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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

1 cancer therapy.” FAC ¶ 11. The active ingredient in both products is filgrastim, a synthetic  
2 version of human granulocyte colony stimulating factor (“G-CSF”). Amgen also accuses Sandoz  
3 of violating California’s unfair competition law (“UCL”). In response, Sandoz asserts numerous  
4 counterclaims for declaratory judgments of compliance with the Biosimilars Price Competition  
5 and Innovation Act (“BPCIA”), non-infringement, and patent invalidity. In March 2015, Sandoz  
6 obtained partial judgment in its favor with respect to the UCL claim and Sandoz’s claim for a  
7 declaratory judgment of compliance with the BPCIA pursuant to Federal Rule of Civil Procedure  
8 54(b). The parties jointly requested to stay these proceedings until the issuance of the Federal  
9 Circuit’s mandate. Dkt. No. 111 at 3.

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

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

### 21 III. LEGAL STANDARD

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

1           The first step in claim construction is to look to the language of the claims themselves. “It  
2 is a ‘bedrock principle’ of patent law that ‘the claims of a patent define the invention to which the  
3 patentee is entitled the right to exclude.’” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir.  
4 2005) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115  
5 (Fed. Cir. 2004)). A disputed claim term should be construed in a manner consistent with its  
6 “ordinary and customary meaning,” which is “the meaning that the term would have to a person of  
7 ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date  
8 of the patent application.” *Phillips*, 415 F.3d at 1312–13. The ordinary and customary meaning  
9 of a claim term may be determined solely by viewing the term within the context of the claim’s  
10 overall language. *See id.* at 1314 (“[T]he use of a term within the claim provides a firm basis for  
11 construing the term.”). Additionally, the use of the term in other claims may provide guidance  
12 regarding its proper construction. *Id.* (“Other claims of the patent in question, both asserted and  
13 unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term.”).

14           A claim should also be construed in a manner that is consistent with the patent’s  
15 specification. *See Markman*, 52 F.3d at 979 (“Claims must be read in view of the specification, of  
16 which they are a part.”). Typically the specification is the best guide for construing the claims.  
17 *See Phillips*, 415 F.3d at 1315 (“The specification is . . . the primary basis for construing the  
18 claims.”); *see also Vitronics Corp. v. Conceptor, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)  
19 (“[T]he specification is always highly relevant to the claim construction analysis. Usually, it is  
20 dispositive; it is the single best guide to the meaning of a disputed term.”). In limited  
21 circumstances, the specification may be used to narrow the meaning of a claim term that otherwise  
22 would appear to be susceptible to a broader reading. *See SciMed Life Sys., Inc. v. Advanced*  
23 *Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) (“Where the specification makes  
24 clear that the invention does not include a particular feature, that feature is deemed to be outside  
25 the reach of the claims of the patent, even though the language of the claims, read without  
26 reference to the specification, might be considered broad enough to encompass the feature in  
27 question.”); *Phillips*, 415 F.3d at 1316 (“[T]he specification may reveal an intentional disclaimer,  
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1 or disavowal, of claim scope by the inventor. In that instance as well, the inventor has dictated the  
 2 correct claim scope, and the inventor’s intention, as expressed in the specification, is regarded as  
 3 dispositive.”). Precedent forbids, however, a construction of claim terms that imposes limitations  
 4 not found in the claims or supported by an unambiguous restriction in the specification or  
 5 prosecution history. *Laitram Corp. v. NEC Corp.*, 163 F.3d 1342, 1347 (Fed. Cir. 1998) (“[A]  
 6 court may not import limitations from the written description into the claims.”); *Comark*  
 7 *Commc’ns., Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998) (“[W]hile claims are to be  
 8 interpreted in light of the specification, it does not follow that limitations from the specification  
 9 may be read into the claims.” (internal quotation marks and alterations omitted)); *SRI Int’l v.*  
 10 *Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc) (“It is the *claims*  
 11 that measure the invention.”) (emphasis in original). A final source of intrinsic evidence is the  
 12 prosecution record and any statements made by the patentee to the United States Patent and  
 13 Trademark Office (“PTO”) regarding the scope of the invention. *See Markman*, 52 F.3d at 980.

