UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC., et al.,

Plaintiffs,

v.

SANDOZ INC., et al.,

Defendants.

Case No. 14-cv-04741-RS
Case No. 16-cv-02581-RS

ORDER GRANTING SUMMARY JUDGMENT OF NONINFRINGEMENT AND DENYING RULE 56(D) MOTION

I. INTRODUCTION

Defendants Sandoz Inc., Sandoz International GmbH, Sandoz GmbH, and Lek Pharmaceuticals d.d. (collectively, "Sandoz") move for summary judgment as to both noninfringement and damages. Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Amgen") oppose summary judgment and move, in the alternative, pursuant to Rule 56(d), to defer a ruling on noninfringement until additional information is produced regarding a pending modification to Sandoz's allegedly infringing process. For the reasons explained below, Sandoz's motion for summary judgment of noninfringement is granted. The motion for summary judgment regarding damages is denied as moot. Amgen's Rule 56(d) motion is denied.[1]

[1] Sandoz and Amgen have filed multiple sealing motions regarding materials submitted as part of their summary judgment filings. Those motions (14-cv-04741, Dkt. No.'s 278, 289, 295, 298, 312, 324, 328, 332, 337; 16-cv-02581, Dkt. No.'s 116, 133, 134, 137, 151, 162, 166, 169, 174) are granted. Amgen additionally moved for leave to file an opposition to a request to strike made by Sandoz in one of its replies. The materials Sandoz seeks to strike are not relied on in this order. Accordingly, Sandoz's request to strike and Amgen's motion (14-cv-04741, Dkt. No. 333, 16-cv-02581, Dkt. No. 170) are denied.

II. BACKGROUND

Amgen and Sandoz compete to develop, manufacture, promote, and sell biopharmaceutical products. The products at issue here are filgrastim and pegfilgrastim. Filgrastim is the pharmaceutical analog of a protein that naturally occurs in the human body. It stimulates the production of a type of white blood cells ("neutrophils") vital to the human immune system and, accordingly, is useful for treating patients undergoing certain forms of cancer therapy (e.g., chemotherapy) that can cause neutrophil deficiency ("neutropenia"). Pegfilgrastim is a modified version of filgrastim that remains in the circulatory system for a substantially longer period of time and thus is "long acting." Amgen began selling filgrastim in 1991 under the brand name Neupogen® and launched a pegfilgrastim product, Neulasta®, in 2002. Sandoz brought to market an FDA-approved biosimilar filgrastim product, Zarxio®, in 2015. Sandoz also has submitted an application to offer a biosimilar pegfilgrastim product that is pending before the FDA.

As explained in the claim construction order, recombinant proteins like filgrastim are manufactured in a multi-step process. The process begins when scientists introduce human DNA into a host cell of a different species, such as *E. Coli* bacteria, causing the bacteria to produce human proteins. Before these proteins can be therapeutically useful, however, they must attain a three-dimensional shape. Trouble arises when the host cells produce proteins that lack this proper shape. These "unfolded" proteins accumulate in the host cell and form insoluble aggregates called "inclusion bodies." To remedy the problem, scientists break open (lyse) the host cell to release the inclusion bodies. They solubilize the inclusion bodies, mixing the proteins with various chemicals to create a solution. They then combine that solution with a "refold buffer" to cause the protein to take a workable, three-dimensional shape.

Once the protein has refolded, it must be separated from the chemicals used for solubilization and refolding. This step is called purification and typically involves applying the solution containing the refolded protein to a "separation matrix." Generally, the separation matrix can function in one of two ways. In "flow-through" purification the separation matrix attracts one or more of the unwanted chemicals used to solubilize and refold the protein. The protein itself,

however, does not attach to the matrix and thus "flows through" and is collected. By contrast, in "capture purification" the separation matrix attracts and binds *the protein* so that the unwanted contaminants and chemicals flow through the matrix and are discarded. The purified protein is then eluted (i.e., released) from the separation matrix and collected.

The present dispute between Amgen and Sandoz began in 2014. Over the past three years, the litigation between the parties has involved multiple issues and multiple patents. The only patent that remains at issue, however, is U.S. Patent No. 8,940,878 ("the '878 patent"), entitled "Capture Purification Processes for Proteins Expressed in a Non-Mammalian System." As the name suggests, the '878 patent generally relates to processes for purifying proteins. Claim 7 of the patent claims one such method. Amgen asserts that one of the steps in Sandoz's process for making and purifying filgrastim and pegfilgrastim ("the AEX step") infringes claim 7. Sandoz contends the AEX step does not infringe because it does not satisfy elements (e), (f) and (g) of claim 7:

> (e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
> (f) washing the separation matrix; and
> (g) eluting the protein from the separation matrix, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

While Amgen Inc. retains ownership of the '878 patent, Amgen Manufacturing Limited ("AML") is responsible for manufacturing Neupogen and Neulasta. AML does not practice the '878 patent method in manufacturing either product.[2]

III. LEGAL STANDARD

Summary judgment is proper "if the pleadings and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). The purpose of summary

[2] Additional background information regarding how recombinant proteins are genetically engineered and purified can be found in the claim construction order (14-cv-04741, Dkt. No. 205).

judgment "is to isolate and dispose of factually unsupported claims or defenses." *Celotex v. Catrett*, 477 U.S. 317, 323-24 (1986). The moving party "always bears the initial responsibility of informing the district court of the basis for its motion, and identifying those portions of the pleadings and admissions on file, together with the affidavits, if any, which it believes demonstrate the absence of a genuine issue of material fact." *Id.* at 323 (citations and internal quotation marks omitted). If it meets this burden, the moving party is then entitled to judgment as a matter of law when the non-moving party fails to make a sufficient showing on an essential element of the case with respect to which he bears the burden of proof at trial. *Id.* at 322-23.

The non-moving party "must set forth specific facts showing that there is a genuine issue for trial." Fed. R. Civ. P. 56(e). The non-moving party cannot defeat the moving party's properly supported motion for summary judgment simply by alleging some factual dispute between the parties. To preclude the entry of summary judgment, the non-moving party must bring forth material facts, i.e., "facts that might affect the outcome of the suit under the governing law . . . . Factual disputes that are irrelevant or unnecessary will not be counted." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-48 (1986). The opposing party "must do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio*, 475 U.S. 574, 588 (1986).

The court must draw all reasonable inferences in favor of the non-moving party, including questions of credibility and of the weight to be accorded particular evidence. *Masson v. New Yorker Magazine, Inc.*, 501 U.S. 496 (1991) (*citing Anderson*, 477 U.S. at 255); *Matsushita*, 475 U.S. at 588 (1986). It is the court's responsibility "to determine whether the 'specific facts' set forth by the nonmoving party, coupled with undisputed background or contextual facts, are such that a rational or reasonable jury might return a verdict in its favor based on that evidence." *T.W. Elec. Service v. Pacific Elec. Contractors*, 809 F.2d 626, 631 (9th Cir. 1987). "[S]ummary judgment will not lie if the dispute about a material fact is 'genuine,' that is, if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson*, 477 U.S. at 248. However, "[w]here the record taken as a whole could not lead a rational trier of fact to find for the

non-moving party, there is no 'genuine issue for trial.'" *Matsushita*, 475 U.S. at 587.

IV. DISCUSSION

A. Noninfringement

Evaluating infringement is a two-part inquiry: 1) claim construction; and 2) comparison of the properly construed claims to the accused process. *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1318 (Fed. Cir. 2003). In the instant case, part one of the inquiry was completed with issuance of the claim construction order on August 4, 2016. Part two is the subject of the present motion.

"[A] determination of infringement, both literal and under the doctrine of equivalents, is a question of fact." *Id.* Because the ultimate burden of proving infringement rests with the patentee, an accused infringer may show that summary judgment of non-infringement is proper either by producing evidence that would preclude a finding of infringement, or by showing that the evidence on file fails to create a material factual dispute as to any essential element of the patentee's case. *See Novartis Corp. v. Ben Venue Labs., Inc.*, 271 F.3d 1043, 1046 (Fed. Cir. 2001). Here, Sandoz can prevail only if no reasonable jury could conclude the accused AEX step infringes claim 7 of the '878 patent either literally or under the doctrine of equivalents.

i. Literal Infringement

To prove literal infringement, a patent holder must establish that every requirement of the claimed method is included in the method accused of infringement. *MicroStrategy Inc. v. Business Objects, S.A.*, 429 F.3d 1344, 1353 (Fed. Cir. 2005). "If . . . even one claim limitation is missing or not met, there is no literal infringement." *Id.* at 1353 (citation omitted).

The overarching thrust of Sandoz's argument is that the claimed protein purification method requires three distinct and sequential steps as well as the application of three distinct solutions. Sandoz's AEX step, by contrast, involves only one step and only one solution. More specifically, Sandoz identifies four requirements of claim 7 it argues are not satisfied by its accused process. First, the eluting step must occur after the washing step. Second, the washing step must occur after direct application of the refold solution. Third and fourth, both the washing

and eluting steps require adding solutions different from the refold solution.

The first ground raised by Sandoz (i.e., that the eluting step must occur after the washing step) is sufficient on its own to support a finding that Sandoz's AEX step does not literally infringe the '878 patent. In construing the phrase "eluting the protein from the separation matrix," the claim construction order noted that the eluting step outlined in 7(g) must occur *after* the washing step described in 7(f). CC Order at 31, 33. This conclusion was reached in heavy reliance on the explicit language of the patent specification:

> The specification teaches, "[a]fter the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution." '878 Patent at 15:60 62. It further explains that the wash buffer may be comprised of any number of components so long as "[t]he pH range is chosen to optimize the chromatography conditions, preserve protein binding, and to retain the desired characteristics of the protein of interest." '878 Patent at 15:55 57 (emphasis added). Thus, the proteins and separation matrix should remain associated during the washing process. In contrast, elution involves cleaving the protein from the matrix with "a solution that interferes with the binding of the absorbent component of the separation matrix to the protein, for example by disrupting the interactions between Protein A and the Fc region of a protein of interest." '878 Patent at 15:65 16:2 (emphasis added). *Accordingly, the specification discloses a natural, logical order of steps. If the washing and eluting steps occurred simultaneously, the protein captured by the separation matrix could once again comingle with the contaminants and components to be washed away.* In light of the fact Amgen has not offered any reasons to believe the claim does not imply a natural order, the construction of the phrase will make clear the step of "eluting the protein from the separation matrix" occurs *after* the step of "washing the separation matrix."

Id. at 31 (emphasis added).

