Caught between a Rock and a Hard Place: Patenting in the Life Sciences and the Written Description Requirement

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Regardless of whether a life science company is a biotech start-up or a pharmaceutical giant, its patents are the keys to the kingdom.[1] In the post-AIA, "first-to-file" world, quickly filing a patent application is more critical than ever.[2] Rushing to file, though, comes with real risk. Applicants seeking patents on emerging life science technologies, like gene-editing, immunotherapy, and RNA interference, often face written description rejections at the Patent Office.[3] Further, even when an inventor successfully obtains claims based on an early filing, those patents may not survive a written description challenge brought by a competitor.[4]

One of the more closely watched patent disputes in recent years is the CRISPR interference between the University of California ("UC") and the Broad Institute ("Broad"). At issue was who first invented the revolutionary CRISPR gene-editing system that relies upon components that bacteria naturally use to defend themselves against bacteriophage.[5]

UC researchers discovered that the bacterial components—a DNA endonuclease and two RNA molecules—could be harnessed and used as a programmable, genome-editing tool.[6] That is, the components could be engineered to cleave specific sites in target DNA. Just months after this publication, three groups reported that they had successfully used the CRISPR system to edit the eukaryotic genome, *in vivo*.[7] This, despite the fact that the components of the CRISPR system are not normally found in eukaryotic cells.[8]

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[1] Houldsworth, A., *Pharma Patent Owners in the US are under Pressure Like They Have Never Been Before*, IAM (Nov. 26, 2018), https://www.iam-media.com/law-policy/us-pharma-patent-owners-under-pressure-never.

[2] *See Helsinn Healthcare S.A. v. Teva Pharmaceuticals USA, Inc*., No. 17-1229, slip op. at 1 (U.S. Jan. 22, 2019) (explaining that the meaning of "on-sale" was not altered by the America Invents Act ("AIA"), and that even a "secret sale" may invalidate a patent); 35 U.S.C. 102(a)(1), (2) (setting forth the requirements for novelty under the AIA by reference to effective filing dates).

[3] *See* Application No. 15/316,792, *Improved T Cell Compositions*, Final Rejection dated Nov. 14, 2018 at 12-13 (rejecting claims for the transduction of T cells in the presence of a PI3K inhibitor because the specification only supports exposing T cells to the inhibitor during the activation or stimulation phases); Application No. 13/842,859, *Methods and Compositions for RNA-Directed Target DNA Modification and for RNA-Directed Modulation of Transcription*, Non-Final Rejection dated Sept. 15, 2015 at 4 (rejecting claims to a modified Cas9 protein that cleaves only one strand of DNA because the claims read on a broad genus of modifications and the specification did not sufficiently describe a representative number of modifications); Application No. 10/832,432, *RNA Interference Mediating Small RNA Molecules*, Applicant Remarks dated Oct. 25, 2005 at 7 (arguing that the disclosure of an RNA strand that is 19-25 nucleotides in length, with one, 3' nucleotide overhang clearly encompasses a claimed, double stranded RNA that is 16-22 nucleotides in length).

[4] *See, e.g.*, *FWP IP Aps v. Biogen MA, Inc*., No. 2017-2019, 2018 U.S. App. LEXIS 29943 (Fed. Cir. Oct. 24, 2018); *Otonomy, Inc. v. Auris Med., AG*, 2017-1850, 2017-1880, 2018 U.S. App. LEXIS 21569 (Fed. Cir. Aug. 1, 2018).

[5] R. Barrangou, et al., *CRISPR Provides Acquired Resistance Against Viruses in Prokaryotes*, Science 315:1709-12 (March 23, 2007).

[6] M. Jinek, et al., *A Programmable dual RNA-guided DNA endonuclease in adaptive bacterial immunity*, Science 337 (6096): 816-21 (Aug. 17, 2012).

[7] *See* M. Adli, *The CRISPR tool kit for genome editing and beyond*, Nature Communications 9 (1911):1-13 at 3 (2018), https://www.nature.com/articles/s41467-018-04252-2 (reviewing publications by the Broad, UC, and Harvard researchers).

[8] *Regents of the Univ. of Cal. v. Broad Inst., Inc*., No. 2017-1907, slip op. at 3 (Fed. Cir. Sept. 10, 2018).

In the CRISPR interference, UC's claims were broadly directed to methods of using CRISPR that contained no restriction on the particular cellular environment, whereas Broad's claims were specifically limited to using CRISPR in eukaryotic cells.[9] The question presented to the Patent Trial and Appeal Board ("PTAB") was whether one set of claims rendered the subject matter of the other set obvious.

Broad emerged victorious and was able to keep its claims after the PTAB determined that a person of ordinary skill in the art would not have had a reasonable expectation of success in applying the CRISPR technology in a eukaryotic cell. In so concluding, the PTAB found that contemporaneous statements by UC's own expert, as well as one of its inventors, supported Broad's position that applying *this particular* prokaryotic system in a eukaryotic environment was unpredictable.[10] As a result, the PTAB concluded that even if UC's claims were prior art, they would not have rendered Broad's claims obvious, meaning there was no interference-in-fact.[11] In terminating the interference, the PTAB did not reach the underlying question of whether either party's claims were patentable.[12] It is likely only a matter of time, though, before those questions are asked in litigation, especially in the context of the written description requirement.

Whether it is future improvements to CRISPR or, more generally, other life-science inventions directed to therapeutic, diagnostic, agricultural, and industrial biotechnology applications, disputes are bound to arise.[13] When they do, it is a good bet that a competitor will challenge the claims based on the adequacy of their respective disclosures.

