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Capturing After-Discovered Embodiments in Biotechnology Patents

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Introduction

Biotechnology is an unpredictable science. When its practitioners wish to enforce their patents, they often run into a serious problem. Unlike chemists or pharmacologists, who for a century or so have used chemical formulas to describe their inventions, biotechnologists, who claim new biological molecules or their uses, have a maddening habit of giving them proper names, such as "t-PA," "interferon," "mono-oxygenase," or "CD20." The problem is that the names they use today to describe and claim their entities may well—due to rapid scientific developments—acquire a different meaning years from today, when the patent holders are ready to assert their rights. Frequently, the proper name used at filing to denote a *specific* material has become, at infringement time, a *category* of materials.

Let us start with an example. In 1957, Isaacs and Lindenmann ("Isaacs") discovered a natural compound produced when cells interfere with viral activity, which they called interferon ("INF").[1] In 1958, they filed a first priority patent application, which issued in 1972 as U.S. Patent 3,699,222.[2] They had no clear idea of what they had obtained, but recognized that they had probably discovered a family across animal species: "the term 'Interferon' is best regarded as a generic term to be qualified in a particular case to indicate its origin, for example, by the use of such terms as monkey kidney Interferon,

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* The opinions expressed here are solely those of the author and should not be attributed to the author's firm or its clients. The author wishes to express thanks to Josh Galgano and Brett Howard who provided invaluable research and discussions.

[1] Derek Burke, *The Discovery of Interferon, the First Cytokine, by Alick Isaacs and Jean Lindenmann in 1957*, BrainImmune (Feb. 14, 2009), http://brainimmune.com/the-discovery-of-interferon-the-first-cytokine-by-alick-isaacs-and-jean-lindenmann-in-1957/.

[2] U.S. Patent No. 3,699,222 (filed May 9, 1958) (issued Oct. 17, 1972).

chick Interferon, calf kidney Interferon."[3] They obtained four remarkably broad (and, by today's standards, remarkably invalid) claims:

Claim 1. Interferon[4]

Claim 2. Human interferon

Claim 3. Monkey interferon

Claim 4. Chick interferon[5]

Fifty-eight years after Isaacs's discovery, it is believed that there is not one, but close to thirty-five molecules named "interferon." The interferons are now classified in three general types: I, II and III with each type consisting of one or more species and many of them having several subspecies.[6] For example, in 1978, Pestka isolated and purified IFN-alpha and IFN-beta, and, in 1982, Goeddel isolated and purified interferon-gamma.[7]

Assuming that the Isaacs patent was still around, would all these interferons be literal infringements of claim 1? Would any of them be infringements? Would the claims be held invalid for lack of enablement of future interferons? Let's assume that, during the life of the patent, a veterinary company discovers a salmon beta interferon and sells it to fish farms for veterinary use. Would this be an infringement of claim 1? What is the fair thing to do for Isaacs, a pioneer discoverer of such an important substance (or, as Isaacs might put it with hindsight, a *category* of substances across molecular, not just animal, types), who isolated and purified the first example?[8]

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[3] *Id.*

[4] These days, without doubt, the USPTO would insist on additional claim limitations that would make the claimed interferon "markedly different" from the natural material (if at all possible). *See* 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74,619 (Dec. 16, 2014) (to be codified at 37 C.F.R. pt. 1). We will not delve in this paper into the recent upheavals on the law of eligibility under 35 U.S.C. § 101 wrought by a trio of U.S. Supreme Court decisions: Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012); Ass'n for Molecular Pathology v. Myriad Genetics, 133 S. Ct. 2107 (2013); and Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014). *Myriad Genetics*, especially, has cast a cloud on the patentability of isolated natural substances, many of which are the subject of this paper. If we encounter claims that may be in doubt because of *Mayo* or *Myriad*, we may say so, but go no further.

[5] '222 Patent.

[6] Sidney Pestka, *The Interferons: 50 Years After Their Discovery, There is Much More to Learn*, 282 J. Bio. Chem. 20047, 20047–48 (2007).

[7] *See id.*; *see also* Patrick W. Gray & David V. Goeddel, *Structure of the Human Immune Interferon Gene*, 298 Nature 859 (1982).