Nothing has been offered to suggest the above construction needs modification. Based on this construction, the method employed by Sandoz does not have the sequential washing and eluting steps required by claim 7. The AEX step entails continuously pumping a refold solution comprised of filgrastim, a particular detergent ("detergent 1"),[3] and other substances into a column containing a separation matrix. There is no pause in the pumping of the refold solution. Nor is there any point at which Sandoz adds a second solution to the column that is compositionally

[3] This nomenclature is adopted to avoid unnecessarily disclosing confidential aspects of Sandoz's accused process.

different than the refold. There simply is no way to conceive of this continuous pumping process as an eluting step *after* a washing step without straining the language of the patent specification and the claim construction order beyond their reasonable meaning.

Amgen nonetheless argues the washing and eluting steps *do occur* sequentially in Sandoz's process if you look at any given location in the column (e.g., "the leading edge of the refold solution in the downstream end") rather than at the column as a whole. The key, according to Amgen, is recognizing that conditions in the column are changing as the refold solution is applied. When the solution is first applied, conditions are such that filgrastim *is binding* to the separation matrix. While the filgrastim is bound, other contaminants in the solution are flowing over and past it through the column and being discarded (i.e., "washing"). Later, the continued application of refold solution causes conditions to change in the column yet again so that the filgrastim binding is reversed and the protein flows out through the column (i.e., "eluting"). Thus, Amgen argues, Sandoz's description of its AEX step as only one step and one solution is misleading. At any given location in the column where filgrastim binds, the washing step and the eluting step are occurring sequentially consistent with claim 7.

Amgen's attempt to redefine Sandoz's accused process in a way that fits the requirements of claim 7 is unavailing. As the claim construction order noted, the patent specification discloses a natural, logical order of steps. Nowhere is that order of steps more clear than with regard to the requirement that the eluting step in element (g) follow the washing step in element (f).

For similar reasons, Sandoz's argument that the washing and eluting solutions must be distinct is equally compelling and provides an additional ground on which to conclude that Sandoz's process does not literally infringe the claimed method. As previously discussed, Sandoz's AEX step uses only one solution. Yet the patent specification describes a "wash buffer" that is "optimized to preserve protein binding" and an eluting solution that "interferes with the binding." '878 Patent at 15:55-62. *See also* CC Order at 31. The opposite purposes of these two solutions suggests they must indeed be distinct, and cannot be, as Amgen contends, a single solution achieving different ends, due to different conditions, at different points in time.

Sandoz's other arguments—that the washing step must come after the application of the refold solution and that the solutions required for eluting and washing must be separate and distinct from the refold solution—are also strong. Those arguments, however, need not be reached. Eluting must follow washing under the claimed method. The accused AEX step has no such sub-steps. So too, the claimed method requires that the washing and elution solutions be distinct. Yet the accused AEX step involves application of only one solution. Either one of these grounds independently supports a finding that Sandoz's process does not literally infringe.

ii. Doctrine of Equivalents

An accused method that does not literally infringe a patent claim may still be found to be infringing under the doctrine of equivalents if it includes steps that are identical or equivalent to the requirements of the claim. *Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). An accused step is considered equivalent to a claim requirement if a person of ordinary skill in the field would think that the differences between the step and the requirement were not substantial. *See Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1057 (Fed. Cir. 2002). An accused step may be insufficiently different from a claim requirement if it performs substantially the same function, in substantially the same way, to achieve substantially the same result. *See Warner-Jenkinson Co.*, 520 U.S. at 39-40; *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950). As the patentee, Amgen bears the burden of establishing equivalency on a limitation-by-limitation basis by particularized testimony and linking argument as to the insubstantiality of the differences between the claimed and accused methods. *Akzo Nobel Coatings, Inc. v. Dow Chem. Co.*, 811 F.3d 1334, 1342 (Fed. Cir. 2016).

Here, the differences between the method claimed by the '878 patent and the accused AEX step are substantial. First, the claimed method and the AEX step do not perform the same function. As explained in the claim construction order, the alleged invention protected by the '878 patent was the discovery that refold solution could be applied directly to a separation matrix without removing components of or diluting the solution. CC Order at 25. The AEX step, by removing an unwanted contaminant ("detergent 1") in advance of capture purification, is in effect doing exactly

what the asserted claims sought to eliminate.

Second, the different functions performed by the two processes are performed in substantially different ways. Sandoz argues this distinction is best illustrated by classifying the claimed method as a "capture purification" process and the accused method as "flow-through." Amgen rejects these classifications as misleading on the grounds that filgrastim actually does bind to at least some portion of the separation matrix during Sandoz's process and is therefore captured. Regardless of how they are labelled, however, the processes are indeed different. The claimed method "discloses a natural, logical order of steps" in which application of the refold solution is followed by a washing step and then an eluting step. The accused method, by contrast, involves only one step: the continuous application of a single solution to a separation matrix.

Lastly, and closely related to the function analysis above, the results produced by the claimed method and the accused method are substantially different. The claimed method, as the patent notes, is a "Capture Purification Process" that produces the protein in question in its purified form. There are no steps beyond the eluting step in element (g). The AEX step, on the other hand, produces a solution that contains the protein to be purified (filgrastim)—and at least one fewer contaminant ("detergent 1") than at the outset of the step—but which requires further purification.

In light of these differences, Amgen cannot prove infringement either literally or under the doctrine of equivalents. Sandoz's motion for summary judgment of noninfringement is granted.

B. Damages

In addition to seeking summary judgment as to noninfringement, Sandoz also moves for summary adjudication of several discrete issues impacting the scope of damages and relief available to Amgen. Specifically, Sandoz asks the Court to find: (1) AML lacks standing to sue for infringement because it is neither an owner nor exclusive licensee of the '878 patent; (2) Amgen Inc. is not entitled to lost profits for Neupogen, because it has never made or sold any Neupogen; (3) Amgen cannot prove the absence of non-infringing alternatives; and (4) the hypothetical negotiation date for determining royalties must be earlier than May 5, 2015. Because Sandoz's

accused method does not infringe the '878 patent, these damages arguments need not be reached.

C. Rule 56(d) Motion

Rule 56(d) of the Federal Rules of Civil Procedure permits denial or continuance of a motion for summary judgment, "[i]f a nonmovant shows by affidavit or declaration that, for specified reasons, it cannot present facts essential to justify its opposition." A party requesting a Rule 56(d) continuance bears the burden of setting forth specific facts he hopes to elicit from further discovery and demonstrating that the facts sought not only exist but also are essential to oppose summary judgment. *Family Home & Fin. Ctr., Inc. v. Fed. Home Loan Mortg. Corp.*, 525 F.3d 822, 827 (9th Cir. 2008). Failing to meet this burden "is grounds for the denial" of a Rule 56(d) motion. *Pfingston v. Ronan Eng. Co.*, 284 F.3d 999, 1005 (9th Cir. 2002).

As discussed previously, Sandoz's accused AEX step involves pumping refold solution into a column containing a separation matrix. The specific matrix Sandoz currently uses, however, will be discontinued in late 2018 or 2019. Sandoz therefore plans to replace its current matrix with a new separation matrix. Amgen argues this change in matrices is significant and moves pursuant to Rule 56(d) to defer a ruling on whether Sandoz's modified process infringes on the claimed method. Such a ruling is not appropriate, Amgen argues, until Sandoz produces more complete documentation regarding how the process will be modified. Specifically, Amgen urges the court to wait until Sandoz submits an application for approval of its modified process to the FDA—which will happen at some point in 2018—and produces that submission and its underlying source documents to Amgen.

The problem with Amgen's request is that the final "process parameters" it hopes to discover (e.g., "column dimensions, flow rate, loading time, and residence time") are not material to the finding of noninfringement. As discussed in the infringement analysis, the method claimed by the '878 patent involves multiple steps and multiple solutions while Sandoz's accused method involves only one continuous step and only one solution. This substantial difference between the methods will not be altered by the replacement of the current matrix with the new matrix. The core function of the new matrix, to capture "detergent 1" as the refold solution moves through the

column, will be materially identical to the function of the current matrix. Sandoz's process will still not contain an eluting step that follows a washing step, as required by claim 7's (f) and (g) elements. It therefore will not infringe. Accordingly, granting Amgen's Rule 56(d) motion would not conserve judicial resources, as Amgen argues, but would instead unnecessarily delay resolution of this already lengthy litigation.

V. CONCLUSION

Sandoz's motion for summary judgment of noninfringement is granted with respect to its accused process as conducted with both the current and new separation matrices. Amgen's Rule 56(d) motion is denied. Sandoz's motion for summary judgment regarding damages is denied as moot. Sandoz is directed to submit a proposed final judgment no later than January 5, 2018.

IT IS SO ORDERED.

Dated: December 19, 2017

RICHARD SEEBORG
United States District Judge

United States District Court
Northern District of California

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC., et al.,

Plaintiffs,

v.

SANDOZ INC., et al.,

Defendants.

Case No. 14-cv-04741-RS

ORDER CONSTRUING CLAIMS

I. INTRODUCTION

Amgen, Inc. and Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH (collectively "Sandoz") compete to develop, manufacture, promote, and sell biopharmaceutical products, including those used to facilitate stem-cell transplantation. Amgen holds two patents at issue in this action: U.S. Patent Nos. 6,162, 427 ("the '427 Patent") and 8,940,878 ("the '878 Patent"). Amgen accuses Sandoz of infringing those patents. The parties seek construction of ten terms pursuant to *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (en banc). For the reasons set forth below, the disputed terms are construed as follows.

II. BACKGROUND

In 2014, Amgen filed claims against Sandoz for infringement of the '427 patent, "Combination of G-CSF with a Chemotherapeutic Agent for Stem Cell Mobilization." Amgen objects to Sandoz's efforts to market and sell ZARXIO®, a drug Amgen contends is biosimilar to its drug, NEUPOGEN®, which is commonly used to "treat[] the side effects of certain forms of

cancer therapy." FAC ¶ 11. The active ingredient in both products is filgrastim, a synthetic version of human granulocyte colony stimulating factor ("G-CSF"). Amgen also accuses Sandoz of violating California's unfair competition law ("UCL"). In response, Sandoz asserts numerous counterclaims for declaratory judgments of compliance with the Biosimilars Price Competition and Innovation Act ("BPCIA"), non-infringement, and patent invalidity. In March 2015, Sandoz obtained partial judgment in its favor with respect to the UCL claim and Sandoz's claim for a declaratory judgment of compliance with the BPCIA pursuant to Federal Rule of Civil Procedure 54(b). The parties jointly requested to stay these proceedings until the issuance of the Federal Circuit's mandate. Dkt. No. 111 at 3.

Amgen then appealed to the Federal Circuit. During the pendency of the appeal, the Federal Circuit entered an injunction to prevent Sandoz from marketing, selling, or importing ZARXIO®. The Federal Circuit affirmed dismissal of the UCL claim, and affirmed in part and reversed in part the order regarding the BPCIA. *See Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015). Sandoz filed a petition for en banc review, which is still pending in the Federal Circuit.