I. Lessons from the Quarry: How the Written Description Requirement Places Patentees between a Rock and a Hard Place.

The bargain an inventor strikes under U.S. patent law is that she discloses her invention in exchange for a limited monopoly. Thus, a patent's specification must

> contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .[14]

By way of example, more than 30 years ago, MIT and Harvard researchers identified a protein that they believed was involved in the development of a subset of blood cells, and sought patents

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[9] *Regents of the Univ. of Cal. v. Broad Inst., Inc*., No. 2017-1907, slip op. at 3-4, 6 (Fed. Cir. Sept. 10, 2018).

[10] *Regents of the Univ. of Cal. v. Broad Inst., Inc*., No. 2017-1907, slip op. at 9-11 (Fed. Cir. Sept. 10, 2018).

[11] *Regents of the Univ. of Cal. v. Broad Inst., Inc*., No. 2017-1907, slip op. at 9-11 (Fed. Cir. Sept. 10, 2018).

[12] *The Broad Inst., Inc. v. The Regents of the Univ. of Cal*., Patent Interference No. 106,048, Decision on Motions (Feb. 15, 2017) at 47, 50 (disregarding UC's citations to its application's teachings regarding expressing the CRISPR system in eukaryotic cells).

[13] *See, e.g.*, A. Taylor, *Companies Using CRISPR to Improve Crops* (Feb. 1, 2019), https://www.the-scientist.com/bio-business/companies-use-crispr-to-improve-crops-65362; K. Bryant, *Top 9 CRISPR Startup Companies Changing the Future of Biotech and Medicine* (Jan. 3, 2019), https://www.synthego.com/blog/crispr-startup-companies; A. Philippidis, *Top 10 Companies Leveraging Gene Editing* (Aug. 27, 2018), https://www.genengnews.com/a-lists/top-10-companies-leveraging-gene-editing.

[14] 35 U.S.C. § 112(a).

on methods of using the protein.[15] Today, that protein—called "NF- κβ"—is known to be involved in the development of multiple diseases, including certain cancers, rheumatoid arthritis, atherosclerosis, and multiple sclerosis.[16] There are more than a dozen drugs approved for clinical use that reduce NF- κβ's activity.[17] But MIT and Harvard's licensee, Ariad Pharmaceuticals, was unsuccessful in its efforts to enforce one of the patents against a competitor, Eli Lilly. Though a jury found Lilly to be liable for well over $1B in infringing sales,[18] the asserted patent was determined to be invalid for lack of written description support.[19]

In an *en banc* opinion, the Federal Circuit upheld the finding of no written description support and confirmed that the U.S. patent statutes include a written description requirement that is separate from the enablement requirement.[20] A patent disclosure must do more than teach a skilled artisan to practice the invention without undue experimentation. It must also include sufficient detail to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed subject matter as of the date she filed her patent application.[21]

How this is accomplished varies depending on the "nature and scope of the claims and on the complexity and predictability" of the technology.[22] An actual reduction to practice is not required, and the specification need not recite an invention *in haec verba*.[23] Indeed, "[u]nder the doctrine of inherent disclosure, when a specification describes an invention that has certain undisclosed yet inherent properties, that specification serves as adequate written description to support a subsequent patent application that explicitly recites the invention's inherent properties."[24] Inventors also need not teach what the skilled artisan already knows.[25] But the description an inventor provides must—from within the four corners of the patent itself—do more than merely make the claimed invention obvious to a skilled artisan.[26]

Ariad had accused Lilly of infringing claims to methods of reducing NF- κβ's activity in human cells.[27] The patent taught three classes of molecules that could—theoretically—reduce the protein's activity, which relied upon NF- κβ's binding to DNA. First, the patent taught that specific inhibitors could be used to either reduce or eliminate the protein's ability to bind to DNA. But the patent's teaching regarding an actual, specific inhibitor had not been added to the

[15] Zhang, Q., et al., *30 Years of NF-κβ: A Blossoming of Relevance to Human Pathobiology*, Cell: 168(1-2):37-57 (Jan. 12, 2017); *see also* U.S. Pat. No. 6,410,516.
[16] Park, MH & Hong, JT, *Roles of NF- κβ in Cancer and Inflammatory Diseases and Their Therapeutic Applications*, Cells 5, 15: 1-13 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4931664/pdf/cells-05-00015.pdf.
[17] Miller, S.C., et al., *Identification of Known Drugs that Act as Inhibitors of NF- κβ Signaling and their Mechanism of Action* Biochemical Pharmacology 79:1272-1280 (2010).
[18] *See Ariad Pharms., Inc. v. Eli Lilly & Co*., No. 1:02-cv-11280 (D. Mass.), D.I. 270 (Plaintiff's Trial Brief); D.I. 346 (Verdict).
[19] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 560 F.3d 1366 (Fed. Cir. 2009).
[20] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1348 (Fed. Cir. 2010).
[21] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010).
[22] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010).
[23] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1352 (Fed. Cir. 2010); *see also Falkner v. Inglis*, 448 F. 3d 1357, 1363, 1366-67 (Fed. Cir. 2006) (affirming the Board of Patent Appeals & Interferences' determination that a claim to a poxvirus vaccine was not invalid when the patent application's disclosure only set forth examples of herpes virus vaccines).
[24] *Yeda Research & Dev. Co., Ltd. v. Abbott GmbH & Co. KG*, 837 F.3d 1341, 1345 (Fed. Cir. 2016) (citation omitted).
[25] *Falkner v. Inglis*, 448 F. 3d 1357, 1363, 1367 (Fed. Cir. 2006).
[26] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1352 (Fed. Cir. 2010).
[27] U.S. Pat. No. 6,410,516 (claims 80, 95,144 and 145).