[8] Let us clarify one point before we continue. It is scientifically accurate to say that a scientist *discovers* a new natural substance, like interferon, and then *invents* a method of isolating and purifying it. It follows that it is reasonable to refer to patent claims to a pro-

Two recent biotechnology cases, *Biogen Idec, Inc. v. GlaxoSmithKline LLC* ("*BiogenIDEC*"),[9] and *AbbVie Deutschland GMBH & Co. v. Janssen Biotech, Inc.*,[10] illustrate contrasting answers to that question. These cases deal with the issues of infringement of filing-date claims by after-discovered technology. The court in *BiogenIDEC* construed the claim narrowly and found no infringement by the after-discovered technology.[11] In contrast, in *AbbVie Deutschland* the court construed the claim generically (and potentially infringed), yet held it invalid by a failure to describe a subclass of substances within the claim that encompassed the after-discovered technology.[12] These two decisions have led us to evaluate the history and state of the law in this area, and to try to place them in the context of the U.S. Court of Appeals for the Federal Circuit's ("Federal Circuit") previous holdings on after-arising technology in the chemical and biological sciences.

This Article explores certain approaches that a pioneering patent holder in biotechnology might take in order to obtain a result that rewards his fundamental discoveries of new substances or methods, which turn out to be *categories* of substances or methods later on.[13] We demonstrate that capturing after-discovered biotech embodiments within such categories is not a straightforward exercise. The case law shows that pioneering biotech inventors are charged with knowing, enabling and describing the latest state of the art and all of its foreseeable embodiments, or else their generic claims may be invalidated under 35 U.S.C. § 112, 1st paragraph. If our inventors

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cess of isolation, as well as to an isolated and/or purified natural substance *per se,* as having been *invented* by the scientist. From a patent point of view, however, the legal concepts of invention and discovery are interchangeable. 35 U.S.C. § 100 (2006). Legally, these words mean one and the same thing. *Id.* ("The term 'invention' means invention or discovery."). Nevertheless, since in this paper we are concerned with capturing embodiments unknown at the filing date, which are *discovered* at a later time (such as IFN-alpha, -beta or -gamma), we will use the terms "discovery" and "invention" in their scientific sense. The words are not interchangeable in this paper. For example, we will refer to an *inventor* of a claim to a purified natural substance. The inventor may believe this to be one species at the filing date but at infringement time, this substance is recognized to be a category of substances, since others have *discovered* additional species of the genus since the filing date. Our scientific usage qualifies the problem we address in this paper to be a part of the classical problem of infringement by so-called "after-arising" technologies. We explore here a particular type of after-arising technology, namely, after-*discovered* technology.

[9] 713 F.3d 1090 (Fed. Cir. 2013).

[10] 759 F.3d 1285 (Fed. Cir. 2014).

[11] *BiogenIDEC*, 713 F.3d at 1095–97.

[12] *AbbVie Deutschland*, 759 F.3d at 1290, 1299.

[13] We use the term "patent holder" to refer broadly to patent applicants and to holders of issued patents or their licensees.

(and the art) are unknowing of yet-to-be-discovered embodiments, then the cases further show that their claims will likely be construed narrowly to what they enabled and described at the filing date, and that the claims will not likely be literally infringed. This Article therefore also explores whether our inventors have invoked equity under the Doctrine of Equivalents ("DoE") for any surviving or narrowly construed claims, and how they have fared. It is foreseeable, however, that if their competitors have designed improved substances that are not factually equivalent to the originally claimed ones, then the claims will not likely be infringed under the DoE either.

We will thus demonstrate that our inventors' best strategy is to try to achieve generic construction of their claims at the outset of the case. They may be able to do this by invoking equity at the *Markman* stage, either directly or by the use of 35 U.S.C. § 112, 6th paragraph. We will propose, taking a cue from another recent decision, *Williamson v. Citrix Online LLC*,[14] that a patent holder with combination claims might use a means-plus-function strategy under paragraph six of 35 U.S.C. § 112. This approach may make it easier to construe claim terms, which, at the filing date, appear to be drawn to one narrow embodiment, but at the time of infringement have been demonstrated to be generic for several embodiments.

The problem addressed in this Article is as much one of unknown future embodiments as it is one of rapidly changing nomenclature in unpredictable technologies, such as biotechnology: A word used in a specific sense at the filing date by the applicant is used by everyone in the art in a generic sense at the infringement date. At the end of the Article, we will return to Isaacs's "interferon."

I. Development of The Law of Future Embodiments

The case law falls broadly into two categories: (1) embodiments that are known to exist at filing, but are not enabled or well described, and (2) embodiments that are not known at the filing date (or, in a variant, are unknown at the first filing date, but become known at the time of subsequent filings or, generally, during prosecution). We will call all of these precedents the "law of future embodiments."[15]

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[14] 770 F.3d 1371 (Fed. Cir. 2014), *superseded by* 792 F.3d 1339 (Fed. Cir. 2015).