Following the issuance of the Federal Circuit's mandate, the parties agreed to lift the stay, and Amgen filed a First Amended Complaint, asserting one additional claim of patent infringement. Amgen now contends Sandoz employs a method of protein capture that infringes the '878 patent, entitled "Capture Purification Processes for Proteins Expressed in a Non-Mammalian System."

III. LEGAL STANDARD

Claim construction is a question of law to be determined by the court. *Markman*, 52 F.3d at 979. "Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). Accordingly, a claim should be construed in a manner that "most naturally aligns with the patent's description of the invention."

The first step in claim construction is to look to the language of the claims themselves. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). A disputed claim term should be construed in a manner consistent with its "ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1312–13. The ordinary and customary meaning of a claim term may be determined solely by viewing the term within the context of the claim's overall language. *See id.* at 1314 ("[T]he use of a term within the claim provides a firm basis for construing the term."). Additionally, the use of the term in other claims may provide guidance regarding its proper construction. *Id.* ("Other claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term.").

A claim should also be construed in a manner that is consistent with the patent's specification. *See Markman*, 52 F.3d at 979 ("Claims must be read in view of the specification, of which they are a part."). Typically the specification is the best guide for construing the claims. *See Phillips*, 415 F.3d at 1315 ("The specification is . . . the primary basis for construing the claims."); *see also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("[T]he specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term."). In limited circumstances, the specification may be used to narrow the meaning of a claim term that otherwise would appear to be susceptible to a broader reading. *See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question."); *Phillips*, 415 F.3d at 1316 ("[T]he specification may reveal an intentional disclaimer,

or disavowal, of claim scope by the inventor. In that instance as well, the inventor has dictated the correct claim scope, and the inventor's intention, as expressed in the specification, is regarded as dispositive."). Precedent forbids, however, a construction of claim terms that imposes limitations not found in the claims or supported by an unambiguous restriction in the specification or prosecution history. *Laitram Corp. v. NEC Corp.*, 163 F.3d 1342, 1347 (Fed. Cir. 1998) ("[A] court may not import limitations from the written description into the claims."); *Comark Commc'ns., Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998) ("[W]hile claims are to be interpreted in light of the specification, it does not follow that limitations from the specification may be read into the claims." (internal quotation marks and alterations omitted)); *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc) ("It is the *claims* that measure the invention.") (emphasis in original). A final source of intrinsic evidence is the prosecution record and any statements made by the patentee to the United States Patent and Trademark Office ("PTO") regarding the scope of the invention. *See Markman*, 52 F.3d at 980.

Courts may also consider extrinsic evidence, such as expert testimony, dictionaries, or technical treatises, especially if such sources are "helpful in determining 'the true meaning of language used in the patent claims.'" *Phillips*, 415 F.3d at 1318 (quoting *Markman*, 52 F.3d at 980). Ultimately, while extrinsic evidence may aid the claim construction analysis, it cannot be used to contradict the plain and ordinary meaning of a claim term as defined within the intrinsic record. *See Phillips*, 415 F.3d at 1322–23.

IV. DISCUSSION

A. The '427 Patent

Hematopoietic stem cells naturally occur in the human body and are capable of proliferation and differentiation into cells that comprise the blood and immune systems. In other words, they are blood-forming stem cells.[1] These cells self-renew and reside primarily in bone marrow.

[1] In the interest of using plain language, this order uses the term "blood-forming stem cells" instead of "hematopoietic stem cells."

Peripheral stem cell transplantation is a process used to replace damaged blood-forming stem cells—the sort of cellular damage chemotherapy usually causes. Peripheral blood is the blood that circulates through the body. Before peripheral stem cell transplantation can occur, the doctor must collect blood-forming stem cells for later transplantation. Collection requires "mobilizing" stem cells in the bone marrow to move into the peripheral blood stream. Once the stem cells have mobilized, doctors collect them using a process called leukapheresis, which separates the stem cells from other types of blood cells. The collected cells are then set aside for later use. The more blood-forming stem cells in the blood stream, the fewer leukapheresis sessions the patient must undergo to collect enough cells for transplantation.

G-CSF is a protein that naturally occurs in the human body. Filgrastim is a pharmaceutical analog of human G-CSF constructed artificially in *E. coli* bacteria using recombinant DNA technology. Since the early 1990s, doctors and researchers have been using G-CSF in connection with chemotherapy to relieve the side effects of chemotherapy. G-CSF has also been used to facilitate mobilization of blood-forming stem cells from the bone marrow into the peripheral blood.

After the stem-cell collection, the patient undergoes myeloablative radiation (bone marrow destruction) or myelotoxic chemotherapy (bone marrow suppression), which destroy blood-forming stem cells in the process. Once chemotherapy has been administered, the collected stem cells can be reintroduced into the bone marrow to allow for further production of new blood cells.

Both parties agree that the '427 patent describes a method that requires administration of G-CSF before administration of a chemotherapeutic agent. The order of administration (G-CSF first, a chemotherapeutic agent second) is the allegedly novel component of the invention. At the time of the invention, a skilled artisan knew that administration of G-CSF alone, a chemotherapeutic agent alone, or a chemotherapeutic agent followed by G-CSF could mobilize blood-forming stem cells into the blood stream. The patentees purport to have reached the revolutionary conclusion that the structured administration of G-CSF first, followed by administration of a chemotherapeutic agent was the most efficient method of stem cell

mobilization. The patent claims to improve on the process of stem cell collection by following the specified order, which relieves patients of the need to attend multiple of leukapheresis sessions.

1. *"hematopoietic stem cell mobilizing-effective amount of G-CSF"*

The term "hematopoietic stem cell mobilizing-effective amount of G-CSF" appears in only claim 1, but is incorporated by reference into claims 2, 3, 4, and 6. Amgen would have the term construed to mean "an amount of G-CSF effective to mobilize hematopoietic stem cells," whereas Sandoz contends the term is indefinite.

When evaluating whether a term is sufficiently definite, courts must analyze that question "from the viewpoint of a person skilled in the art at the time the patent was filed." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2128 (2014) (emphasis, internal quotation marks, and alteration omitted). As noted, the claims "are to be read in light of the patent's specification and prosecution history." *Id.* When examining the definiteness of a term, courts "must take into account the inherent limitations of language," and therefore "[s]ome modicum of uncertainty . . . is the price of ensuring the appropriate incentives for innovation." *Id.* (internal quotation marks omitted). "At the same time, a patent must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." *Id.* at 2129 (internal quotation marks omitted). "Cognizant of the competing concerns," the Supreme Court requires "that a patent's claim, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Id.*

The first step required is to define who is a person skilled in the relevant art. This patent was written for those who practice stem-cell transplantation or study stem-cell biology. A person skilled in the relevant art is therefore one who has obtained a Ph.D. in biological sciences or an M.D. In addition, this person is one with significant experience with stem-cell biology, hematopoiesis, and stem-cell transplantation.

Turning to the question of whether such a skilled artisan understands the phrase "hematopoietic stem cell mobilizing-effective amount of G-CSF," Sandoz takes aim at the word "effective" and offers three arguments for why the term is indefinite. First, it argues neither the

claim language nor the specification inform skilled artisans about how many blood-producing stem cells must mobilize to be considered "effective." In other words, a skilled artisan has no way to discern whether mobilization of one stem cell, ten stem cells, or a thousand stem cells is "effective." Second, Sandoz insists the claim, specification, and prosecution history do not provide information for skilled artisans to tailor the procedure to the species of the patient (human, mouse, dog, horse, etc.). The final argument is that the patent does not explain how artisans should measure the level of stem-cell mobilization. At the time of the invention, practitioners knew of four methods for measuring the extent of stem cell mobilization, all of which varied considerably in terms of accuracy, consistency, and practicality. *See* Sandoz's Expert Negrin Decl. ¶¶ 45-46.

Whether adjectival limitations are indefinite depends on the context of each individual patent. In *Takeda Pharm. Co. v. Mylan Inc.*, No. 13-CV-04001-LHK, 2014 WL 5862134, at *10-11 (N.D. Cal. Nov. 11, 2014), the district court deemed the term "effective amount" definite because the patent described the proper dose of the drug ("about 0.5 to 1,500 mg/day"), and the claim covered treatment of a specific type of disease—reflux esophagitis. *Id.* at *10. In contrast, another district court concluded the term "% identity" was indefinite because "the specification identifie[d] a non-inclusive list of five methods to calculate '% identity' and provide[d] that sequence alignment can be performed using any commercially available or independently developed software." *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, 117 F. Supp. 3d 632, 641 (D. Del. 2015). Similarly, in *Andrulis Pharm. Corp. v. Celgene Corp.*, No. CV 13-1644(RGA), 2015 WL 3978578, at *3-4 (D. Del. June 26, 2015), the term "enhanced therapeutically-effective amounts of thalidomide" was held to be indefinite because "enhanced" could mean "less than additive, additive, or greater than additive." *Id.* at *3.

Here, the claim itself offers little guidance, but the specification provides more direction. It teaches, "[t]he [G-CSF] dosage may depend on various factors such as mode of application, species, age, or individual condition. According to the invention, from 5 to 300 μg/kg/day of G-

CSF sc.[2] is applied." Pai Decl. Ex. 1, '427 Patent 3:4-7. G-CSF administration occurs "once per day over two to three days." '427 Patent 4:5-8. Amgen points to portions of the specification that explain, "[n]umerous substances" are capable of causing mobilization of blood-producing stem cells, such as G-CSF and "[s]ome chemotherapeutic agents." '427 Patent 1:32-37. These passages make clear that, at the time the patent was filed, skilled artisans knew G-CSF caused blood-producing stem cells to mobilize, and that any amount ranging from 5 to 300 µg/kg/day of G-CSF sc. would cause stem cells to mobilize enough to enable collection.

The prosecution history of the '427 patent offers skilled artisans further guidance and additional support for Amgen's proposed construction. Three papers identified in the specification refer to various G-CSF dosage amounts within the range stated in the specification. Two papers examined the efficacy of subcutaneous doses of 10 µg/kg/day. Wu Decl. Ex 4 at 861 (Long et al., *Cancer* 76(5):860-68 (1995)); Wu Decl. Ex. 6 at 146 (Pierelli et al., *J. Hematotherapy* 2:145-53 (1993)). Another study tested the comparative potency of subcutaneous or intravenous doses of 10 µg/kg/day or 5 µg/kg/day. Wu Decl. Ex. 5 at 2177 (Nademanee et al., *J. Clinical Oncology* 12(10):2176-86 (1994)). These three studies supply a person skilled in the art with more information to determine with a reasonable degree of certainty how much G-CSF to administer to achieve more than a *de minimus* level of stem-cell mobilization.