disclosure until two years after the patent was filed.[28] Second, the patent taught the use of dominantly interfering molecules, which were truncated forms of the protein described as retaining the ability to bind to DNA, thereby blocking the native form of the protein from binding. There was, however, no disclosure of a dominantly interfering molecule.[29] Finally, the patent proposed the use of decoy molecules, and set forth several examples. Except none of the examples had ever been tested to determine their impact—if any—on the protein's activity.[30] Thus, as of the date the patent was filed in 1989, each class of disclosed inhibitor was purely hypothetical.

As the Federal Circuit explained, no matter how groundbreaking research may be—or even how necessary it is to the later, patentable inventions of others—patents are not awarded for theories.

> [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of 'invention'—that is conceive of the complete and final invention with all its claimed limitations—and disclose the fruits of that effort to the public.[31]

In a similar vein, where a genus is claimed "by its function or result," then the accompanying specification must "recite sufficient materials to accomplish that function."[32]

Prior to *Ariad*, courts addressed similar scenarios in which inventors attempted to claim something they did not possess at the time of filing, or, at least, had not disclosed in their applications. As expected, these patentees did not fare well when their specifications disclosed too little. For example, claims to methods of inhibiting prostaglandin synthesis using a non-steroidal compound were found invalid for lack of written description when the inventors failed to disclose even a *single* non-steroidal compound that could be used according to their claims.[33] Likewise, claims to recombinant, mammalian insulin genes that covered more than 6300 species were invalid when the accompanying specification disclosed only a *single*, mammalian insulin gene.[34]

But sheer numerosity is not the answer. A specification that indiscriminately discloses a myriad of possibilities is also likely to be inadequate. In *In re Ruschig*, the patent specification made a general disclosure of "half a million possible compounds."[35] Despite this, the written description requirement was not satisfied, as there was insufficient teaching as to *which* of the "half a million" compounds were suitable. The court likened the disclosure to an applicant pointing to

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[28] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 560 F.3d 1366, 1374 (Fed. Cir. 2009).
[29] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 560 F.3d 1366, 1375 (Fed. Cir. 2009).
[30] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 560 F.3d 1366, 1375 (Fed. Cir. 2009).
[31] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1353 (Fed. Cir. 2010) (internal quotation marks omitted).
[32] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1352 (Fed. Cir. 2010).
[33] *Univ. of Rochester v. G.D. Searle & Co*., 358 F.3d 916, 918, 927 (Fed. Cir. 2004).
[34] *Regents of Univ. of Cal. v. Eli Lilly & Co*., 119 F.3d 1559, 1567 (Fed. Cir. 1997); *see also Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004) (affirming a decision by the Board of Patent Appeals & Interferences that disclosure of a murine, CD40CR antibody is insufficient to support a genus claim to CD40CR antibodies); *see also* CJ Burgin, et al., *How many species of mammals are there?* J. Mammology 99(1):1-14 (Feb. 1, 2018).
[35] *In re Ruschig*, 379 F.2d 990, 993 (C.C.P.A. 1967).

trees in the woods and further explained that the specification lacked "blaze marks which single out particular trees" demonstrating that the inventors actually possessed what was claimed.[36]

That said, as a particular technological field evolves, claims drawn to the subject matter may require less support. This is because a patent's disclosure is read in view of "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue."[37] For instance, the level of detail required to support claims involving basic, recombinant DNA technology has decreased over time.

By way of example, claims with a 1970s priority date that recited an engineered human insulin gene were invalid for lack of written description support because the specification did not disclose a human insulin gene sequence. Instead, the specification provided only a method of obtaining the gene sequence, as well as the amino acid sequence of the human insulin protein.[38] By contrast, when the Federal Circuit considered a similar patent application filed just a decade later, in the late 1980s, it agreed that the state of the art had progressed significantly—i.e., the *complete* amino acid sequence of a protein was known—and one of ordinary skill in the art would have understood the inventor to be in possession of the limited genus of nucleotide molecules that could encode that protein.[39]

The speed at which the state of the art advances in the life sciences shows no sign of slowing down. As a result, patentees will likely continue to find themselves stuck between the proverbial rock and a hard place. File a patent application too late and risk being beat by a competitor. File too soon and risk not adequately describing the claimed invention. As potential patentees assess whether they have "enough" to file a patent application, consideration should be given to several recent decisions addressing the adequacy, *vel non*, of patent disclosures in the life sciences. These decisions tend to fall into a few categories, as discussed below.

II. Lessons from the Quarry: When Litigants Find Themselves Between the Rock and a Hard Place.

A. Aim for a Cohesive Disclosure.

Patent holders facing a written description challenge are at a disadvantage when they assemble support for their claims from disparate teachings in their specifications.

In a recent appeal of an interference proceeding, the Federal Circuit considered a priority dispute between two competitors that claimed to have invented a method of treating tinnitus. The claim required a composition comprising a suspension of an antibiotic and a thermosetting polymer.[40]

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[36] *In re Ruschig*, 379 F.2d 990, 993, 995 (C.C.P.A. 1967).