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

#### 20 IV. DISCUSSION

##### 21 A. The ’427 Patent

22 Hematopoietic stem cells naturally occur in the human body and are capable of  
 23 proliferation and differentiation into cells that comprise the blood and immune systems. In other  
 24 words, they are blood-forming stem cells.<sup>1</sup> These cells self-renew and reside primarily in bone  
 25 marrow.

26 \_\_\_\_\_  
 27 <sup>1</sup> In the interest of using plain language, this order uses the term “blood-forming stem cells”  
 28 instead of “hematopoietic stem cells.”

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

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

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

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

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

3 1. “*hematopoietic stem cell mobilizing-effective amount of G-CSF*”

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

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

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

25 Turning to the question of whether such a skilled artisan understands the phrase  
26 “hematopoietic stem cell mobilizing-effective amount of G-CSF,” Sandoz takes aim at the word  
27 “effective” and offers three arguments for why the term is indefinite. First, it argues neither the  
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1 claim language nor the specification inform skilled artisans about how many blood-producing  
 2 stem cells must mobilize to be considered “effective.” In other words, a skilled artisan has no way  
 3 to discern whether mobilization of one stem cell, ten stem cells, or a thousand stem cells is  
 4 “effective.” Second, Sandoz insists the claim, specification, and prosecution history do not  
 5 provide information for skilled artisans to tailor the procedure to the species of the patient (human,  
 6 mouse, dog, horse, etc.). The final argument is that the patent does not explain how artisans  
 7 should measure the level of stem-cell mobilization. At the time of the invention, practitioners  
 8 knew of four methods for measuring the extent of stem cell mobilization, all of which varied  
 9 considerably in terms of accuracy, consistency, and practicality. *See* Sandoz’s Expert Negrin  
 10 Decl. ¶¶ 45-46.

11 Whether adjectival limitations are indefinite depends on the context of each individual  
 12 patent. In *Takeda Pharm. Co. v. Mylan Inc.*, No. 13-CV-04001-LHK, 2014 WL 5862134, at  
 13 \*10-11 (N.D. Cal. Nov. 11, 2014), the district court deemed the term “effective amount” definite  
 14 because the patent described the proper dose of the drug (“about 0.5 to 1,500 mg/day”), and the  
 15 claim covered treatment of a specific type of disease—reflux esophagitis. *Id.* at \*10. In contrast,  
 16 another district court concluded the term “% identity” was indefinite because “the specification  
 17 identifie[d] a non-inclusive list of five methods to calculate ‘% identity’ and provide[d] that  
 18 sequence alignment can be performed using any commercially available or independently  
 19 developed software.” *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, 117 F. Supp. 3d 632, 641  
 20 (D. Del. 2015). Similarly, in *Andrulis Pharm. Corp. v. Celgene Corp.*, No. CV 13-1644(RGA),  
 21 2015 WL 3978578, at \*3-4 (D. Del. June 26, 2015), the term “enhanced therapeutically-effective  
 22 amounts of thalidomide” was held to be indefinite because “enhanced” could mean “less than  
 23 additive, additive, or greater than additive.” *Id.* at \*3.

24 Here, the claim itself offers little guidance, but the specification provides more direction.  
 25 It teaches, “[t]he [G-CSF] dosage may depend on various factors such as mode of application,  
 26 species, age, or individual condition. According to the invention, from 5 to 300 µg/kg/day of G-  
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1 CSF sc.<sup>2</sup> is applied.” Pai Decl. Ex. 1, ’427 Patent 3:4-7. G-CSF administration occurs “once per  
 2 day over two to three days.” ’427 Patent 4:5-8. Amgen points to portions of the specification that  
 3 explain, “[n]umerous substances” are capable of causing mobilization of blood-producing stem  
 4 cells, such as G-CSF and “[s]ome chemotherapeutic agents.” ’427 Patent 1:32-37. These  
 5 passages make clear that, at the time the patent was filed, skilled artisans knew G-CSF caused  
 6 blood-producing stem cells to mobilize, and that any amount ranging from 5 to 300 µg/kg/day of  
 7 G-CSF sc. would cause stem cells to mobilize enough to enable collection.