While the range of the amounts of G-CSF to administer is admittedly wide and variable depending on the size or species of the subject, a skilled artisan is not without any guidance to figure out how much G-CSF to administer. After all, "breadth is not indefiniteness." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1341 (Fed. Cir. 2005). To the extent a skilled artisan may have difficulty adjusting the amount of G-CSF to administer depending on the species of the subject, the lack of precision in the claim and specification impacts only his or her ability to practice all embodiments of the claim—a question of enablement, not indefiniteness. *See Takeda*, 2014 WL 5862134, at *10 (citing *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371,

[2] "sc." stands for "subcutaneous." Negrin Decl. ¶ 40.

1382 (Fed. Cir. 2001) (noting that "'inoperable embodiments' raise 'an issue of enablement, and not indefiniteness")). Overall, the patent communicates the purpose of G-CSF administration: to cause more than a *de minimus* number of blood-producing stem cells to enter the peripheral blood. While the claim and specification could have offered more precise guideposts, the disclosures provide those skilled in the art with sufficient information to figure out how to accomplish that goal. Accordingly, the phrase "hematopoietic stem cell mobilizing-effective amount of G-CSF" is not indefinite. It will be construed as follows: "an amount of G-CSF effective to mobilize hematopoietic stem cells."

2. *"A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment"*

The second phrase to construe is the preamble to claim 1. Although it appears in only claim 1, claims 2, 3, 4, and 6 incorporate the preamble by reference. Both parties agree the preamble limits the scope of the claim, but they disagree about how to construe it. The crux of the dispute is about the phrase "a method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment." Amgen construes the phrase as follows: "In the practice of the method, a patient in need of a stem cell transplant receives a transplant of peripheral stem cells." Sandoz offers the following construction: "In the practice of the method of treating a disease, a patient receives a transplant of peripheral stem cells." The fight boils down to whether peripheral stem cell transplantation is itself disease treatment, or whether it is a component of disease treatment to alleviate the side effects of treatment (namely chemotherapy). The text of the claim itself and the intrinsic record support Sandoz's construction.

To begin, the phrase "such treatment" must have an antecedent. *See Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (noting the phrase "to a patient in need of such treatment" must have an antecedent basis). Sandoz argues the antecedent is "a method of treating a disease," whereas Amgen insists it refers back to "peripheral stem cell transplantation." Under Sandoz's construction, the treatment (usually chemotherapy) necessitates stem-cell transplantation. To practice the treatment method, the doctor mobilizes, collects, and transplants blood-producing

stem cells into the patient. In contrast, under Amgen's reading it is the disease (primarily cancer) that requires peripheral stem cell transplantation. While "such treatment" surely requires an antecedent, both proposed constructions are grammatically correct, and therefore to construe the terms requires a more searching inquiry.

The text of the whole claim lends support to Sandoz's construction. The method claim 1 includes two steps: (1) administration of G-CSF, and (2) administration of a chemotherapeutic agent. The claim describes the quantity of G-CSF to be administered as "stem cell mobilizing," whereas the chemotherapeutic agent is described as "disease treating." *See* '427 Patent at 10:26-29. In other words, one substance mobilizes stem cells, while the other treats a disease. The claim suggests the transplantation itself does not treat disease.

The specification bears out this interpretation. It explains the purpose of the claimed method: "The use of high-dosage chemotherapy or bone marrow ablation by irradiation requires subsequent incorporation of hematopoietic stem cells into the patient, in which case recovery of such cells is required." '427 Patent at 1:18-21. Mobilization of blood-forming stem cells "has a crucial influence on the efficiency of" peripheral stem cell recovery. '427 Patent at 1:22-24. The method claimed by the patent improves upon the process of collecting stem cells by increasing the number of stem cells in the peripheral blood, thereby reducing the number of leukaphereses required. *See* '427 Patent at 1:24-27 ("At present, 2-3 leukaphereses are required for successful peripheral stem cell transplantation, resulting in considerable stress for the patients."); *id.* at 1:55-61 ("As the required number of leukaphereses is extremely stressing for the patient in the run-up to the treatment of particular diseases, e.g., in preparing myeloablative or myelotoxic therapy, the invention was based on the object of achieving a superior yield of stem cells or a decrease in the number of leukophereses via enhanced mobilization of stem cells."). Finally, the specification teaches that administration of G-CSF followed by administration of a chemotherapeutic agent is part of the "run-up to a, e.g. antitumor therapy," and therefore is not the disease treatment itself. '427 Patent at 4:24-25.

Thus, the specification clarifies any ambiguity in the text of the claim about whether peripheral stem-cell transplantation is a treatment for disease or a component of disease treatment.[3] It is the latter. Accordingly, Sandoz has the better construction, and it is adopted.

3. *"disease treating-effective amount of at least one chemotherapeutic agent"*

The next phrase up for construction is "disease treating-effective amount of at least one chemotherapeutic agent."[4] It appears in claim 1, and the patentee also incorporated the term by reference into claims 2, 3, 4, and 6. Amgen proposes defining the phrase as "an amount of at least one chemotherapeutic agent sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation." Sandoz offers the following construction: "an amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed." The crux of the dispute revolves around whether the chemotherapeutic agent treats a disease such as cancer (Sandoz's construction), or whether the chemotherapeutic agent's purpose is to mobilize blood-producing stem cells for collection and subsequent peripheral transplantation (Amgen's construction). The text of the claim and the specification compel adoption of Sandoz's proposal.

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[3] This is not to say all forms of peripheral stem-cell transplantation are not treatments. Sandoz's expert witness, Robert S. Negrin, M.D., has explained the difference between two types of stem-cell transplants: allogeneic transplants and autologous transplants. Allogeneic transplants involve transplantation of a healthy donor's stem cells, and are used to treat certain cancers. *See* Negrin Sur-Reply Decl. ¶ 12. In contrast, autologous transplants involve using the patient's own stem cells. *Id.* ¶ 11. Autologous transplants do not treat diseases; they counteract the negative side effects of disease treatments such as myelotoxic chemotherapy or radiation. *Id.* The '427 Patent obviously addresses autologous transplants, not allogeneic transplants.

[4] In *Amgen, Inc. v. Apotex Inc.*, No. 15-61631-CIV, 2016 WL 1375566, at *5-6 (S.D. Fla. Apr. 7, 2016), the district court construed this very phrase. The court adopted Amgen's proposed construction, concluding a "disease treating-effective amount" of the chemotherapeutic agent is an amount "needed to achieve the goal of enhancing stem cell mobilization for recovery from blood and subsequent transplantation." *Id.* at *6. Prior claim construction orders are not binding or dispositive unless "an earlier suit . . . trigger[s] application of the doctrine of collateral estoppel." *W. v. Quality Gold, Inc.*, No. 5:10-CV-03124-JF HRL, 2011 WL 6055424, at *2 (N.D. Cal. Sept. 16, 2011). Sandoz was not a party to the Florida action, and therefore the doctrine of collateral estoppel is wholly inapplicable.

In *Apotex*, rather than proposing a construction, the defendant argued the term "disease treating-effective amount" is indefinite. *See Apotex*, 2016 WL 1375566, at *5. The district court did not weigh in on the question presented here, and therefore its construction is of limited weight.

"[T]he context in which a term is used in the asserted claim can be highly instructive." *Phillips*, 415 F.3d at 1314. There are three parts to claim 1—the preamble and two limitations: the first limitation is a description of step one (administration of G-CSF); the second limitation is a description of step two (administration of the chemotherapeutic agent). Rather than referring to the two steps of the claimed process as "stem-cell mobilizing," the patentee chose to use different descriptors for G-CSF and chemotherapeutic agents. G-CSF is "hematopoietic stem cell mobilizing," whereas the chemotherapeutic agent is "disease treating." *See* '427 Patent at 10:27-29. "Different claim terms are presumed to have different meanings." *Bd. of Regents v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008). Here, the patentee chose to use two different words, and thus the two terms presumably carry different meanings.

A natural reading of these two terms suggests they are not synonyms. Nevertheless, claims "do not stand alone. Rather they are part of a fully integrated written instrument, consisting principally of a specification that concludes with the claims." *Phillips*, 811 F.3d at 1315 (internal quotation marks and citation omitted). Thus, if the specification suggests the two phrases describe similar functions, then the claim must be construed accordingly. Indeed, there is some evidence in the specification that the purpose of administering a chemotherapeutic agent is the same as that for G-CSF administration. The specification teaches about stem-cell mobilizing characteristics of chemotherapeutic agents. *See, e.g.*, '427 1:35-36 (citing Richman et al., Blood, Vol. 47, No. 6 1031 (1976)) ("Some chemotherapeutic agents are also known to possess the ability of mobilizing bone marrow stem cells . . . ."); '427 Patent at 1:5-9 ("The present invention relates to the novel use of G-CSF and a chemotherapeutic agent or a combination of chemotherapeutic agents to produce a pharmaceutical preparation for enhanced mobilization of hematopoietic stem cells in the treatment of diseases requiring peripheral stem cell transplantation."); '427 Patent at 3:13-17 ("Surprisingly, it was determined that administration of G-CSF prior to opening of the endothelial barrier induced by chemotherapeutic agents significantly increases the stem cell mobilization and thus, can improve leukapheresis efficiency."). Yet, these references to the chemotherapeutic agent's ability to open the endothelial barrier cannot supplant language of the claim itself. In

claim 4, the patentee chose to describe one function of a chemotherapeutic agent: its ability to "open[] the endothelial barrier of the patient to render the endothelial barrier permeable for stem cells." '427 Patent at 10:36-38. Claim 4 demonstrates the patentee's ability to differentiate between two of chemotherapeutic agents' known functions: opening the endothelial barrier and treating disease (typically cancer). Thus, while the specification provides critical context for understanding the claim language, it cannot "be used to rewrite, the chosen claim language. Specifications teach. Claims claim." *SuperGuide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004) (internal quotation marks omitted).

Here, in claim 1, the patentee claimed the disease-treating function of chemotherapeutic agents. It shall therefore be construed as follows: "an amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed."

4. "chemotherapeutic agent"

The term "chemotherapeutic agent" appears in claims 1, 4, 5, and 6, and claims 2 and 3 incorporate the term by reference to claim 1. On the one hand, Amgen would construe the term as an "exogenous substance that is capable of damaging or destroying microorganisms, parasites or tumor cells and that may open the endothelial barrier." On the other hand, Sandoz would prefer to construe the phrase as an "exogenous substance suited and used to damage or destroy microorganisms, parasites or tumor cells." While the two constructions are similar, there are two points of dispute. First, they disagree about whether chemotherapeutic agents perform two functions (damaging and destroying microorganisms *and* opening the endothelial barrier), or just one (damaging and destroying microorganisms). Second, they part company over whether the chemotherapeutic agent must be "capable of" those functions, or "suited and used" for a certain purpose. At the *Markman* hearing, Amgen agreed to drop any reference to opening the endothelial barrier from its construction. Dkt. No. 199, Hr'g Tr. 118:23-119:1. Thus, the only remaining dispute is whether to use the words "capable of" or "suited and used for."

