Terifay, declare as follows:

1. I am employed by Regeneron Pharmaceuticals, Inc. (“Regeneron”) as Executive Vice President, Commercial. In this role, I am responsible for sales, marketing, market access, and reimbursement for the drug PRALUENT® (“Praluent”).

2. I testified at the injunction hearing held before the Court on March 23-24, 2016. I submit this declaration in support of Regeneron and Sanofi’s motion to stay the permanent injunction in the case.

**Praluent is Significant to Regeneron**

3. Regeneron was founded in 1988 by Dr. Leonard Schleifer based on the desire to perform world-class research and the principle that dedication to strong science would lead to important new medicines. It was not until 2011, however, that Regeneron had its first significant

product. And, it was not until 2014 that Regeneron took in more money on a cumulative basis than it had spent since its inception in 1988.

4. In general, approximately 450 Regeneron employees work on Praluent. There are sales representatives, field reimbursement managers, marketing employees, trade and access managers, operations people, medical affairs employees, research and development employees, clinical and regulatory employees, and manufacturing employees. Praluent has been a significant reason for Regeneron growing its business as quickly as it has. Each product requires employees with therapeutic experience in that disease state. The Praluent employees are experienced in the cardiovascular disease and biologics market. Regeneron does not have any other drugs in late-stage development in the cardiovascular disease area.

5. Regeneron has only three products approved for sale in the United States by the FDA: Praluent, Eylea®, and Arcalyst®. And, Praluent is projected to be an important product over the long term..

6. Since 2009, Regeneron, in conjunction with Sanofi, spent significant resources to develop Praluent and bring it to market. Significant resources were also spent on U.S. commercialization, which includes educational, marketing, and sales expenditures.

**Praluent has been Well Accepted by Physicians, Despite Significant Obstacles to Market Access for the Entire PCSK9 Inhibitor Class**

7. From what we have seen so far in the launch-to-date sales data, physicians prefer the 75 mg low dose option of Praluent. Since its launch, about 80% of Praluent sales to date have been for the low dose and approximately 20% of Praluent sales have been of the 150 mg high dose. Regeneron's prescription numbers show that approximately 85% of our prescriptions have been for the low dose and approximately 15% for the higher dose. We expect the low dose will continue to be the large majority of our sales.

8. Preference for Praluent is also demonstrated by the amount of exclusive contracts for Praluent. Regeneron, Sanofi, and Amgen have competitively negotiated contracts with healthcare providers (*i.e.*, insurance companies). To date, decisions about coverage of Praluent and/or Repatha have been made for over 90 percent of people covered by commercial insurance. For about half of those insured people, the commercial insurance contracts are parity contracts, with coverage for both Praluent and Repatha. The other half are contracts that are exclusive for one of the products. Over 50% of people commercially insured with an exclusive formulary have exclusive access to Praluent. Similarly, decisions about coverage of Praluent and/or Repatha have been made for over 90 percent of people who are insured through Medicare. And, over 70% of people on Medicare have exclusive access to Praluent.

9. Since launch over 102,000 prescriptions, for over 18,000 patients, have been dispensed for Praluent and the number grows each day. Praluent total prescriptions currently represent at least 50 percent of the PCSK9 inhibitor market.

**Absent a Stay, the Injunction Would Irreparably Harm Regeneron**

10. Unless the injunction is stayed pending appeal, the injunction will harm Regeneron in ways that would be difficult to calculate and impossible to fully reimburse.

11. Absent a stay, the injunction will cause Regeneron to lose sales of Praluent and associated future profits.

12. Absent a stay, the injunction will injure Regeneron in less tangible ways. The physicians who prescribe Praluent depend on Regeneron's ability to continue supplying the drugs that they prescribe. The injunction will injure Regeneron's hard-earned reputation for reliability. It would damage Regeneron's good will and injure its customer relationships.

13. An injunction without a stay would cause a disruption to Regeneron's business operations. Praluent is a major product for Regeneron's long-term success. The future profits from Praluent will help fund Regeneron's research and development for other products. An injunction without a stay would deprive physicians of a drug that they prefer for particular patients and physicians; patients would be denied a low-dose option in the PCSK9 inhibitor market if they need less cholesterol reduction than achieved with high-dose options. Staying the injunction would lessen the therapeutic options available to physicians and their patients.