8 The prosecution history of the ’427 patent offers skilled artisans further guidance and  
 9 additional support for Amgen’s proposed construction. Three papers identified in the specification  
 10 refer to various G-CSF dosage amounts within the range stated in the specification. Two papers  
 11 examined the efficacy of subcutaneous doses of 10 µg/kg/day. Wu Decl. Ex 4 at 861 (Long et al.,  
 12 *Cancer* 76(5):860-68 (1995)); Wu Decl. Ex. 6 at 146 (Pierelli et al., *J. Hematotherapy* 2:145-53  
 13 (1993)). Another study tested the comparative potency of subcutaneous or intravenous doses of  
 14 10 µg/kg/day or 5 µg/kg/day. Wu Decl. Ex. 5 at 2177 (Nademanee et al., *J. Clinical Oncology*  
 15 12(10):2176-86 (1994)). These three studies supply a person skilled in the art with more  
 16 information to determine with a reasonable degree of certainty how much G-CSF to administer to  
 17 achieve more than a *de minimus* level of stem-cell mobilization.

18 While the range of the amounts of G-CSF to administer is admittedly wide and variable  
 19 depending on the size or species of the subject, a skilled artisan is not without any guidance to  
 20 figure out how much G-CSF to administer. After all, “breadth is not indefiniteness.” *SmithKline*  
 21 *Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1341 (Fed. Cir. 2005). To the extent a skilled  
 22 artisan may have difficulty adjusting the amount of G-CSF to administer depending on the species  
 23 of the subject, the lack of precision in the claim and specification impacts only his or her ability to  
 24 practice all embodiments of the claim—a question of enablement, not indefiniteness. *See Takeda*,  
 25 2014 WL 5862134, at \*10 (citing *Exxon Research & Eng’g Co. v. United States*, 265 F.3d 1371,

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 27 <sup>2</sup> “sc.” stands for “subcutaneous.” Negrin Decl. ¶ 40.

1 1382 (Fed. Cir. 2001) (noting that “‘inoperable embodiments’ raise ‘an issue of enablement, and  
2 not indefiniteness’’). Overall, the patent communicates the purpose of G-CSF administration: to  
3 cause more than a *de minimus* number of blood-producing stem cells to enter the peripheral blood.  
4 While the claim and specification could have offered more precise guideposts, the disclosures  
5 provide those skilled in the art with sufficient information to figure out how to accomplish that  
6 goal. Accordingly, the phrase “hematopoietic stem cell mobilizing-effective amount of G-CSF” is  
7 not indefinite. It will be construed as follows: “an amount of G-CSF effective to mobilize  
8 hematopoietic stem cells.”

9 2. *“A method of treating a disease requiring peripheral stem cell transplantation in a  
10 patient in need of such treatment”*

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

22 To begin, the phrase “such treatment” must have an antecedent. *See Rapoport v. Dement*,  
23 254 F.3d 1053, 1059 (Fed. Cir. 2001) (noting the phrase “to a patient in need of such treatment”  
24 must have an antecedent basis). Sandoz argues the antecedent is “a method of treating a disease,”  
25 whereas Amgen insists it refers back to “peripheral stem cell transplantation.” Under Sandoz’s  
26 construction, the treatment (usually chemotherapy) necessitates stem-cell transplantation. To  
27 practice the treatment method, the doctor mobilizes, collects, and transplants blood-producing  
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1 stem cells into the patient. In contrast, under Amgen’s reading it is the disease (primarily cancer)  
2 that requires peripheral stem cell transplantation. While “such treatment” surely requires an  
3 antecedent, both proposed constructions are grammatically correct, and therefore to construe the  
4 terms requires a more searching inquiry.

5 The text of the whole claim lends support to Sandoz’s construction. The method claim 1  
6 includes two steps: (1) administration of G-CSF, and (2) administration of a chemotherapeutic  
7 agent. The claim describes the quantity of G-CSF to be administered as “stem cell mobilizing,”  
8 whereas the chemotherapeutic agent is described as “disease treating.” *See* ’427 Patent at  
9 10:26-29. In other words, one substance mobilizes stem cells, while the other treats a disease.  
10 The claim suggests the transplantation itself does not treat disease.