Sandoz generated its construction directly from the specification, which defines "chemotherapeutic agents." '427 Patent 2:37-39 ("[C]hemotherapeutic agents are understood to

be exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells."). "[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess." *Phillips*, 415 F.3d at 1316. It may also "reveal an intentional disclaimer, or disavowal, of claim scope by the inventor." *Id.* When the inventor provides a definition, his or her chosen lexicography is dispositive. *Id.* Amgen must therefore mount a strong case in order to change the definition the patentee included in the specification.

Amgen tries to do so by arguing the definition from the specification might be read to limit the scope of the claim to those chemotherapeutic agents known and used at the time of the invention. As a general matter, patentees need not "describe in [their] specification every conceivable and possible future embodiment of [their] invention." *SRI Int'l*, 775 F.2d at 1121. The specification lists various types of cytostatic agents (alkylating agents, metal complex cytostatic agents, antimetabolites, natural substances, antibiotic agents, hormones and hormone antagonists, and "other compounds") and offers examples of each group. *See* '427 Patent at 2:40-54. This list of examples suggests the patentee did not intend the claim to be limited to those chemotherapeutic agents known and used at the time of the invention.

This fact alone does not necessarily militate in favor of deviating from the definition provided in the specification or Amgen's proposed construction. The concern is that there are many agents, like battery acid, which are technically capable of damaging or destroying microorganisms, parasites, and tumors, but are not used or suited for that purpose.[5]

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[5] In *Apotex*, the district court adopted the construction of "chemotherapeutic agent" Amgen now offers. *See* 2016 WL 1375566, at *5. Once again, the *Apotex* court's constructions are of limited persuasive value because it confronted different proposed constructions than those at issue here. Apotex suggested the following construction, which limited chemotherapeutic agents to those that open the endothelial barrier: "Therapeutic agents which open the endothelial barrier, rendering it permeable for stem cells and/or exogenous substances suited and used to damage or destroy microorganisms, parasites or tumors." *Id.* Thus, the district court did not address or consider whether "capable" is a synonym for "suited and used for," or whether the construction of this term should mention anything about opening the endothelial barrier.

At the hearing, Amgen offered two alternative constructions: "an exogenous substance that is *suitable for use to* damage or destroy microorganisms, parasites or tumor cells and that may open the endothelial barrier" or "an exogenous substance that is suited to damage or destroy . . . ." *See* Tr. Hr'g 121:1-4; 122:14-22. Sandoz did not agree to either proposal for the simple reason that the patentee chose a definition and cannot change that definition at a later time, and its position is certainly correct as a matter of law. *Phillips*, 415 F.3d at 1316.

That there may be factual disputes as this case progresses does not counsel in favor of adopting Amgen's construction. In the absence of any reason to deviate from the patentee's definition of "chemotherapeutic agent," it shall be adopted for the purposes of this litigation. Accordingly, the term "chemotherapeutic agent" shall mean "exogenous substance suited and used to damage or destroy microorganisms, parasites, or tumor cells."

5. "comprising administering . . . G-CSF; and thereafter administering . . . at least one chemotherapeutic agent"

The fifth phrase requiring construction appears or is incorporated into claims 1, 2, 3, 4, and 6: "comprising administering . . . G-CSF; and thereafter administering . . . at least one chemotherapeutic agent." Amgen proposes the following construction: "G-CSF and the at least one chemotherapeutic agent are given in combination for purposes of stem cell mobilization, and the order in which G-CSF and the chemotherapeutic agent(s) are administered for that purpose is G-CSF first followed by the chemotherapeutic agent(s)."[6] Sandoz contends the word "comprising" means "including but not limited to," and allows for additional steps before, in

[6] Initially, Amgen proposed a lengthier construction of the phrase: "G-CSF and the at least one chemotherapeutic agent are given in combination for purposes of stem cell mobilization, and the order in which G-CSF and the chemotherapeutic agent(s) are administered for that purpose is G-CSF first followed by the chemotherapeutic agent(s). Other than the foregoing stem cell mobilization step, the method for treating a disease requiring peripheral stem cell transplantation involves additional steps such as collection of cells by leukapheresis, myeloablative and/or myelotoxic therapy, and transplanting the collected peripheral stem cells back into the patient. The term 'comprising' allows for these additional steps." At the *Markman* hearing, Amgen withdrew the second sentence, and so this order will focus on only the first. *See* Tr. Hr'g 137:3-138:6 ("[W]e would be perfectly happy to just go with the first sentence of the proposal.").

between, and after the steps recited in the claim. It also offers the following construction of the remainder of the phrase: "In the practice of the method, at least one administration of G-CSF must occur before at least one administration of a chemotherapeutic agent." Thus, there are two disputes to resolve: (1) whether to construe the word "comprising" (and how), and (2) whether to include some explanation about the purpose of each step. For the reasons discussed below, the construction Sandoz advances must be adopted.

"Comprising" is a term of art, which means "including but not limited to." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1319 (Fed. Cir. 2009). Sandoz's thus accords with longstanding rules of patent interpretation. Amgen urges declining to adopt the traditional construction of the word "comprising" out of fear that such construction would obfuscate the novelty of the invention, i.e. the precise order of administration (G-CSF first, and chemotherapeutic agent(s) second).[7] The trouble with this position is the simple fact the word "comprising" appears in the claim, and therefore must be construed. Amgen has not adequately explained how Sandoz's construction fails to convey the essence of the method claimed: the order of administration. Accordingly, the word "comprising" must be construed as usual to mean "including but not limited to." This construction naturally implies there may be steps before, in between, and after the steps recited in the claim.

The crux of the second dispute is whether Amgen's proposed construction improperly imports a purpose limitation into the claim. Critically, Amgen's suggested reading emphasizes that the purpose of administering a chemotherapeutic agent is to mobilize blood-forming stem

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[7] Indeed, numerous portions of the specification make clear the invention relates to the timing of the administration of G-CSF and the chemotherapeutic agent—G-CSF first, the chemotherapeutic agent second. *See* '427 Patent at 3:18-23 ("By administering G-CSF prior to administration of the chemotherapeutic agent(s) . . ."); *id.* at 1:66-21:11 ("The G-CSF and chemotherapeutic agent administration forms can be taken out separately and administered successively according to the optimum application regimen."); *id.* at 3:5-17 ("The administration of the chemotherapeutic agent(s) is initiated either immediately after the second or third G-CSF injection or on the fourth day . . . . [I]t was determined that administration of G-CSF prior to opening of the endothelial barrier induced by chemotherapeutic agents significantly increases the stem cell mobilization . . . ."); *id.* at 3:31-41 ("[T]he administration of G-CSF prior to administration of the chemotherapeutic agent . . . for enhanced mobilization of hematopoietic stem cells.").

cells, and not to treat disease. As addressed above, Sandoz hotly contests this point. No reiteration of the arguments about whether the purpose of administration of the chemotherapeutic agent is necessary for there is no textual basis to import a purpose limitation into the claim. The text of the claim and the specification make clear the method encompasses a specific order of administration (G-CSF, followed by a chemotherapeutic agent). Sandoz's proposed construction aligns with both, and therefore must be adopted in full. Accordingly, the word "comprising" means "including but not limited to," and allows for additional steps before, in between, and after the steps recited in the claim. In the practice of the method, at least one administration of G-CSF must occur before at least one administration of a chemotherapeutic agent.

6. "opens the endothelial barrier of the patient to render the endothelial barrier permeable for stem cells"

The final term in the '427 Patent to construe pertains to only claim 4: "opens the endothelial barrier of the patient to render the endothelial barrier permeable for stem cells." Amgen proposes construing the claim to mean "enhances the transit of stem cells from the bone marrow to the peripheral blood," whereas Sandoz contends it should mean "disrupts the bone marrow endothelial barrier." This dispute boils down to whether the phrase encompasses all mechanisms by which the chemotherapeutic agent allows stem cells to travel from bone marrow into the peripheral blood or whether the claim is limited to one mechanism, namely breaking down the barrier altogether.

The text of the claim does not resolve this dispute, but the specification offers some guidance. At the time of the alleged invention, skilled artisans were aware that administration of cytotoxic agents caused the number of stem cells to increase in the peripheral blood. What was unknown at the time was how exactly blood cells moved from bone marrow into the peripheral blood. One article described the process as an "[i]njury to the supporting structure of the marrow." Wu Decl. Ex. 10 at 1037, Richman et al., *Blood* 47(6): 1031-39 (1976) (cited at '427 Patent at 1:35-37). Another researcher explained, "[A] cytotoxic conditioning regimen can induce membrane instability leading to massive loss of the endothelial membrane." Wu Decl. Ex. 11 at

373, Shirota et al., *Exp. Hematol* 19:369-73 (1991) (cited by '427 Patent at 1:50-54). Yet another researcher described the process as a "disrupt[ion] [of] normal marrow endothelial cell barriers." Wu Decl. Ex. 12 at 1965 (Nebren et al., *Blood* 81(7):1960-67 (1993) (cited by '427 Patent cover). Researchers had observed disruption of the endothelial barrier of some kind, which then caused the stem cells to enter the peripheral blood stream. While researchers generally abstained from identifying this disruption as the only reason blood-producing stem cells are released into the blood stream, the available articles would inform a skilled artisan that the probable method involved destruction of the endothelial barrier. Amgen believes its construction captures this state of affairs.

Sandoz for its part has derived its construction from the prosecution history. During the patent prosecution, the PTO rejected the claim because the specification did not adequately disclose information about how to use chemotherapeutic agents that increase the permeability of the endothelial barrier. Pai Decl. Ex. 7, June 30, 2000 Resp. to Office Action at 3. In response to this inquiry, the patentee stated, "cyclophosphamide is one of the examples of cytotoxic agents that disrupt normal bone marrow endothelial cell barriers." *Id.* Sandoz argues that this history suggests the clarification about the meaning of the word "open" and using the term "disrupt" as its synonym was an essential precursor for approval.

Ultimately, Sandoz's position boils down to two concerns. The first issue involves whether jurors might believe "opening" the endothelial barrier leaves the barrier intact, which implies a temporary removal, like a door or a curtain. "Disrupt" on the other hand connotes a more damaging process, whereby the barrier may repair over time, but not immediately. Amgen maintains there may be mechanisms for opening the endothelial barrier that do not involve disruption. The trouble with Amgen's proposed construction is the fact it untethers the claim from the specification and the prosecution history. That the patentee chose to use "disrupt" as a synonym for "open" with the PTO militates in favor of using "disrupt" in the construction of this phrase.