14. The necessary steps that Regeneron must take to respond to an injunction and the potential disruption to Regeneron's business, cannot be overstated. Nor can the harm to Regeneron be overstated if Regeneron is forced to remove Praluent from the market for an extended period of time, even if it is ultimately allowed to reintroduce Praluent at a later date.

15. Absent a stay, to comply with a permanent injunction, Regeneron would have to initiate a complex and burdensome logistical operation to remove Praluent from all stages in the supply chain, including component supply, manufacturing, packaging, and distribution. This is a massive, complex and costly logistical undertaking. If the foregoing had to be reinstated due to a re-launch of Praluent, it is not something that could be simply undone. A re-launch would be an even more costly and complex undertaking than a shut down. At the same time, all contracts covering Praluent would likely be voided, which would have an immediate adverse impact on patients. For example, for the contracts exclusive to Praluent, it would take several months to change formulary guidance and complete a new contract with Amgen. In the meantime patients would be without treatment. To date, over 102,000 prescriptions have been dispensed for Praluent and the number grows each day. Tens of thousands of people would lose access to a critical drug absent a stay.

16. The challenge involved with re-launching a product after it was initially launched would be much more difficult than launching the product initially. Contracts representing over 90% of covered patients have already been negotiated and finalized. A large portion of these contracts are exclusive for Praluent. Presumably if these contracts are voided due to the injunction, the healthcare providers will be forced to negotiate with Amgen, which is the only other anti-PCSK9 inhibitor on the market. Those new Repatha contracts will likely not be able to be voided if Praluent reenters the market. The injunction will cause Praluent to lose market share that it will never be able to regain when it reenters the market.

17. Because customer confidence and brand reliability are critical to sales of Praluent, removal of the drug from the market, for however long, would put any re-launch of Praluent at a severe disadvantage. This is particularly true in the case of a completely new drug class such as the PCSK9 inhibitors.

18. These harms go beyond Praluent and would affect Regeneron's entire product line and future product line. Regeneron is a small pharmaceutical company. The harms from the injunction would damage Regeneron's business in ways that are likely to be long-lasting and irreparable, and are by no means limited regardless of whether the injunction remains in place for a matter of days, weeks, months, or years.

19. These injuries would not go away even if the injunction is reversed on appeal. Trying to re-launch Praluent after it has been removed from the market by a court order would be a daunting task and could not suffice to overcome the intangible injuries to good will and reputation that an injunction would cause.

20. Absent a stay, Regeneron's internal and field-based employees would be negatively affected. While Regeneron would make every effort to move people to other

positions, we have only two other marketed products that are already staffed. Two other potential launch products are already staffed with employees with other skills sets. No other launches are planned in the near future in the same disease area as Praluent. Ultimately, Regeneron would need to lay off a large majority of the approximately 450 employees working on Praluent.

21. If Praluent reenters the market, Regeneron would need to rehire the employees it was forced to lay off in order to manufacture, market, and sell Praluent. The employees laid off may have taken other jobs and may not be available for rehire or may not want to rejoin a company that just laid them off. And, experience in the disease state is a requirement for employees, so it may be difficult to find new employees. If Regeneron did find qualified employees, it is still time consuming and a great expense to train new employees about a complex new pharmaceutical product. Moreover, such a large lay-off would reflect badly on Regeneron's image and reputation among potential employees, negatively affecting hiring and retention for all of our current and future products.

**Other Implications Absent a Stay**

22. Approximately 30 percent of insured patient lives (representing more than 18MM lives) exclusively have access to PRALUENT through their insurance plans. If product availability ends within 45 days, there will likely be a significant gap in access to a PCSK9 inhibitor due to the time that it would take Amgen to negotiate pricing with these PRALUENT exclusive providers, the time to finalize contracts, and the time to get member plans to adapt their systems and policies. This may lead to high-risk patients being left without coverage for important anti-PCSK9 treatment.

I declare under penalty of perjury under the laws of the United States of America and the State of

New York that the foregoing is true and correct and that this declaration was executed in Tarrytown, New York on January 13, 2017.

  
Robert Terifay