11 The specification bears out this interpretation. It explains the purpose of the claimed  
12 method: “The use of high-dosage chemotherapy or bone marrow ablation by irradiation requires  
13 subsequent incorporation of hematopoietic stem cells into the patient, in which case recovery of  
14 such cells is required.” ’427 Patent at 1:18-21. Mobilization of blood-forming stem cells “has a  
15 crucial influence on the efficiency of” peripheral stem cell recovery. ’427 Patent at 1:22-24. The  
16 method claimed by the patent improves upon the process of collecting stem cells by increasing the  
17 number of stem cells in the peripheral blood, thereby reducing the number of leukaphereses  
18 required. *See* ’427 Patent at 1:24-27 (“At present, 2-3 leukaphereses are required for successful  
19 peripheral stem cell transplantation, resulting in considerable stress for the patients.”); *id.* at  
20 1:55-61 (“As the required number of leukaphereses is extremely stressing for the patient in the  
21 run-up to the treatment of particular diseases, e.g., in preparing myeloablative or myelotoxic  
22 therapy, the invention was based on the object of achieving a superior yield of stem cells or a  
23 decrease in the number of leukaphereses via enhanced mobilization of stem cells.”). Finally, the  
24 specification teaches that administration of G-CSF followed by administration of a  
25 chemotherapeutic agent is part of the “run-up to a, e.g. antitumor therapy,” and therefore is not the  
26 disease treatment itself. ’427 Patent at 4:24-25.

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

4 3. “*disease treating-effective amount of at least one chemotherapeutic agent*”

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

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16  
17 <sup>3</sup> This is not to say all forms of peripheral stem-cell transplantation are not treatments. Sandoz’s  
18 expert witness, Robert S. Negrin, M.D., has explained the difference between two types of stem-  
19 cell transplants: allogeneic transplants and autologous transplants. Allogeneic transplants involve  
20 transplantation of a healthy donor’s stem cells, and are used to treat certain cancers. *See* Negrin  
21 Sur-Reply Decl. ¶ 12. In contrast, autologous transplants involve using the patient’s own stem  
22 cells. *Id.* ¶ 11. Autologous transplants do not treat diseases; they counteract the negative side  
23 effects of disease treatments such as myelotoxic chemotherapy or radiation. *Id.* The ’427 Patent  
24 obviously addresses autologous transplants, not allogeneic transplants.

21 <sup>4</sup> In *Amgen, Inc. v. Apotex Inc.*, No. 15-61631-CIV, 2016 WL 1375566, at \*5-6 (S.D. Fla. Apr. 7,  
22 2016), the district court construed this very phrase. The court adopted Amgen’s proposed  
23 construction, concluding a “disease treating-effective amount” of the chemotherapeutic agent is an  
24 amount “needed to achieve the goal of enhancing stem cell mobilization for recovery from blood  
25 and subsequent transplantation.” *Id.* at \*6. Prior claim construction orders are not binding or  
26 dispositive unless “an earlier suit . . . trigger[s] application of the doctrine of collateral estoppel.”  
27 *W. v. Quality Gold, Inc.*, No. 5:10-CV-03124-JF HRL, 2011 WL 6055424, at \*2 (N.D. Cal. Sept.  
28 16, 2011). Sandoz was not a party to the Florida action, and therefore the doctrine of collateral  
estoppel is wholly inapplicable.

26 In *Apotex*, rather than proposing a construction, the defendant argued the term “disease  
27 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.

1            “[T]he context in which a term is used in the asserted claim can be highly instructive.”  
 2     *Phillips*, 415 F.3d at 1314. There are three parts to claim 1—the preamble and two limitations:  
 3     the first limitation is a description of step one (administration of G-CSF); the second limitation is a  
 4     description of step two (administration of the chemotherapeutic agent). Rather than referring to  
 5     the two steps of the claimed process as “stem-cell mobilizing,” the patentee chose to use different  
 6     descriptors for G-CSF and chemotherapeutic agents. G-CSF is “hematopoietic stem cell  
 7     mobilizing,” whereas the chemotherapeutic agent is “disease treating.” See ’427 Patent at  
 8     10:27-29. “Different claim terms are presumed to have different meanings.” *Bd. of Regents v.*  
 9     *BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008). Here, the patentee chose to use two  
 10    different words, and thus the two terms presumably carry different meanings.