Second, Sandoz contends the articles referenced in the specification merely hypothesize about how opening the endothelial barrier facilitates stem-cell transit from bone marrow into the peripheral drug. An open door certainly facilitates movement from the outside to the inside, but it does not cause such movement. During the *Markman* hearing, Sandoz agreed to amend its proposed construction to include a purpose limitation: to disrupt the bone marrow endothelial barrier to facilitate the permeability of the endothelial barrier for stem cells. Tr. Hr'g 156:9–157:4. The words "facilitate the permeability of the endothelial barrier for stem cells" appears in the specification, '427 Patent at 1:53–55, and therefore resolves at least one of Amgen's concerns, namely that the construction must communicate the purpose of the opening, *see* Tr. Hr'g 158:9 – 159:12 (Amgen counsel: "I don't think we have any difficulty with the language that's in the specification. . . . If we building the idea that its' facilitating permeability, maybe we have captured that.").

All in all, the following construction aligns with the specification and prosecution history, and is therefore adopted: "disrupts the bone marrow endothelial barrier to facilitate permeability of the endothelial barrier for stem cells."

B. The '878 Patent

Recombinant proteins are genetically engineered proteins. Scientists introduce human DNA encoding into a host cell of a different species, such as *E. Coli*, to create recombinant proteins. Introduction of human DNA into the host cell causes the bacteria to produce human proteins even though the bacteria would not produce such proteins naturally. This process has been used to engineer various human proteins since the 1980s.

To be therapeutically useful, a recombinant protein must attain a three-dimensional shape. Trouble arises when the host cells produce the recombinant proteins "unfolded," meaning the proteins do not have the proper three-dimensional shape. These unfolded recombinant proteins accumulate in the host cell and form insoluble aggregates called "inclusion bodies." To remedy this problem, scientists break open (lyse) the host cell to release the inclusion bodies. Next, the scientists solubilize the inclusion bodies, which is a process of mixing the protein with various

chemicals to create a solution. That solution is then combined with a "refold buffer" to cause the protein to take a workable, three-dimensional shape.

Once the protein has refolded, the scientists must then separate the refolded recombinant protein from the chemicals used to solubilize and to refold the protein. This step is called purification and typically involves a "separation matrix." The separation matrix utilizes characteristics of the protein to be isolated to trap the protein in the matrix. The unwanted chemicals and proteins that do not have the targeted properties will not associate with the separation matrix and can be discarded.

There are two types of purification: flow-through purification and capture purification. The process of flow-through purification involves applying the solution containing the refolded protein to a resin. Resin attracts the chemicals used to solubilize and to refold the protein. The refolded proteins do not attach to the resin, and therefore they "flow through" the resin and remain in the solution.

In contrast, capture purification utilizes a resin designed to trap protein. The unwanted substances and chemicals stay in the solution and flow over the resin. Scientists discard the solution containing the unwanted contaminants and chemicals, leaving only the resin with the protein to be purified. The process of elation causes the resin to release the purified protein.

At the time of the alleged invention, skilled artisans believed the solution containing the solubilized and refolded protein had to be diluted to remove certain components of the refold solution before they could apply the separation matrix to it. Pai Decl. Ex. 2, Patent '878 at 1:44-46. Skilled artisans believed these contaminants would interfere with the protein's ability to affiliate with the separation matrix. The patentees allegedly discovered that this dilution step was unnecessary; scientists can apply the separation matrix to the refolding solution without diluting the solution first. '878 Patent at 15:33-37. The method disclosed in the patent removes a costly, time-consuming step in the purification process. '878 Patent at 4:55-60.

1. "directly applying the refold solution to a separation matrix"

The first phrase of the '878 Patent to construe appears in claims 7, 8, 11, 13, 14, 15, 16,

and 17. Amgen construes the phrase "directly applying the refold solution to a separation matrix" to mean "applying the refold solution to a column that contains the separation matrix without removing components of or diluting the refold solution." Sandoz offers a slightly different construction of the phrase: "applying the refold solution to a separation matrix without diluting the refold solution or removing one or more of a denaturant, a reductant, a surfactant, an aggregation suppressor, a protein stabilizer, and a redox component." There are two points of disagreement between the parties. First, Amgen does not wish to list the components of the refold solution, whereas Sandoz believes such components should be specified. The crux of the dispute is whether the claim allows for steps between the refolding process and the purification process, which remove components of the refold solution that are *not* required for refolding. Second, they part company over whether the refold solution is applied to a column or whether the claim covers other methods of applying separation matrices, such as batch processes. For the reasons discussed below the phrase will be construed as follows: "applying the refold solution to a separation matrix without removing components of or diluting the refold solution."

a. "Directly Applying"[8]

Amgen and Sandoz agree the patent teaches a method of purification that does not require dilution of the refold solution. Sandoz's construction is drawn from the claim itself, which lists the components "comprising" a solubilization solution: one or more of a denaturant, a reductant, and a surfactant. '878 Patent at 22:9-13. Claim 7 further defines a "refold solution" as "comprising the solubilization solution and a refold buffer." '878 Patent at 22:14-15. The "refold buffer" "compris[es] one or more of" a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component. '878 Patent at 22:15-20. Thus, according to Sandoz's expert, Nigel J.

[8] Along with the reply brief, Amgen submitted a declaration to rebut the extrinsic evidence Sandoz submitted. Sandoz sought to strike the declaration or, in the alternative, to file a sur-reply brief. Because the submission of new evidence and new argument in reply was improper, Sandoz received leave to file a sur-reply. One of the sur-reply declarations submitted included an interrogatory response. Amgen objected to the admission of this exhibit, but really used the objection as an opportunity to argue why the submitted exhibit did not actually support Sandoz's argument. Accordingly, the objection is overruled.

Titchener-Hooker, Ph.D., a skilled artisan would understand the "refold solution," which is applied to the separation matrix includes the listed components. Sandoz's Expert Titchener-Hooker Decl. ¶¶ 31-32.

Amgen contends the word "directly" means there are no intermediary steps of any kind between refolding and purification. The dispute about proper construction of the word "directly revolves around whether the claim allows for removal of components of the refold solution that are *not* required for refolding.

The proper starting point is, of course, the text of the claim. A person skilled in the art could read the claim and reasonably conclude no dilution steps of any kind are allowed between refolding and washing. Yet, "directly" could also mean the refold solution need not pass through something to come into contact with the separation matrix. Accordingly, the text of the claim itself does not resolve the dispute.

The specification teaches the method claimed involves applying "the refold solution comprising the refolded protein of interest" "directly to the separation matrix, without the need for diluting or removing *the components of the solution required for refolding the protein*." '878 Patent at 15:25-29 (emphasis added). Similarly, in the prosecution history, the patentee used related language after the PTO rejected the proposed claims because it believed U.S. Patent No. 7,138,370 anticipated the claimed method. Patent '370 disclosed a method of protein purification requiring three processing steps before the refold solution could be applied to the separation matrix: dialysis, precipitation, and centrifugation. To remedy this problem, the patentee added the word "directly" to the claim to emphasize that the disclosed method did not require removal of "the components of the solution required for refolding the protein." Wu Decl. Ex. 13 at 3. Amgen insists these statements in the specification and prosecution history make clear no dilution whatsoever is required.

The trouble with this position is the fact claim 7's steps (c) and (d) and preamble recites the components that comprise the refold solution: one or more of a denaturant, a reductant, a surfactant, an aggregation suppressor, a protein stabilizer, and a redox component—the very

components listed in Sandoz's construction. That said, Sandoz's construction does not fully capture the claim because, in the world of patents, the word "comprising" means "including but not limited to." *Exergen*, 575 F.3d at 1319. The six components listed in the claim are not necessarily the only components of the refold solution. Moreover, the patentee's attempt to distinguish the claimed method from the prior art, and the '370 Patent, in particular, clarify that the patentee believed there should not be any intermediary steps between the refolding process and application of such solution to the separation matrix.

b. "Column"

The second point of conflict is whether the refold solution must be applied to a column containing the separation matrix or whether the claim contemplates other methods of bringing the separation matrix in contact with the refold solution. Amgen and Sandoz agree on at least one point: that the claim, specification, and prosecution history all contemplate that scientists could load the refold solution into a column containing the separation matrix. Conflict has arisen, however, because there are various methods of chromatography used to bring into contact separation matrices and refold solution. The column method involves loading the refold solution into a column containing a separation matrix. As the solution flows down the column, it flows past the separation matrix and down into a collection vessel, where either the contaminants or protein collect. There are, however, other methods scientists used to accomplish the same goal, such as batch processing and filtration systems. '878 Patent at 16:47-54. The batch method employs resin beads with the separation matrices. Scientists pour the refold solution into a container containing these resin beads, and then they discard the excess solution. Despite the fact that there are multiple methods of chromatography, Amgen contends claim 7 is limited to the column method even though the claim does not specify the chromatography method used.

The most significant problem with Amgen's proposal is that the word "column" does not appear in the claim, and thus there is no reasonable argument for the proposition "column" is a synonym for any word appearing therein. "[A] bedrock principle of patent law [is] that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips*,

415 F.3d at 1312 (internal quotation marks omitted). Amgen therefore faces an uphill battle to show its construction including the word "column" is proper.

Amgen first turns to the specification, which describes three embodiments of the method—all of which describe column chromatography. Sandoz correctly notes the first two examples describe affinity separation matrices, which do not pertain to claim 7. Nevertheless, a skilled artisan reading the specification would read about only column processes—a fact suggesting, but not establishing, that the method involves column application. Yet, the specification also teaches:

> [A]ny or all steps of the invention can be carried out *by any mechanical means*. As noted, the separation matrix can be disposed in a column. The column can be run with or without pressure and from top to bottom or bottom to top. The direction of the flow of fluid in the column can be reversed during the purification process. Purifications can also be carried out using a batch process in which the solid support is separated from the liquid used to load, wash, and elute the sample by any suitable means, including gravity, centrifugation, or filtration. Moreover, purifications can also be carried out by contacting the sample with a filter that adsorbs or retains some molecules in the sample more strongly than others.

'878 Patent at 16:42-54 (emphasis added). The specification thus makes clear the method is not limited to column chromatography alone and even offers additional methods. In light of the fact the Federal Circuit has rejected the notion "that if a patent describes a single embodiment, the claims of the patent must be construed as being limited to that embodiment," *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004), the simple fact most examples disclosed in the specification involve column chromatography is not dispositive.

The second problem with Amgen's "column" proposal is that the specification describes the process of putting the refold mixture into the column as "loading," whereas the word "applying" implies a broader range of mechanisms. *See* Titchener-Hooker Decl. ¶35. For that reason, Titchener-Hooker contends that had the patentee wished to limit the method claimed to the column process, it should have used the word "loading." *Id.* (citing '878 Patent at 18:7-17, 19:4-17).