[15] There is yet another category of future embodiments, illustrated by Bayer CropScience AG v. Dow AgroSciences LLC, 728 F.3d 1324 (Fed. Cir. 2013), a case we will not discuss in further detail because it does not deal with a claim term that has gone from specific at filing to categorical at infringement. *Id. Bayer CropScience* deals with the issue of *incorrectly understood* embodiments. *Id.* at 1330. The patent holders described at filing what they thought was a novel "mono-oxygenase" enzyme molecule (and a gene encoding it), only to find years later that their understanding of what they had in hand at the filing date was not quite what they

A threshold question is whether, and under what circumstances, when confronted with biological technology that has changed from the filing to the infringement dates, a court will find a claim invalid for lack of compliance with 35 U.S.C. § 112 (a), (referred to, before enactment of the America Invents Act, as "35 U.S.C. § 112, 1st paragraph"), or will construe the claim narrowly and preserve its validity. This is not an academic question. While a narrow claim construction may lead to no literal infringement, it saves the claim for an argument that it may still be infringed under the Doctrine of Equivalents ("DoE").[16]

A. Embodiments Known or Foreseeable at the Filing Date

The basic legal premise in this area goes back to *In re Hogan*,[17] a 1977 case that held that, because future *unknown* embodiments could not be described or enabled at filing, claims cannot be rejected by the U.S. Patent and Trademark Office ("USPTO") as unpatentable for lack of enablement.[18] In contrast, when, at the time of filing, those of skill in the art know or should know of, or can

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thought. *Id.* at 1326. The claimed term "mono-oxygenase," used initially for the involved enzyme, remained in the claim for seven years, even though the science showed, before issuance, that the enzyme was really a "di-oxygenase"; the patent holder never corrected the mistake. *Id*. The claimed term further implies an enzymatic mechanism that later turned out to be incorrect (i.e., a "mono-oxygenase" catalyzes a different biochemical reaction than a "di-oxygenase"). *Id*. at 1331. Even though the holders had discovered a di-oxygenase, the Federal Circuit construed the claims as narrowly drawn to the named mono-oxygenase, and held that the di-oxygenase enzyme of Dow Agro did not literally infringe. *Id*. at 1332. In further supporting its conclusion of a narrow interpretation of claim 1, the Federal Circuit pointed out that a broadly interpreted claim, i.e., one drawn to any enzyme having the biological activity of a 2,4 D mono-oxygenase (such as the di-oxygenase of Dow Agro), might be invalid for lack of generic written description. *Id.* The court recognized that claim construction is not normally influenced by the possibility of claim invalidity, but could not resist warning of such broad construction and its possible infirmity under 35 U.S.C. § 112(a). *Id*. at 1330.

[16] The DoE gives inventors relief from those who would modify the claimed invention in ways that, while avoiding literal infringement, are seen as having substantially appropriated the invention. *See* Graver Tank & Mfg., Co. v. Linde Air Prods. Co., 339 U.S. 605, 608, *reh'g denied*, 340 U.S. 845 (1950). The modern formulation of the DoE uses the concept of "insubstantial differences," or uses a three-way test, which asks if the accused product performs substantially the same function, in substantially the same manner, to achieve substantially the same result, as the claimed product. *See id.*

[17] 559 F.2d 595 (C.C.P.A. 1977).

[18] *Id.* at 603. For a more detailed discussion of Hogan, see the author's article: Jorge Goldstein, AbbVie Deutschland *and Unknown Embodiments: Has the Written Description Requirement for Antibodies Gone Too Far?*, 90 Pat. Trademark & Copyright J. (BNA) 1959 (2015).

or should foresee, embodiments, but do not know how to enable them, the USPTO—and the courts in litigation—may reject generic claims for lack of enablement.[19] And, in litigation, while a broadly issued claim (at least in theory) is literally infringed by the after-discovered embodiment, the court may invalidate the claim and never reach the question. Representative of these situations are the *Plant Cases*, *Chiron v. Genentech*, and *AbbVie Deutschland v. Janssen*.