11            A natural reading of these two terms suggests they are not synonyms. Nevertheless, claims  
 12    “do not stand alone. Rather they are part of a fully integrated written instrument, consisting  
 13    principally of a specification that concludes with the claims.” *Phillips*, 811 F.3d at 1315 (internal  
 14    quotation marks and citation omitted). Thus, if the specification suggests the two phrases describe  
 15    similar functions, then the claim must be construed accordingly. Indeed, there is some evidence in  
 16    the specification that the purpose of administering a chemotherapeutic agent is the same as that for  
 17    G-CSF administration. The specification teaches about stem-cell mobilizing characteristics of  
 18    chemotherapeutic agents. See, e.g., ’427 1:35-36 (citing Richman et al., *Blood*, Vol. 47, No. 6  
 19    1031 (1976)) (“Some chemotherapeutic agents are also known to possess the ability of mobilizing  
 20    bone marrow stem cells . . . .”); ’427 Patent at 1:5-9 (“The present invention relates to the novel  
 21    use of G-CSF and a chemotherapeutic agent or a combination of chemotherapeutic agents to  
 22    produce a pharmaceutical preparation for enhanced mobilization of hematopoietic stem cells in the  
 23    treatment of diseases requiring peripheral stem cell transplantation.”); ’427 Patent at 3:13-17  
 24    (“Surprisingly, it was determined that administration of G-CSF prior to opening of the endothelial  
 25    barrier induced by chemotherapeutic agents significantly increases the stem cell mobilization and  
 26    thus, can improve leukapheresis efficiency.”). Yet, these references to the chemotherapeutic  
 27    agent’s ability to open the endothelial barrier cannot supplant language of the claim itself. In  
 28

1 claim 4, the patentee chose to describe one function of a chemotherapeutic agent: its ability to  
 2 “open[] the endothelial barrier of the patient to render the endothelial barrier permeable for stem  
 3 cells.” ’427 Patent at 10:36-38. Claim 4 demonstrates the patentee’s ability to differentiate  
 4 between two of chemotherapeutic agents’ known functions: opening the endothelial barrier and  
 5 treating disease (typically cancer). Thus, while the specification provides critical context for  
 6 understanding the claim language, it cannot “be used to rewrite, the chosen claim language.  
 7 Specifications teach. Claims claim.” *SuperGuide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d  
 8 870, 875 (Fed. Cir. 2004) (internal quotation marks omitted).

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

12 4. “*chemotherapeutic agent*”

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

26 Sandoz generated its construction directly from the specification, which defines  
 27 “chemotherapeutic agents.” ’427 Patent 2:37-39 (“[C]hemotherapeutic agents are understood to  
 28

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

8 Amgen tries to do so by arguing the definition from the specification might be read to limit  
9 the scope of the claim to those chemotherapeutic agents known and used at the time of the  
10 invention. As a general matter, patentees need not “describe in [their] specification every  
11 conceivable and possible future embodiment of [their] invention.” *SRI Int’l*, 775 F.2d at 1121.  
12 The specification lists various types of cytostatic agents (alkylating agents, metal complex  
13 cytostatic agents, antimetabolites, natural substances, antibiotic agents, hormones and hormone  
14 antagonists, and “other compounds”) and offers examples of each group. *See* ’427 Patent at  
15 2:40-54. This list of examples suggests the patentee did not intend the claim to be limited to those  
16 chemotherapeutic agents known and used at the time of the invention.

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

21  
22  
23 <sup>5</sup> In *Apotex*, the district court adopted the construction of “chemotherapeutic agent” Amgen now  
24 offers. *See* 2016 WL 1375566, at \*5. Once again, the *Apotex* court’s constructions are of limited  
25 persuasive value because it confronted different proposed constructions than those at issue here.  
26 *Apotex* suggested the following construction, which limited chemotherapeutic agents to those that  
27 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.