In sum, the text of the claim and intrinsic record do not support Amgen's proposal to limit the claim to the column process. At the same time, neither the intrinsic record nor the extrinsic record support Sandoz's attempt to list the components of the refold solution that need not be removed before the solution is applied to the separation matrix. Accordingly the phrase "directly applying the refold solution to a separation matrix must be construed as follows: "applying the refold solution to a separation matrix without removing components of or diluting the refold solution."

2. "under conditions suitable for the protein to associate with the matrix"

The phrase "under conditions suitable for the protein to associate with the matrix" relates to claims 7, 8, 11, 13, 14, 15, 16, and 17. There are two points of disagreement about how properly to construe this phrase: the construction of the words "protein" and "associate." For the reasons discussed below, the phrase shall be construed as follows: "under conditions suitable for the protein to be purified to bind to the matrix."

a. Protein

Amgen believes the word "protein" refers to any protein expressed by the non-mammalian expression system, not just the protein of interest, i.e., the recombinant protein expressed by the host cell. In contrast, Sandoz argues "protein" refers to a specific protein the scientists intended the non-mammalian organism to express (G-CSF, for example).

Both parties argue the text of the claim supports their respective constructions. Amgen points to the preamble of claim 7: "A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system . . . ." '878 Patent at 22:3-5. The patentee chose to use "a protein" instead of "the protein" to make clear the method could be used to capture any protein expressed by a non-mammalian organism.

More importantly, the patentee defined the word "protein" in the specification as follows: "the terms 'protein' and 'polypeptide' are used interchangeably and mean any chain of at least five naturally or non-naturally occurring amino acids linked by peptide bonds." '878 Patent at 5:62-65. When an inventor has expressly defined a term in the specification, it controls for

construction purposes. *See Phillips*, 415 F.3d at 1316. In contrast, the patentee refers to the "protein of interest," meaning the protein the scientists caused bacteria to express, throughout the disclosure. *See e.g.*, '878 Patent at 4:8-9 ("[T]he present invention relates to a method of isolating a protein of interest . . . ."); '878 Patent at 4:31-32 (same). According to Amgen, the patentee's conscious decision to use the word "protein" instead of "protein of interest" in claim 7's text is significant and counsels in favor of using the specification's definition of "protein."

Sandoz begins with the text and structure of the claim. Step (a) of Claim 7 involves "expressing a protein," whereas steps (c), (e), and (g) involve doing something to "the protein." '878 Patent at 22:3-6, 22:9-25. The Federal Circuit has explained "[s]ubsequent use of the definite articles 'the' or 'said' in a claim refers back to the same term recited earlier in the claim." *Wi-Lan, Inc. v. Apple, Inc.*, 811 F.3d 455, 462 (Fed. Cir. 2016). Thus, Sandoz contends the steps refer back to the antecedent basis: the protein expressed in a non-native expression system is the protein to be purified.

In addition, Sandoz correctly points out that the method claimed is one of protein purification, and therefore all steps listed in the claim drive towards the purification of one specific protein. Indeed, the specification teaches, "[a]fter the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution." '878 Patent at 15:43-46. The process of washing removes unwanted protein from the refold mixture, leaving only the sought-after protein stuck to the separation matrix. Once all unwanted materials have been washed away, the final step of the claimed process is elution, whereby the protein disassociates from the matrix. The end result is a clean protein ready for future use. All these steps lead to the electable conclusion the method claimed and the steps claim 7 describes target a specific protein.

That the clean protein emerging from the process is the expressed protein does not, however, necessarily follow from the text of the claim. Accordingly, Sandoz's construction must be rejected for that reason. Nevertheless, the method claimed is also more targeted than Amgen suggested. The targeted protein is the protein to be purified. Thus, in the context of claim 7 (and

all derivative claims), the word "protein" means "the protein to be purified."[9]

b. Associate

The parties also dispute whether "associate" is a synonym for "bind." Amgen insists binding is merely one of the mechanisms by which proteins associate with separation matrices. Sandoz believes binding is the only mechanism by which the proteins interact with the separation matrix.

Amgen derives its construction from the specification and its definition of "separation matrix":

> As used herein, the term "separation matrix" means any absorbent material that utilizes *specific, reversible interactions* between synthetic and/or biomolecules, e.g., the property of Protein A to bind to an Fc region of an IgG antibody or other Fc-containing protein, in order to effect the separation of the protein from its environment. In other embodiments the specific, reversible interactions can be base[d] on a property such as isoelectric point, hydrophobicity, or size.

'878 Patent at 14:65-15:5 (emphasis added). Amgen reads this section to mean binding is just an example of the type of reversible interactions the process involves, whereas other embodiments of the method involve resins that retard the flow of the refold solution through the column or which trap large proteins and permit smaller proteins to flow through. While there is a temptation to treat the specification's definition of "separation matrix" as a definition for associate, it is not. The specification defines "separation matrix," and not "associate." Accordingly, the specification offers some, but not definitive, support for Amgen's proposed construction.

Sandoz has identified portions of the specification that support its position, where the patentee used the words "associate" and "bind" interchangeably. For example: "After the protein of interest has *associated* with the separation matrix, the separation matrix is washed to remove *unbound* protein, lysate, impurities and unwanted components of the refold solution." '878 Patent

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[9] Recently, the *Apotex* court construed the word "protein" in accord with Amgen's proposed construction. *See* Dkt. 195-1 at 14-17. While the court's opinion is persuasive authority, its value goes only so far. First, the court was construing a different patent. Second, in *Apotex*, the defendant argued the word "protein" should be construed to mean "protein of interest," whereas Sandoz has not proposed such a construction.

at 15:43-46 (emphasis added). The patentee differentiated between proteins "associated with" the separation matrices and those components and proteins "unbound" from the matrices—a telling choice of words which implies the words are synonyms for the same process. In addition, when describing the elution process, the specification teaches, "[t]he protein of interest can be eluted using a solution that interferes with the *binding* of the absorbent component of the separation matrix to the protein." '878 Patent at 15:65-67. Thus, the specification equates binding with associating.

Sandoz's final argument is that the other steps listed in the claim clarify that "associate" means "bind." Step (g) of claim 7 states, "the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin." '878 Patent at 22:25-28. Figure 4 of the patent, titled "demonstration of Dynamic Binding Capacity for Ion Exchangers and Mixed mode Resins," describes "a plot demonstrating the binding profiles of a refolded, non-mammalian non-native limited solubility complex protein to six different ion exchange resins." '878 Patent at 3:22-29, Figure 4. This figure, Sandoz argues, demonstrates the ion exchanges and mixed mode resins operate by binding to proteins of interest.

Ultimately, Amgen's proposed construction does not make sense in the context of the claim as a whole. There are some interactions between resin and protein, which do not facilitate protein capture. For example, the proteins and resins may repel one another, but the repellence does not facilitate protein capture or purification. Although Amgen has provided examples of how proteins interact with separation matrices that do not involve a binding mechanism, they do not lend support for its construction. Sizing resins that trap proteins of a certain size while allowing smaller components to pass through are not non-affinity resins. Claim 7 discloses a capture method involving a non-affinity resin, *see* '878 Patent at 22:26, and therefore sheds no light on the question of whether the claimed method covers interactions other than binding interactions. Similarly, isocratic protein separations, which retard the transit of some proteins moving through a column containing a separation matrix, do not employ "reversible interactions." The interaction between the resin and the protein never reverses; the protein simply takes longer to pass through

the column. *See* Titchener-Hooker Sur-Reply Decl. ¶ 40.

Ultimately, most problematic aspect of Amgen's proposed construction is that it is confusing and no clearer than the text of the claim itself. Accordingly, the word "associate" will be construed to mean "bind."

c. *"washing the separation matrix"*

The phrase "washing the separation matrix" must be construed to shed light on the meaning of claims 7, 8, 11, 13, 14, 15, 16, and 17. Amgen proposes construing the phrase as "adding a solution into the column that contains the separation matrix, to remove materials in the refold solution that do not interact with the separation matrix." Sandoz on the other hand proposes the following construction: "applying a solution to remove unbound protein, lysate, impurities, and unwanted components of the refold solution from the separation matrix while preserving binding of the expressed protein."

The parties' disagreements are familiar and involve the meaning of "associate," whether the chromatography method described is the column method, and whether the protein captured is the expressed protein. Each of these issues has been previously addressed and resolved. The claim shall not be limited to the column method of chromatography. The claim covers the capture of proteins other than the protein of interest. Finally, the proteins bind to the separation matrix when they "associate" with it.

Nevertheless, there remains one material difference between the two proposed constructions about which the parties offer no argument for their disagreement: whether to list the components to be washed away. Sandoz lists those components (lysate, unbound protein, impurities, etc.), whereas Amgen suggests anything that "do[es] not interact with the separation matrix" will be removed. Sandoz offers no reason to list (or to limit) the components to be washed away. Amgen's proposal is therefore not only simpler, but seems accurately to describe the process set forth in claim 7.

In sum, the phrase must be construed as a hybrid of the two proposals. "Washing the separation matrix" shall mean "adding a solution to the separation matrix to remove materials in

the refold solution while preserving binding of the protein to be purified."

d. *"eluting the protein from the separation matrix"*

The final phrase to construe—"eluting the protein from the separation matrix"— informs the scope of claims 7, 8, 11, 13, 14, 15, 16, and 17. Amgen would construe the phrase to mean "adding a solution into the column that contains the separation matrix, which as the effect of reversing the interactions between protein and the separation matrix." Sandoz proposes to construe the phrase to mean "applying a solution that reverses the binding of the expressed protein to the separation matrix." Under Sandoz's proposed construction, "this step must occur after the step of 'washing the separation matrix.'"

The disputes about how properly to construe the phrase are linked to the parties' disagreement about the meaning of "associate," "protein," and "separation matrix," and have been resolved. There is, however, one unique feature of this phrase: whether the eluting step must occur after the washing step. Amgen believes this claim does not properly present the issue of the order of the steps because Sandoz did not seek to construe the word "and" (as in "washing . . . and eluting"). Indeed, Amgen is so confident of this point, it did not even respond to Sandoz's argument.

As an initial matter, Sandoz has not waived its right to seek construction of this phrase or to argue the claim has an implied order of steps. "As a general rule, unless the steps of a method claim actually recite an order, the steps are not ordinarily construed to require one." *Mformation Techs., Inc. v. Research in Motion Ltd.*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (internal quotation marks omitted). A claim may have a required order of steps, however, when "as a matter of logic or grammar, [the claim] requires that the steps be performed in the order written, or the specification directly or implicitly requires an order of steps." *Id.* (internal quotation marks omitted). Thus, by designating "eluting the protein from the separation matrix" for construction, Sandoz adequately notified Amgen of its intent to seek construction and limited the number of terms to be construed to ten, as required by the local patent rules. *See* Local Patent Rule 4-1(b).