1. The Plant Cases *and Vegetable Plant Cells: Lack of Enablement*[20]

These are two plant transformation cases, *Plant Genetic Systems v. DeKalb Genetics Corp.*[21] and *Monsanto Co. v. Syngenta Seeds, Inc.*[22] The specifications and the state of the art only enabled transforming dicotyledonous plant cells (such as transgenic tobacco) but did not enable the accused, later-arising monocotyledonous plant cells, such as transgenic maize.[23] Because the claim term "plant cell" is broad enough to include both monocots and dicots, the claims were held invalid under 35 U.S.C. § 112, 1st paragraph for failure to enable their full scope.[24] The questions of infringement, either literal or under the DoE, were never reached.[25]

2. Chiron Corp. v. Genentech, Inc.[26] *and Humanized Antibodies: Nascent Technology*

Over eleven years after its original application, Chiron had filed a series of Continuation-in-Part applications ("CIPs"), which ended with the issuance of U.S. Patent 6,054,561, asserted in litigation. The court held that the broad generic claim of the '561 patent (to "monoclonal antibodies"), while stipulated by the parties to be literally infringed by the accused antibody (the later-arising *humanized* antibody of Genentech), was invalid for lack of novelty over intervening prior art.[27] While the concept of humanizing antibodies was first published around the time of filing of the second CIP application (and the CIP might have otherwise benefitted from the publication), the second CIP did not contain any description or enablement for humanization. The court held that humanization was nascent technology and, following the rule

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[19] *See* Goldstein, *supra* note 18, at 1959.

[20] The *Plant Cases* are based on the reasoning and analyses of *In re* Goodman, 11 F.3d 1046 (Fed. Cir. 1993), an ex parte appeal from the USPTO Board.

[21] 315 F.3d 1335 (Fed. Cir. 2003).

[22] 503 F.3d 1352 (Fed. Cir. 2007).

[23] *Compare Plant Genetic Sys.*, 315 F.3d at 1346, *with Monsanto*, 503 F.3d at 1362.

[24] *See Monsanto*, 503 F.3d at 1361–62; *Plant Genetic Sys.*, 315 F.3d at 1345.

[25] *See Monsanto*, 503 F.3d at 1357; *Plant Genetic Sys.*, 315 F.3d at 1346.

[26] 363 F.3d 1247 (Fed. Cir. 2004).

[27] *See id.* at 1260.

in *Genentech Inc. v. Novo Nordisk*[28] (for proper enablement, nascent technology requires a specific and useful teaching in the patent specification), agreed that the second CIP filing date failed to support the broad claim.[29] The intervening publication of Chiron's own PCT application (showing murine antibodies) then became a statutory bar with respect to the later enabled, third CIP, filing. The broad claim was invalidated for lack of novelty.[30]

The lower court had construed the claim term "monoclonal antibody," as including "monoclonal antibodies no matter how subcategorized, e.g., hybrid, altered, chimeric, or humanized."[31] This broad construction of the term meant that the after-arising humanized antibodies of Genentech were literally encompassed by the claim term "monoclonal antibodies," rendering moot any analysis under the DoE.[32]

3. AbbVie Deutschland *and Functionally Defined Antibodies: Lack of Written Description*

In *AbbVie Deutschland*, the court extended the rule of the *Plant Cases* and *Chiron v. Genentech* to invalidity based on insufficient written description of a genus of antibodies.[33] There was only sufficient description of one subgenus of 300 antibodies (V_H3-type), but that was not representative of another subgenus (V_H5-type, also within the claim) that encompassed the accused, after-arising antibody.[34] The broad claim in *AbbVie Deutschland* was held invalid for being broader than the written description.[35] The question of literal infringement was not reached.[36]

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[28] 108 F.3d 1361 (Fed. Cir. 1997).

[29] *Chiron*, 363 F.3d at 1255–57.

[30] *Id.* at 1252, 1261. *Chiron v. Genentech* takes the *Hogan* and *Plant Cases* a step further: The case establishes the rule that it is irrelevant whether Chiron subjectively knew or did not know of the development of humanization; Chiron was charged with knowing the development and should have included it in the second CIP. The *Chiron* requirement thus is, knew or *should have known. See id.* at 1254.

[31] Chiron Corp. v. Genentech, Inc., 266 F. Supp. 2d 1172, 1192 (E.D. Cal. 2002).

[32] *See id.*

[33] AbbVie Deutschland GMBH v. Janssen Biotech, Inc., 759 F.3d 1285, 1290 (Fed. Cir. 2014).

[34] *Id.* at 1300–01. An analysis of *AbbVie Deutschland* and the author's belief that it has taken the *Hogan* and the *Plant Cases* too far is beyond the scope of this paper. The author has recently published a lengthy critique of the decision in the article cited *supra* note 18.