[37] *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[38] *Regents of Univ. of Cal. v. Eli Lilly & Co*., 119 F.3d 1559, 1567 (Fed. Cir. 1997); *see also Fiers v. Revel*, 984 F.2d 1164, 1167-71 (Fed. Cir. 1993) (affirming a decision by the Board of Patent Appeals & Interferences that, as of 1979, disclosure of a method for isolating DNA encoding a protein did not adequately describe DNA encoding that protein).

[39] *In re Wallach*, 378 F.3d 1330, 1333 (Fed. Cir. 2004). Where the inventors had erred, though, was in filing an application when they only had a partial amino acid sequence, but wanted to claim a complete gene sequence. *Id*. at 1334.

[40] *Otonomy, Inc. v. Auris Med., AG*, No. 2017-1850, -1880, 2018 U.S. App. LEXIS 21569, at *5 (Fed. Cir. Aug. 1, 2018).

During oral argument, the party that prevailed before the PTAB admitted that its priority application lacked an "explicit disclosure of a *single embodiment* of a suspended" antibiotic. Instead, the application taught a suspension of ketamine with a thermosetting polymer, "together with a separate teaching that an antibiotic" could be optionally added. This was insufficient to satisfy the written description requirement. The Federal Circuit reversed the priority award, as it was error to have allowed the prevailing party to "piece together disparate bits of disclosure."[41]

Similarly, a medical device manufacturer lost its claims to an endometrial ablation device for largely the same reason. The claims required the ablation device to have *both* mechanical *and* inflation expansion capabilities.[42] During a post-grant review proceeding, a competitor successfully argued that the claims lacked written description support because the application's disclosure described mechanical and inflation expansion capabilities as "mutually exclusive alternatives."[43] Patentee had attempted to rely on a statement in the specification explaining that "aspects of the first and second exemplary embodiments and their methods of operation may be combined without departing from the scope of the present invention."[44] But there was no guidance whatsoever as to *which* aspects of those embodiments could be combined, or how one would go about making such a combination. The patent's disclosure neither stated nor suggested that a device with a mechanical inflation mechanism might be modified to include a balloon inflation mechanism for additional expansion.[45]

Patent owners have also learned that context matters. Written description challenges are sometimes successful even when the claim limitations are *literally* recited in the patent specification.

For example, Novozymes lost a written description challenge to Dupont, in a case in which it had attempted to assert a claim on

> An isolated variant of a parent alpha-amylase, wherein:
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> (a) the variant has at least 90% sequence identity to SEQ ID NO: 6 [BSG alpha-amylase],
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> (b) the variant comprises a substitution of serine at position 239 relative to the parent alpha-amylase, using the amino acid sequence of SEQ ID NO: 8 [BLA alpha-amylase] for determining position numbering, and
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> (c) the variant has increased thermostability relative to the parent alpha-amylase, wherein thermostability is determined at pH 4.5, 90° C. and 5 ppm calcium and has alpha-amylase activity.[46]

On appeal, Novozymes argued that the patent disclosure expressly disclosed each claim limitation:

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[41] *Otonomy, Inc. v. Auris Med., AG*, No. 2017-1850, -1880, 2018 U.S. App. LEXIS 21569, at *10-11 (Fed. Cir. Aug. 1, 2018).
[42] *Minerva Surgical, Inc. v. Hologic, Inc*., PGR2017-00002, 2018 Pat. App. LEXIS 9161, at *14-16 (P.T.A.B. May 8, 2018).
[43] *Minerva Surgical, Inc. v. Hologic, Inc*., PGR2017-00002, 2018 Pat. App. LEXIS 9161, at *32 (P.T.A.B. May 8, 2018).
[44] *Minerva Surgical, Inc. v. Hologic, Inc*., PGR2017-00002, 2018 Pat. App. LEXIS 9161, at *34 (P.T.A.B. May 8, 2018).
[45] *Minerva Surgical, Inc. v. Hologic, Inc*., PGR2017-00002, 2018 Pat. App. LEXIS 9161, at *35-41 (P.T.A.B. May 8, 2018).
[46] *Novozymes A/S v. Dupont Nutrition Biosciences APS*, 723 F.3d 1336, 1341 (Fed. Cir. 2013).

- BSG alpha-amylase was disclosed as one of seven, possible parent alpha-amlyases;

- The specification taught that a variation could be made at any of 33 different amino acid positions, including residue 239; and

- The specification instructed that variants should function at high temperatures ("especially 85°-95°"), at a low pH ("especially 4.5-5"), and at low calcium concentrations ("especially 5 ppm calcium").[47]

The problem for Novozymes was that its specification nowhere disclosed any *actual* alpha-amylase variant, with a substitution at S239, which retained enzymatic activity and had increased thermostability.[48] Similar to *Ariad*, the Federal Circuit explained that Novozymes' claim appeared to be wholly hypothetical.

More recently, the Federal Circuit considered claims reciting a method for treating multiple sclerosis with a 480 mg daily dose of fumaric acid.[49] It affirmed the PTAB's decision in an interference, in which the claims had been invalidated based on an inadequate written description. Like in *Novozymes*, while there was literal support for each individual claim limitation, there was no teaching that supported the entirety of the invention that was claimed.

First, the principal focus of the application was not treating multiple sclerosis with fumaric acid. Rather, the focus was on how to minimize the gastro-intestinal side-effects of fumaric acid through controlled release formulations.[50] The disclosure had a detailed discussion of treating psoriasis, and then added a laundry list of over 20 different diseases that could also be treated with fumaric acid, including multiple sclerosis.