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

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

12           5. “*comprising administering . . . G-CSF; and thereafter administering . . . at least one*  
13           *chemotherapeutic agent*”

14           The fifth phrase requiring construction appears or is incorporated into claims 1, 2, 3, 4, and  
15 6: “comprising administering . . . G-CSF; and thereafter administering . . . at least one  
16 chemotherapeutic agent.” Amgen proposes the following construction: “G-CSF and the at least  
17 one chemotherapeutic agent are given in combination for purposes of stem cell mobilization, and  
18 the order in which G-CSF and the chemotherapeutic agent(s) are administered for that purpose is  
19 G-CSF first followed by the chemotherapeutic agent(s).”<sup>6</sup> Sandoz contends the word  
20 “comprising” means “including but not limited to,” and allows for additional steps before, in  
21

22 \_\_\_\_\_  
23 <sup>6</sup> Initially, Amgen proposed a lengthier construction of the phrase: “G-CSF and the at least one  
24 chemotherapeutic agent are given in combination for purposes of stem cell mobilization, and the  
25 order in which G-CSF and the chemotherapeutic agent(s) are administered for that purpose is G-  
26 CSF first followed by the chemotherapeutic agent(s). Other than the foregoing stem cell  
27 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.”).

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

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

18 The crux of the second dispute is whether Amgen’s proposed construction improperly  
 19 imports a purpose limitation into the claim. Critically, Amgen’s suggested reading emphasizes  
 20 that the purpose of administering a chemotherapeutic agent is to mobilize blood-forming stem  
 21

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22 <sup>7</sup> Indeed, numerous portions of the specification make clear the invention relates to the timing of  
 23 the administration of G-CSF and the chemotherapeutic agent—G-CSF first, the chemotherapeutic  
 24 agent second. *See* ’427 Patent at 3:18-23 (“By administering G-CSF prior to administration of the  
 25 chemotherapeutic agent(s) . . .”); *id.* at 1:66-21:11 (“The G-CSF and chemotherapeutic agent  
 26 administration forms can be taken out separately and administered successively according to the  
 27 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.”).

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

10 6. *“opens the endothelial barrier of the patient to render the endothelial barrier*  
11 *permeable for stem cells”*

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

20 The text of the claim does not resolve this dispute, but the specification offers some  
21 guidance. At the time of the alleged invention, skilled artisans were aware that administration of  
22 cytotoxic agents caused the number of stem cells to increase in the peripheral blood. What was  
23 unknown at the time was how exactly blood cells moved from bone marrow into the peripheral  
24 blood. One article described the process as an “[i]njury to the supporting structure of the  
25 marrow.” Wu Decl. Ex. 10 at 1037, Richman et al., *Blood* 47(6): 1031-39 (1976) (cited at ’427  
26 Patent at 1:35-37). Another researcher explained, “[A] cytotoxic conditioning regimen can induce  
27 membrane instability leading to massive loss of the endothelial membrane.” Wu Decl. Ex. 11 at  
28

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

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

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

1           Second, Sandoz contends the articles referenced in the specification merely hypothesize  
2 about how opening the endothelial barrier facilitates stem-cell transit from bone marrow into the  
3 peripheral drug. An open door certainly facilitates movement from the outside to the inside, but it  
4 does not cause such movement. During the *Markman* hearing, Sandoz agreed to amend its  
5 proposed construction to include a purpose limitation: to disrupt the bone marrow endothelial  
6 barrier to facilitate the permeability of the endothelial barrier for stem cells. Tr. Hr’g 156:9–  
7 157:4. The words “facilitate the permeability of the endothelial barrier for stem cells” appears in  
8 the specification, ’427 Patent at 1:53–55, and therefore resolves at least one of Amgen’s concerns,  
9 namely that the construction must communicate the purpose of the opening, *see* Tr. Hr’g 158:9 –  
10 159:12 (Amgen counsel: “I don’t think we have any difficulty with the language that’s in the  
11 specification. . . . If we building the idea that its’ facilitating permeability, maybe we have  
12 captured that.”).