[35] *AbbVie Deutschland*, 759 F.3d at 1301–02.

[36] *Id.* at 1302.

Since there was no narrower surviving claim drawn to the well-described sub-genus of 300 antibodies (a claim that may have given the patent holder recourse to the DoE), the DoE issue was not reached.[37]

B. Embodiments Unknown or Unforeseeable at the Filing Date

Given *Hogan*, the *Plant Cases*, *Chiron v. Genentech*, and *AbbVie Deutschland*, the issue for unknowing patent holders is not invalidity. The only questions left for the court are those of claim interpretation and application. The issue becomes how the court construes and applies the claims in the context of infringement. In this context, the courts have handed down a series of decisions, ending recently with *BiogenIDEC* where, in most instances, the claims were construed narrowly to encompass only that which the inventor had described on the filing date. The claims survived, but in such narrow fashion that they were not literally infringed. There are two or three exceptions to this rule of narrow interpretation, where the claims were construed generically and infringed literally.

We thus classify cases of unknowing holders into two categories: *first,* those cases where the claims were construed narrowly and held not literally infringed, and, *second*, those where the claims were construed broadly and held literally infringed. For the first category, we will touch upon pleadings under the DoE, and for the second category we will touch upon pleadings under the Reverse DoE.[38]

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[37] *See id.* at 1290. A search among the 74 claims of the '128 patent at issue in *AbbVie Deutschland* reveals not a single one drawn to a subgenus of 300 antibodies with VH3–type heavy chains, even though a written description of the subgenus is present. *See* U.S. Patent No. 6,914,128 B1 (filed Mar. 24, 2000).

[38] It is well settled that if a patentee is able to establish literal infringement, the burden shifts to the accused infringer to show non-infringement. SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1124 (Fed. Cir. 1985). But, in Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605 (1950), the court noted that equity could prevent extension of literal infringement in some cases: "where a device is so far changed in principle . . . that it performs the same or a similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the doctrine of equivalents may be used to restrict the claim." *Id.* at 608–09 (citation omitted). This is now known as the Reverse DoE. The Reverse DoE has been discussed previously in the biotechnology context. *See e.g.*, Karl Bozicevic, *The "Reverse Doctrine of Equivalents" in the World of Reverse Transcriptase*, 71 J. Pat. & Trademark Off. Soc'y 353 (1989); Jorge A. Goldstein, *The Scope and Enforcement of Biotechnology Patents*, Biotechnology Patent Conference Workbook, American Type Culture Collection 7, 11–12 (1986).

1. Claims Construed Narrowly and not Literally Infringed

a. Genentech, Inc. v. Wellcome Foundation[39] *and Tissue Plasminogen Activator*

This decision shows the Federal Circuit struggling with construction of the claim term "tissue plasminogen activator" ("t-PA") in Genentech's '075 patent, and whether it should be construed broadly enough to capture Wellcome's later-arising FE1X, a smaller version of t-PA.[40]

Of the four definitions of t-PA in the specification, ranging from the narrowest, most structural one limited to natural t-PA, to the broadest, most functional one, the court chose the narrowest definition, stating that "the others are hopelessly overbroad," and would have been held not patentable by the USPTO.[41] While the validity of the claim was implicitly maintained, the claim was not literally infringed by the accused FE1X t-PA, which was missing a substantial portion of the natural molecule.[42]

In deciding whether the narrowly construed "human t-PA" was or was not equivalent to the accused smaller FE1X t-PA, the court applied the way-function-result test of the DoE and found that, while both substances performed substantially the same function in the body (dissolving blood clots), the results achieved by both substances were substantially different (they had very different half-lives).[43] The substances were deemed not equivalent.[44]

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[39] 29 F.3d 1555 (Fed Cir 1994). While this case does not deal with after-*discovered* embodiments, it is relevant in that it does show the court's general thinking on after-*arising* biotechnology.

[40] *Id.* at 1558, 1559 n.4, 1563–65. Claim 1 of Genentech's '075 patent is as follows: "A DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator," a claim that is seriously defective under the standards of *Myriad Genetics*. U.S. Patent No. 4,766,075 A (filed Apr. 7, 1983).

[41] *Wellcome Found.*, 29 F.3d at 1564.

[42] *Id.* at 1559 n.4, 1567.

[43] *Id.* at 1567, 1569.