Second, when the specification referred to a 480 mg dose, it did not teach that the dose should be delivered daily, or that it should be used to treat multiple sclerosis. The 480 mg dose was disclosed in a scale-up table, which explained that an administered dose could range "from 240 to 360 mg, 360 to 480 mg, 480 to 600 mg, 600 to 720 mg, 720 to 840 mg, 840 to 960 mg, or 960 to 1080 mg, given in one to three administrations." The claimed dose was "identified as both the low and high end of ranges within a broader, overall disclosed dosage range of 240 to 1080 mg/day."[51] But the scale-up table was not helpful in supporting the claims because the patent explicitly taught that the *daily dose to administer would vary*, depending on many factors, including the weight and age of the patient, and which disease was being treated."[52] And a different part of the specification taught a scale-up period, during which the dose would increase over a nine-week regimen.[53] During that nine-week period, a 480 mg dose would be delivered

[47] *Novozymes A/S v. Dupont Nutrition Biosciences APS*, 723 F.3d 1336, 1348 (Fed. Cir. 2013).
[48] *Novozymes A/S v. Dupont Nutrition Biosciences APS*, 723 F.3d 1336, 1345 (Fed. Cir. 2013).
[49] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018).
[50] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018).
[51] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943, at *7,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018) (internal citations omitted).
[52] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943, at *14 n.7,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018) (internal citations omitted) (emphasis added).
[53] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943, at *8,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018) (internal citations omitted).

only once, in week seven, which was contrary to what the claims required (a *daily* 480 mg dose).[54] The losing party had failed to explain "why a skilled artisan would have understood the week seven interim dosage to be therapeutically effective," as a *daily* dose, or why that particular dose should be used with multiple sclerosis patients.[55]

B. Antibody claims present a thorny genus/species problem.

Antibody claims directed to a genus of amino acid sequences rarely, if ever, are sufficient to encompass the entirety of the invention. As a result, patentees frequently resort to describing their antibody with functional claim language. And while the Federal Circuit has recognized that "the written description requirement can—in *some* cases be satisfied by [a] functional description"— it has made clear that "such [a] functional description can be sufficient only if there is *also* a structure-function relationship known to those of ordinary skill in the art."[56]

In such instances, when a "patent claims a genus using functional language to define a desired result, the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and does so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."[57] "A patent can achieve this result in one of two ways: (1) it can disclose a representative number of species falling within the scope of the genus, or (2) it can disclose structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus."[58] Patentees face significant hurdles when relying on either of these techniques to describe antibody inventions.

To disclose a "representative number of species," the patentee must describe not just a sufficient number of embodiments, but she must also demonstrate that those embodiments encompass the full functional range of the claimed invention. For example, in *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.* the representative claim recited "[a] neutralizing isolated human antibody, or antigen-binding portion thereof that binds to human IL-12 and disassociates from human IL-12 with a k_{off} rate constant of $1x10^{-2}$ s^{-1} or less, as determined by surface plasmon resonance."[59] Despite "describe[ing] the amino acid sequence of about 300 antibodies having a range of IL-12 binding affinities," the Federal Circuit explained that the patents lacked sufficient written description.[60] In particular, the Federal Circuit explained:

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[54] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943, at *8,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018) (internal citations omitted).

[55] *FWP IP ApS v. Biogen MA, Inc.*, No. 2017-2019, 2018 U.S. App. LEXIS 29943, at *13-14,____ F. App'x ____ (Fed. Cir. Oct. 24, 2018) (internal citations omitted).

[56] *In re Wallach*, 378 F.3d 1330, 1335 (Fed. Cir. 2004) (emphasis added); *see also Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (stating that written description requirement would be satisfied "if the functional characteristic of preferential binding . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed").

[57] *AbbVie Deutschland GmbH & Co. v. Janseen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (citation and internal quotation marks omitted).

[58] *Baxalta Inc. v. Genentech, Inc.*, Civil Action No. 17-509-TBD, 2018 U.S. Dist. LEXIS 132453, at *22 (D. Del. Aug. 7, 2018) (citing *AbbVie Deutschland GmbH & Co. v. Janseen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014)).

[59] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1292 (Fed. Cir. 2014) (citation omitted).

[60] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (Fed. Cir. 2014) (citation omitted).

> One factor in considering the question [of written description] is how large a genus is involved and what species of the genus are described in the patent. If the genus is not large or, even if it is, the specification discloses species representing the genus throughout its scope, the requirement may be met. On the other hand, analogizing the genus to a plot of land, if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. He only described a portion of it.[61]

Further relying upon the "plot-of-land" analogy, the Federal Circuit explained that a disclosure that "merely draw[s] a fence around a perceived genus is not a description of the genus."[62] Importantly, the patentee "needs to show that one has truly invented the genus, i.e., that one has conceived and described sufficient representative species encompassing the breadth of the genus . . . Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus."[63]

Indeed, in *Abbvie*, the disclosed antibodies shared 90% or more amino acid sequence similarity in the variable regions."[64] Because of this, the antibody claims were invalid for lack of written description because the patents described "structurally similar antibodies" that were "not representative of the full variety or scope of the genus."[65] In other words—from a structural perspective—the described species found in the specification only occupied a small corner of the claimed genus. After *Abbvie*, in order to satisfy the written description requirement using functional language, a patentee likely needs to describe antibodies of varying structures, including with greater sequence diversity, different types of heavy chains, and/or different types of light chains.