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

16           **B. The ’878 Patent**

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

22           To be therapeutically useful, a recombinant protein must attain a three-dimensional shape.  
23 Trouble arises when the host cells produce the recombinant proteins “unfolded,” meaning the  
24 proteins do not have the proper three-dimensional shape. These unfolded recombinant proteins  
25 accumulate in the host cell and form insoluble aggregates called “inclusion bodies.” To remedy  
26 this problem, scientists break open (lyse) the host cell to release the inclusion bodies. Next, the  
27 scientists solubilize the inclusion bodies, which is a process of mixing the protein with various  
28

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

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

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

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

18           At the time of the alleged invention, skilled artisans believed the solution containing the  
19 solubilized and refolded protein had to be diluted to remove certain components of the refold  
20 solution before they could apply the separation matrix to it. Pai Decl. Ex. 2, Patent ’878 at  
21 1:44-46. Skilled artisans believed these contaminants would interfere with the protein’s ability to  
22 affiliate with the separation matrix. The patentees allegedly discovered that this dilution step was  
23 unnecessary; scientists can apply the separation matrix to the refolding solution without diluting  
24 the solution first. ’878 Patent at 15:33-37. The method disclosed in the patent removes a costly,  
25 time-consuming step in the purification process. ’878 Patent at 4:55-60.

26           1.       *“directly applying the refold solution to a separation matrix”*

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

28

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

15 a. “Directly Applying”<sup>8</sup>

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

23 \_\_\_\_\_  
24 <sup>8</sup> Along with the reply brief, Amgen submitted a declaration to rebut the extrinsic evidence Sandoz  
25 submitted. Sandoz sought to strike the declaration or, in the alternative, to file a sur-reply brief.  
26 Because the submission of new evidence and new argument in reply was improper, Sandoz  
27 received leave to file a sur-reply. One of the sur-reply declarations submitted included an  
28 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.

1 Titchener-Hooker, Ph.D., a skilled artisan would understand the “refold solution,” which is  
2 applied to the separation matrix includes the listed components. Sandoz’s Expert Titchener-  
3 Hooker Decl. ¶¶ 31-32.

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

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

13 The specification teaches the method claimed involves applying “the refold solution  
14 comprising the refolded protein of interest” “directly to the separation matrix, without the need for  
15 diluting or removing *the components of the solution required for refolding the protein.*” ’878  
16 Patent at 15:25-29 (emphasis added). Similarly, in the prosecution history, the patentee used  
17 related language after the PTO rejected the proposed claims because it believed U.S. Patent No.  
18 7,138,370 anticipated the claimed method. Patent ’370 disclosed a method of protein purification  
19 requiring three processing steps before the refold solution could be applied to the separation  
20 matrix: dialysis, precipitation, and centrifugation. To remedy this problem, the patentee added the  
21 word “directly” to the claim to emphasize that the disclosed method did not require removal of  
22 “the components of the solution required for refolding the protein.” Wu Decl. Ex. 13 at 3. Amgen  
23 insists these statements in the specification and prosecution history make clear no dilution  
24 whatsoever is required.

25 The trouble with this position is the fact claim 7’s steps (c) and (d) and preamble recites  
26 the components that comprise the refold solution: one or more of a denaturant, a reductant, a  
27 surfactant, an aggregation suppressor, a protein stabilizer, and a redox component—the very  
28

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

8 b. “Column”

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

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

1 415 F.3d at 1312 (internal quotation marks omitted). Amgen therefore faces an uphill battle to  
2 show its construction including the word “column” is proper.

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

8  
9 [A]ny or all steps of the invention can be carried out *by any*  
10 *mechanical means*. As noted, the separation matrix can be disposed  
11 in a column. The column can be run with or without pressure and  
12 from top to bottom or bottom to top. The direction of the flow of  
13 fluid in the column can be reversed during the purification process.  
14 Purifications can also be carried out using a batch process in which  
15 the solid support is separated from the liquid used to load, wash, and  
16 elute the sample by any suitable means, including gravity,  
17 centrifugation, or filtration. Moreover, purifications can also be  
18 carried out by contacting the sample with a filter that adsorbs or  
19 retains some molecules in the sample more strongly than others.

20 ’878 Patent at 16:42-54 (emphasis added). The specification thus makes clear the method is not  
21 limited to column chromatography alone and even offers additional methods. In light of the fact  
22 the Federal Circuit has rejected the notion “that if a patent describes a single embodiment, the  
23 claims of the patent must be construed as being limited to that embodiment,” *Liebel-Flarsheim*  
24 *Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004), the simple fact most examples disclosed  
25 in the specification involve column chromatography is not dispositive.