The specification teaches, "[a]fter the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution." '878 Patent at 15:60-62. It further explains that the wash buffer may be comprised of any number of components so long as "[t]he pH range is chosen to optimize the chromatography conditions, *preserve protein binding*, and to retain the desired characteristics of the protein of interest." '878 Patent at 15:55-57 (emphasis added). Thus, the proteins and separation matrix should remain associated during the washing process. In contrast, elution involves cleaving the protein from the matrix with "a solution *that interferes with the binding* of the absorbent component of the separation matrix to the protein, for example by *disrupting the interactions* between Protein A and the Fc region of a protein of interest." '878 Patent at 15:65-16:2 (emphasis added). Accordingly, the specification discloses a natural, logical order of steps. If the washing and eluting steps occurred simultaneously, the protein captured by the separation matrix could once again comingle with the contaminants and components to be washed away. In light of the fact, Amgen has not offered any reasons to believe the claim does not imply a natural order, the construction of the phrase will make clear the step of "eluting the protein from the separation matrix" occurs after the step of "washing the separation matrix."

As discussed above, the method claim 7 describes is not limited to the "expressed protein" or the "protein of interest." Accordingly, the protein eluted from the separation matrix is "the purified protein." After all, if elution is the final step of the purification process, the resulting protein is "purified." Thus, the phrase "eluting the protein from the separation matrix" shall mean "applying a solution that reverses the binding of the purified protein to the separation matrix."

V. CONCLUSION

The disputed claim terms of the patents-in-suit are construed as set forth as follows:

	'427 Claim Term	Construction
1.	"hematopoietic stem cell mobilizing-effective amount of G-CSF"	An amount of G-CSF effective to mobilize hematopoietic stem cells.
2.	"A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment"	The preamble limits the scope of the claim. In the practice of the method of treating a disease, a patient receives a transplant of peripheral stem cells.
3.	"disease treating-effective amount of at least one chemotherapeutic agent"	An amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed.
4.	"chemotherapeutic agent"	Exogenous substance suited and used to damage or destroy microorganisms, parasites, or tumor cells.
5.	"comprising administering . . . G-CSF; and thereafter administering . . . at least one chemotherapeutic agent"	The word "comprising" means "including but not limited to," and allows for additional steps before, in between, and after the steps recited in the claim. In the practice of the method, at least one administration of G-CSF must occur before at least one administration of a chemotherapeutic agent.
6.	"opens the endothelial barrier of the patient to render the endothelial barrier permeable for stem cells"	Disrupts the bone marrow endothelial barrier to facilitate permeability of the endothelial barrier for stem cells.

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Northern District of California

	'878 Claim Term	Construction
7.	"directly applying the refold solution to a separation matrix"	Applying the refold solution to a separation matrix without removing components of or diluting the refold solution.
8.	"under conditions suitable for the protein to associate with the matrix"	Under conditions suitable for the protein to be purified to bind to the matrix.
9.	"washing the separation matrix"	Applying a solution to remove unbound protein, lysate, impurities, and unwanted components of the refold solution from the separation matrix while preserving binding of the expressed protein.
10.	"eluting the protein from the separation matrix"	Applying a solution that reverses the binding of the purified protein to the separation matrix. This step must occur after the step of "washing the separation matrix."

A further Case Management Conference shall be held on September 15, 2016, at 10:00 a.m. in Courtroom 3, 17th Floor, United States Courthouse, 450 Golden Gate Avenue, San Francisco, California. The parties shall file a Joint Case Management Statement at least one week prior to the Conference.

IT IS SO ORDERED.

Dated: August 4, 2016

RICHARD SEEBORG
United States District Judge

United States District Court
Northern District of California

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

AMGEN INC. and AMGEN MANUFACTURING, LIMITED,

Plaintiffs,

v.

SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH,

Defendants.

Case No. 3:14-cv-04741-RS

STIPULATION AND [~~PROPOSED~~] ORDER FOR ENTRY OF JUDGMENT REGARDING U.S. PATENT NO. 6,162,427

WHEREAS Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Amgen") filed a complaint against Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH (collectively, "Sandoz") in the Northern District of California (the "Court") on October 24, 2014 (Docket No. 1), and a first amended and supplemental complaint on October 15, 2015 (Docket No. 145), alleging, among other things, infringement of United States Patent Number 6,162,427 ('427 patent);

WHEREAS Sandoz has appeared and denied infringement, and Sandoz Inc. has counterclaimed for declaratory judgment of invalidity of the '427 patent (Docket Nos. 22, 149);

WHEREAS the Court construed certain disputed claim terms associated with claims 1-4, and 6 of the '427 patent ("Asserted Claims") in an order dated August 4, 2016 (Docket No. 205);

WHEREAS the parties have completed fact discovery regarding the '427 patent;

WHEREAS Amgen has provided an expert report regarding the alleged infringement of the Asserted Claims of the '427 patent, and Sandoz has provided an expert report regarding the alleged invalidity of the Asserted Claims of the '427 patent;

WHEREAS the time to add or amend infringement and invalidity contentions or add or amend the Asserted Claims has passed;

WHEREAS the parties agree that Amgen may preserve its right to appeal the claim construction order after a final judgment is entered pursuant to 28 U.S.C. §§ 1291 & 1292(c)(2);

THEREFORE Amgen and Sandoz agree that:

1. Amgen and Sandoz stipulate that Sandoz does not infringe the Asserted Claims of the '427 patent within the meaning of any provision of 35 U.S.C. § 271 in light of the claim constructions included in the August 4, 2016 order, Docket No. 205.

2. Amgen and Sandoz stipulate that the Court may enter a judgment of non-infringement in favor of Sandoz and against Amgen for Amgen's Third Cause of Action of its First Amended and Supplemental Complaint filed on October 15, 2015 (Docket No. 145) and

Sandoz's Sixth Counterclaim of Sandoz Inc.'s Answer to Amended Complaint filed November 2, 2015 (Docket No. 149).

3. Amgen and Sandoz stipulate that Sandoz Seventh Counterclaim of Sandoz Inc.'s Answer to Amended Complaint filed November 2, 2015 (Docket No. 149) for a declaration of invalidity for the '427 Patent will be dismissed without prejudice and that Sandoz will be allowed to assert the Seventh Counterclaim in the event this matter is remanded for further consideration following any appeal.

4. This Stipulation and [Proposed] Order are without prejudice to Amgen's right to appeal the Claim Construction Order (Docket No. 205), and any final judgment based thereon pursuant to 28 U.S.C. §§ 1291 & 1292(c)(2).

5. No party will conduct any further discovery or pretrial activities related to allegations of liability or damages regarding the '427 patent, including any activity related to Sandoz's alleged defense and counterclaim that the '427 patent is invalid.

6. Neither party shall be obligated to pay the opposing party any money in connection with this stipulation or resolution, and Sandoz agrees not to seek its costs with respect to the '427 patent. Neither party shall use as evidence or rely on the fact of this stipulation or the judgment in favor of Sandoz and against Amgen directed to the '427 patent to argue that this case is exceptional.

7. (i) Neither party shall use as evidence or rely on the fact of this stipulation or the judgment in favor of Sandoz and against Amgen directed to the '427 patent in connection with the continuing litigation involving United States Patent Number 8,940,878, (ii) neither party shall assert in any forum that this stipulation or the judgment in favor of Sandoz and against Amgen directed to the '427 patent is inconsistent with positions regarding infringement taken by any party or its experts prior to the date of this stipulation, and (iii) neither party shall use as evidence or rely on the contents of this stipulation or the judgment in favor of Sandoz and against Amgen directed to the '427 patent in continuing litigation relating to Amgen's unfair

competition and conversion claims except to note the fact that judgment has entered with respect to the '427 patent and that the '427 patent was the only patent asserted against Sandoz by Amgen prior to October 15, 2015. For the avoidance of doubt, this stipulation has no impact on the claims, defenses, or prayer for relief of either party related to the validity of, infringement of, or relief available for the '878 patent.

8. Neither party shall issue a press release or make an affirmative press statement regarding this stipulation.

Respectfully submitted,

Dated: September 13, 2017

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SIGNATURE ATTESTATION

Pursuant to Civil Local Rule 5-1(i)(3), I hereby certify that concurrence in the filing of this document has been obtained from each of the other Signatories shown above.

Dated: September 13, 2017

By: /s/ Sue Wang
Sue Wang

PURSUANT TO STIPULATION, IT IS SO ORDERED.

Dated: 9/13, 2017

THE HONORABLE RICHARD SEEBORG
UNITED STATES DISTRICT COURT JUDGE

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

AMGEN INC. and
AMGEN MANUFACTURING LIMITED,

Plaintiffs,

vs.

SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, LEK PHARMACEUTICALS, D.D.

Defendants.

Case No. 3:16-CV-02581-RS

JOINT STIPULATION OF DISMISSAL OF ALL CLAIMS AND COUNTERCLAIMS RELATED TO U.S. PATENT NO. 5,824,784, AND ~~PROPOSED~~ ORDER

Pursuant to Civil Local Rule 7-12, Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively, "Amgen") and Defendant Sandoz Inc., by and through their counsel, jointly stipulate to the dismissal, without prejudice, of all claims and counterclaims related to U.S. Patent No. 5,824,784 ("the '784 Patent") on the terms set forth herein:

1. Amgen's cause of action directed solely to the '784 Patent, specifically the Third Cause of Action of its Complaint filed May 12, 2016 [Dkt. No. 1], is hereby dismissed without prejudice.

2. Sandoz Inc.'s counterclaims directed solely to the '784 Patent, specifically the Third Counterclaim and the Fourth Counterclaim of Sandoz Inc.'s Answer and Affirmative Defenses and Counterclaims filed June 23, 2016 [Dkt. No. 18], are hereby dismissed without prejudice.

3. The parties agree that neither party is a prevailing party with respect to the '784 Patent, and accordingly no party shall be entitled to attorneys' fees or costs with respect to the '784 Patent, either now or at any future point in the case. To avoid any doubt, this stipulated dismissal of the '784 Patent shall play no role in any argument for or determination of attorneys' fees and costs in this litigation.

Dated: December 1, 2016
Respectfully submitted,

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ECF ATTESTATION

I, Vernon M. Winters, am the ECF User whose ID and Password are being used to file this document. I attest that concurrence in the filing of this document has been obtained from the above signatories.

Dated: December 1, 2016

SIDLEY AUSTIN LLP

By: */s/ Vernon M. Winters*

PURSUANT TO STIPULATION, IT IS SO ORDERED.

Dated: 12/7, 2016

THE HONORABLE RICHARD SEEBORG
UNITED STATES DISTRICT COURT JUDGE