The *Abbvie* Court noted the difficulties that patentees face when claiming antibodies, explaining that "functionally defined genus claims can be inherently vulnerable to invalidity challenges for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus."[66] And the problem of using functional language to claim antibody inventions has only become more pronounced in light of the Federal Circuit's recent decision in *Amgen v. Sanofi*.[67]

The claim-in-question recited:

> An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or

[61] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299-1300 (Fed. Cir. 2014) (citation omitted).
[62] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).
[63] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).
[64] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (Fed. Cir. 2014) (citation omitted).
[65] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).
[66] *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) (citation omitted).
[67] *Amgen v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017).

> S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDL[-]R.[68]

Sanofi argued that the patent lacked a sufficient written description and, over its objection, the district court instructed the jury:

> In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a *newly characterized antigen* by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine.[69]

Reference to a "newly characterized antigen" did not come out of thin air, but was consistent with Patent Office training materials for examiners on written description. According to the Patent Office, an "adequate description of a purified antigen" would—in some instances—be sufficient for one of ordinary skill in the art to accept that the inventor was "in possession of antibodies which bind to the purified antigen."[70]

The jury found in favor of Amgen, but on appeal, Sanofi argued that the disclosure of an antigen could not satisfy the written description requirement for a claim to an antibody, which is an entirely different molecule. The Federal Circuit agreed, stating that the jury instruction was improper, as it permitted "a finding of adequate written description merely from a finding of ability to make and use."[71] In so stating, the Federal Circuit abrogated the "newly characterized antigen" test, explaining that it is not based on "generally known" or "accurately and readily" ascertainable scientific principles.[72] Essentially, the jury instruction "flout[ed] basic legal principles of the written description requirement" and was improper because it "allow[ed] patentees to claim antibodies by describing something that is not the invention, i.e., the antigen."[73]

Post-*Amgen*, the USPTO issued clarifying guidance, explaining that patent examiners need to conform their analysis to *Amgen*'s elimination of the "newly characterized antigen" test:

> The *Amgen* court expressly stated that the so-called "newly characterized antigen" test, which had been based on an example in USPTO-issued training materials and was noted in dicta in several earlier Federal Circuit decisions, should not be used in determining whether there is adequate written description under 35 U.S.C. §112(a) for a claim drawn to an antibody.[74]

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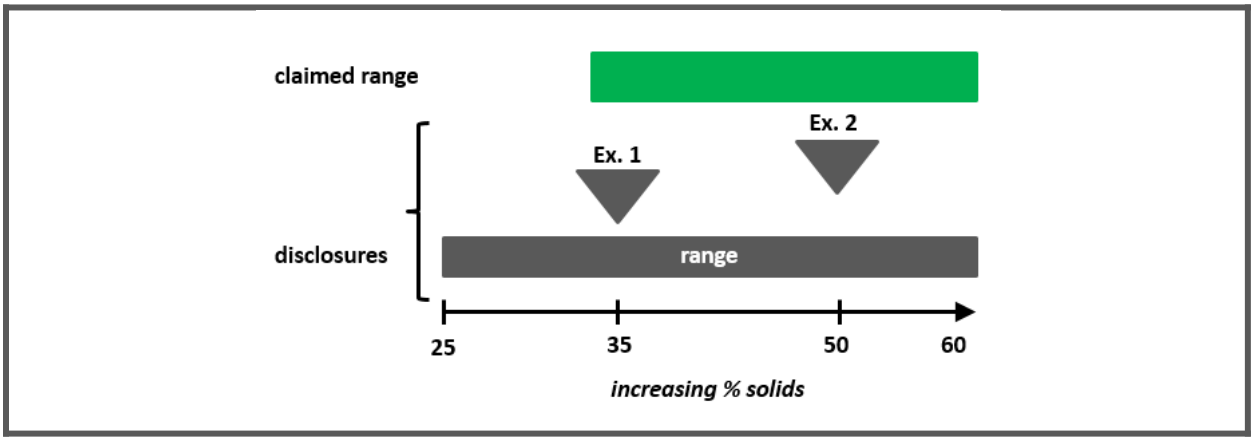
[68] *Amgen v. Sanofi*, 872 F.3d 1367, 1372 (Fed. Cir. 2017) (citation omitted).
[69] *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1376 (Fed. Cir. 2017) (emphasis added).
[70] USPTO, *Written Description Training Materials* at 47 (March 1, 2008, rev 1), https://www.uspto.gov/sites/default/files/web/menu/written.pdf.
[71] *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017).
[72] *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017).
[73] *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017).
[74] USPTO, *Memorandum from Robert W. Bahr, Deputy Commissioner for Patent Examination Policy to Patent Examining Corps* (Feb. 22, 2018), https://www.uspto.gov/sites/default/files/documents/amgen_22feb2018.pdf.

Predictably, post-*Amgen*, numerous patent office written description rejections have been appealed and subsequently affirmed on appeal.[75]

C. When Claiming Ranges, the Devil is in the Details.

Claiming a range of values presents the same problem as claiming a genus. Whether a claimed range is adequately supported generally turns on whether a sufficient number of representative species within the range are disclosed in the specification.

In *In re Wertheim*, which involved a patent on an improved process for freeze drying coffee, applicants sought claims to minimize the loss of volatiles that required concentrating an extract to a high solids level of "between 35% and 60%.[76] The Court of Customs explained that the specification disclosed a process generally employing solids levels from 25-60%, but—more importantly—included specific examples with 36% solids and 50% solids.[77] The disclosed range, coupled with specific examples near the outer bounds of that range, provided an adequate written description.