26 The second problem with Amgen’s “column” proposal is that the specification describes  
27 the process of putting the refold mixture into the column as “loading,” whereas the word  
28 “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).

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

8 2. *“under conditions suitable for the protein to associate with the matrix”*

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

14 a. Protein

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

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

24 More importantly, the patentee defined the word “protein” in the specification as follows:  
25 “the terms ‘protein’ and ‘polypeptide’ are used interchangeably and mean any chain of at least five  
26 naturally or non-naturally occurring amino acids linked by peptide bonds.” ’878 Patent at  
27 5:62-65. When an inventor has expressly defined a term in the specification, it controls for

28

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

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

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

24 That the clean protein emerging from the process is the expressed protein does not,  
25 however, necessarily follow from the text of the claim. Accordingly, Sandoz’s construction must  
26 be rejected for that reason. Nevertheless, the method claimed is also more targeted than Amgen  
27 suggested. The targeted protein is the protein to be purified. Thus, in the context of claim 7 (and  
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1 all derivative claims), the word “protein” means “the protein to be purified.”<sup>9</sup>

2 b. Associate

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

7 Amgen derives its construction from the specification and its definition of “separation  
8 matrix”:

9 As used herein, the term “separation matrix” means any absorbent  
10 material that utilizes *specific, reversible interactions* between  
11 synthetic and/or biomolecules, e.g., the property of Protein A to bind  
12 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.

13 ’878 Patent at 14:65-15:5 (emphasis added). Amgen reads this section to mean binding is just an  
14 example of the type of reversible interactions the process involves, whereas other embodiments of  
15 the method involve resins that retard the flow of the refold solution through the column or which  
16 trap large proteins and permit smaller proteins to flow through. While there is a temptation to treat  
17 the specification’s definition of “separation matrix” as a definition for associate, it is not. The  
18 specification defines “separation matrix,” and not “associate.” Accordingly, the specification  
19 offers some, but not definitive, support for Amgen’s proposed construction.

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

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25 <sup>9</sup> Recently, the *Apotex* court construed the word “protein” in accord with Amgen’s proposed  
26 construction. See Dkt. 195-1 at 14-17. While the court’s opinion is persuasive authority, its value  
27 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.

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

8 Sandoz’s final argument is that the other steps listed in the claim clarify that “associate”  
9 means “bind.” Step (g) of claim 7 states, “the separation matrix is a non-affinity resin selected  
10 from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.”  
11 ’878 Patent at 22:25-28. Figure 4 of the patent, titled “demonstration of Dynamic Binding  
12 Capacity for Ion Exchangers and Mixed mode Resins,” describes “a plot demonstrating the  
13 binding profiles of a refolded, non-mammalian non-native limited solubility complex protein to  
14 six different ion exchange resins.” ’878 Patent at 3:22-29, Figure 4. This figure, Sandoz argues,  
15 demonstrates the ion exchanges and mixed mode resins operate by binding to proteins of interest.

16 Ultimately, Amgen’s proposed construction does not make sense in the context of the  
17 claim as a whole. There are some interactions between resin and protein, which do not facilitate  
18 protein capture. For example, the proteins and resins may repel one another, but the repulsion  
19 does not facilitate protein capture or purification. Although Amgen has provided examples of how  
20 proteins interact with separation matrices that do not involve a binding mechanism, they do not  
21 lend support for its construction. Sizing resins that trap proteins of a certain size while allowing  
22 smaller components to pass through are not non-affinity resins. Claim 7 discloses a capture  
23 method involving a non-affinity resin, *see* ’878 Patent at 22:26, and therefore sheds no light on the  
24 question of whether the claimed method covers interactions other than binding interactions.  
25 Similarly, isocratic protein separations, which retard the transit of some proteins moving through a  
26 column containing a separation matrix, do not employ “reversible interactions.” The interaction  
27 between the resin and the protein never reverses; the protein simply takes longer to pass through  
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1 the column. *See* Titchener-Hooker Sur-Reply Decl. ¶ 40.

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

5 c. *“washing the separation matrix”*

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

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

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

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

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

2 d. “*eluting the protein from the separation matrix*”

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

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

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

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	<b>'427 Claim Term</b>	<b>Construction</b>
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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	'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