The court noted "an important practical distinction" between the claims in *In re Wertheim* and the claims discussed above in *In re Ruschig*.[78] The latter application had attempted to claim "broad, generic chemical compound inventions . . . in which each compound within the genus is a separate embodiment of the invention."[79] By contrast, in *In re Wertheim*, the recited range was but one of several limitations in the claimed process, which resulted in greater predictability. Given the disclosure, one skilled in the art would readily appreciate, for example, the import of using 34% solids versus 35% solids. This scenario was very different than the one in *In re Ruschig*, in which a person skilled in the art was faced with the unpredictability of the properties

[75] *See, e.g.*, *Ex Parte Kim*, Appeal 2017-006385, 2018 Pat. App. LEXIS 8762, at *4-5 (P.T.A.B. Oct. 30, 2018) (noting that claims used only functional language and relying upon *Amgen*, *inter alia*, to reject claims); *Ex Parte Hawiger*, Appeal 2016-004126, 2018 Pat. App. LEXIS 3152, at *5 (P.T.A.B. April 26, 2018) (same).
[76] *In re Wertheim*, 541 F.2d 257, 258-59, 264 (C.C.P.A. 1976).
[77] *In re Wertheim*, 541 F.2d 257, 265 (C.C.P.A. 1976).
[78] *In re Wertheim*, 541 F.2d 257, 264 (C.C.P.A. 1976).
[79] *In re Wertheim*, 541 F.2d 257, 264 (C.C.P.A. 1976).

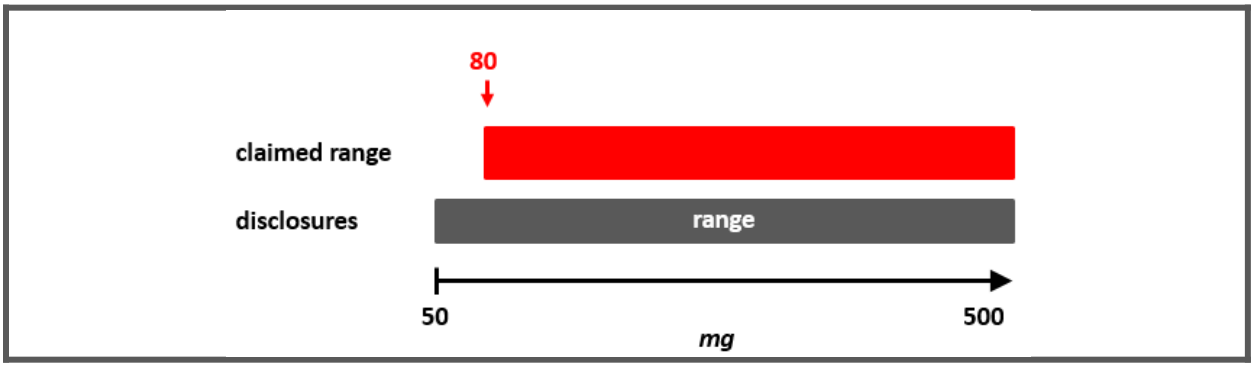
of "the next adjacent homolog of a compound whose properties are disclosed in the specification."[80]

Regardless, in the life sciences, disclosures similar to those in *In re Wertheim* may not be sufficient.

1. Disclosure of a broad range may not support a narrower claimed range.

In *Grunenthal GmbH v. Antecip Bioventures II LLC*, the inventors had claimed "[a] method of treating complex regional pain syndrome" by administering "about 80 to about 500 mg of zoledronic acid . . . ."[81] Grunenthal filed a petition for post-grant review at the PTAB, arguing that the claims lacked adequate written description support.

As the PTAB recognized, the specification provided "literal support" for the claimed range, including for example, "the range of about 50 mg to about 500 mg,"[82] which included *one* of the claimed range endpoints of "about 500 mg."[83]



Nevertheless, the disclosure was inadequate to support the claim because nothing in the specification "clearly allowed persons of ordinary skill in the art to recognize" the *other range* endpoint of "about 80 mg."[84] There was no teaching that 80 mg was a preferred endpoint, or even a discussion of an 80 mg dose, so nothing suggested the importance or criticality of the "about 80 mg" endpoint.[85]

Though the disclosure in *Grunenthal* was similar to that in *Wertheim*, including a specific example near the outer bound of the claimed range, support for *both* of the endpoints in *Gruenthal* could only be "derived from an inordinate amount of picking and choosing from disparate disclosures of various embodiments reciting broader ranges."[86]

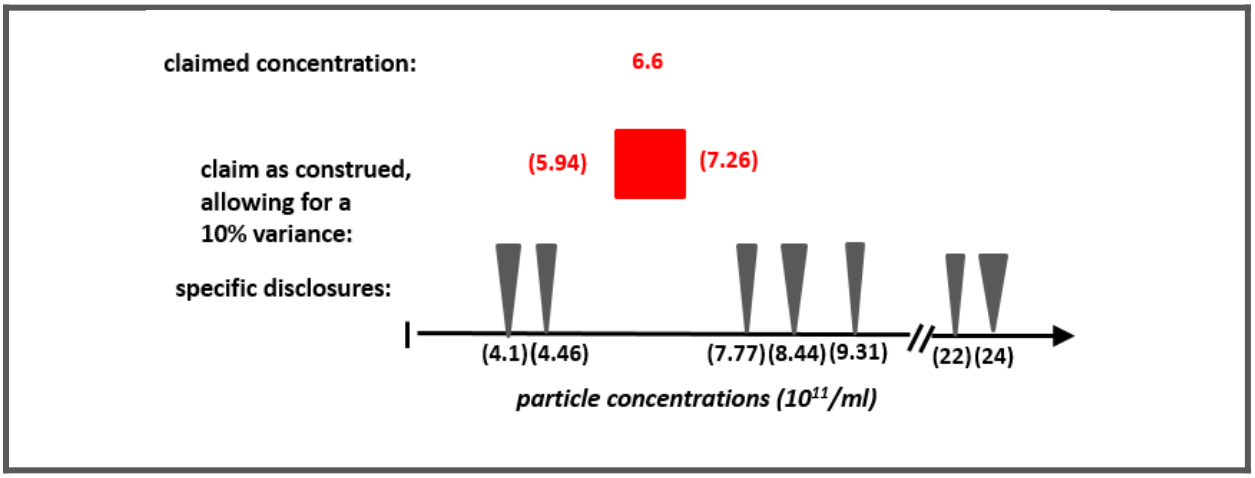
2. Disclosure of specific values within a range may not support a different,

[80] *In re Wertheim*, 541 F.2d 257, 264 (C.C.P.A. 1976).
[81] *Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper 43 (PTAB June 22, 2018).
[82] *Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper 43 at 15 (PTAB June 22, 2018) (internal quotation marks omitted).
[83] *Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper 43 at 15 (PTAB June 22, 2018).
[84] *Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper 43 at 16 (PTAB June 22, 2018).
[85] *Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper 43 at 16 (PTAB June 22, 2018).
[86] *Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper 43 at 17 (PTAB June 22, 2018).

particular value within that range.

In *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, claims were directed to a method of removing hair by using nanoparticles to damage hair follicles.[87] The claims recited a composition of nanoparticles at "a concentration of about 6.6×10^{11} particles per ml."[88] After construing "about" to be "within 10%," the Court stated that the "about 6.6 x 10^{11} particles per ml" claim limitation encompassed a range from "5.94×10^{11} to 7.26×10^{11} particles per ml."[89]

The specification of the patent in question had "seven specific compositions," with concentrations that spanned the claimed range—4.10×10^{11}, 4.46×10^{11}, 7.77×10^{11}, 8.44×10^{11}, 9.31×10^{11}, 22×10^{11}, and 24×10^{11} particles per ml.[90]



Despite this teaching, the Federal Circuit explained that "[t]he disclosure of a broad range of values does not by itself provide written description support for a particular value within that range."[91] Instead, "where a specification discloses a broad range of values and a value within that range is claimed," the disclosure "must allow one skilled in the art to immediately discern the limitation at issue in the claims."[92] That was not the case in *General Hospital*. Even when the claims were construed in a fashion most favorable to the patentee, the accompanying disclosure failed to identify or single out the value that was claimed. The Federal Circuit found this disclosure to be insufficient to satisfy the written description requirement.[93]

III. Conclusion

[87] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1370 (Fed. Cir. 2018).
[88] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1370 (Fed. Cir. 2018).
[89] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1370 (Fed. Cir. 2018).
[90] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018).
[91] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018).
[92] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018) (citation and internal quotation marks omitted).
[93] *The General Hospital Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1372-73 (Fed. Cir. 2018); *see also Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995) (explaining that a 50% overlap between the claimed values and the disclosed values is insufficient to satisfy the written description requirement).

Going forward, companies seeking patent protection over life science inventions will want to work closely with patent counsel in order to assess when they have "enough." That is, given the state of the art for their particular technology, do they have sufficient information to file a fulsome-enough disclosure to support the proposed claims? And, in fact, what—exactly—do they need to claim in the first place?

Consider a recent win by Broad, in fending off institution—for the time being, at least—of a post-grant review challenging claims directed to follow-on CRISPR technology.[94] The claims at issue were drawn to a second-generation endonuclease and an engineered polynucleotide designed to form a complex with the endonuclease that hybridized a target DNA sequence within a eukaryotic cell.[95]

In denying institution, the PTAB disagreed with Petitioner's narrower construction of the disputed claim term. In so concluding, the PTAB stated that it was "cognizant that rejecting Petitioner's *narrower* interpretation of the claims in favor of Patent Owner's *broader* interpretation" could lead to future written description disputes.[96] Nevertheless, "Petitioner chose not to present any arguments that the challenged claims [were] unpatentable under th[e adopted] broader interpretation," and the PTAB "decline[d] to parse the Petition to make these arguments for Petitioner.[97] In other words, it is too early to tell if Broad has successfully navigated between the rock and hard place in the quarry that is the written description requirement. Written description law in the life sciences will continue to evolve, and technologies with far-reaching potential, like CRISPR, will likely be at the leading edge of these written description inquiries.

[94] *Benson Hill Biosystems, Inc. v. The Broad Institute, Inc*., PGR2018-00072, Paper 11 (P.T.A.B. Jan. 22, 2019) (Decision Denying Institution).
[95] *Benson Hill Biosystems, Inc. v. The Broad Institute, Inc*., PGR2018-00072, Paper 11 at 4 (P.T.A.B. Jan. 22, 2019) (Decision Denying Institution).
[96] *Benson Hill Biosystems, Inc. v. The Broad Institute, Inc*., PGR2018-00072, Paper 11 at 18 (P.T.A.B. Jan. 22, 2019) (Decision Denying Institution).
[97] *Benson Hill Biosystems, Inc. v. The Broad Institute, Inc*., PGR2018-00072, Paper 11 at 18 (P.T.A.B. Jan. 22, 2019) (Decision Denying Institution).