[44] *Id.* at 1569. The court commented in dicta on the difficulty of trying to ascertain if the two bioactive substances operated in substantially the same manner:

> We are mindful that the state of the science in this area of endeavor is very imprecise. Thus, it would be inappropriate to [require] plaintiffs/appellees to prove the specific mechanism by which FE1X binds to fibrin, or to prove that the different properties and structure exhibited by FE1X bear no relation to the binding function. Our only point is that the showing that the K2 region plays a role in the binding function of each is insufficient, particularly in view of the profound differences in the properties and structure possessed by each.

Id. (citation omitted). *Wellcome Foundation* illustrates the uncertainty involved in applying to biological substances a three-step equivalency test, using legal constructs from other ages and other technologies.

b. Schering Corp. v. Amgen Inc.[45] *and Alpha-type Interferon (2000)*

In this case, the Schering '901 patent described and claimed DNA sequences that coded on expression "for a polypeptide of the [interferon IFN alpha] type."[46] At the time of filing, the inventor Weissmann had isolated from leukocytes a polypeptide with interferon activity and called it "leukocyte interferon." While his patent application was pending, an international committee on interferon nomenclature renamed the leukocyte interferon alpha-type interferon.[47] Weissmann voluntarily amended his specification and claims, and the claims issued with the new nomenclature, referring to certain deposits made at DSM.[48] As the years passed, scientists discovered the existence of several IFN-alpha subtypes, such as IFN-alpha-1, -2, and -3.[49] Amgen's accused product was an artificial recombinant DNA sequence that coded for a consensus sequence of "alpha-types."[50] The consensus sequence was a collection of gene sequences from a number of different IFN-alpha subtypes, but did not contain a specific sequence for any single IFN-alpha subtype.[51] In

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[45] 222 F.3d 1347 (Fed. Cir. 2000) [hereinafter *Schering IV*].

[46] *Id.* at 1350. Claim 1 is as follows:

> A recombinant DNA molecule consisting of segments of DNA from different genomes which have been joined end-to-end outside of living cells and which have the capacity to infect some host and to be maintained therein, and the progeny thereof, comprising a DNA sequence selected from the group consisting of:
>
> (a) the DNA inserts of Z-pBR322(Pst)/HcIF-2h (DSM 1700), Z-pBR322(Pst)/HcIF-SN35 (DSM 1701), Z-pBR322 (Pst)/HcIF-SN42 (DSM 1702) and Z-pKT287(Pst)/HcIF-2h-AH6 (DSM 1703),
>
> (b) DNA sequences which hybridize to any of the foregoing DNA inserts and which code on expression for *a polypeptide of the IFN-Y type*, and
>
> (c) DNA sequences which code on expression for *a polypeptide of the IFN-*α *type* coded for on expression by any of the foregoing DNA sequences and inserts,
>
> said DNA sequences and inserts being operatively linked to an expression control sequence in said recombinant DNA molecule.

Id. (emphasis added).

[47] *See id.* at 1349.

[48] *See id.* DSM stands for Deutsche Sammlung von Mikroorganismen (also known as Leibniz-Institut DSMZ - Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), an International Depositary Authority in Braunschweig, Germany. *Leibniz-Institut DSMZ - Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH*, DSMZ, https://www.dsmz.de/about-us.html (last visited Feb. 6, 2016).

[49] *Schering IV*, 222 F.3d at 1353.

[50] *Id.* at 1351.

[51] *Id.*

going back to the deposited inserts of the claim, Amgen demonstrated that Weissmann had in fact isolated one subtype, alpha-1.

On appeal, the Federal Circuit construed the claims as limited to the deposited alpha-1 subtype, and held that the consensus sequence of Amgen did not literally infringe.[52] The court acknowledged that, at the time of filing, the scientific community recognized that Schering's invention "was the sole interferon polypeptide produced by leukocytes,"[53] and that "[t]o grant broader coverage would reward Dr. Weissmann for inventions he did not make."[54]

Unfortunately, the Federal Circuit did not address the question as to whether a claim drawn only to the alpha subtype-1 was infringed under the DoE by Amgen's consensus of alpha sequences. Once confronted with a narrow interpretation of the claim by the lower court, Schering conceded that it could not succeed in proving infringement.[55]

c. Amgen Inc. v. Hoechst Marion Roussel, Inc.[56] *and Erythropoietin*

Amgen owned numerous patents, including one '080, directed to the production of erythropoietin ("EPO") as well as to the EPO itself,[57] a "naturally occurring hormone that controls the formation of red blood cells in bone marrow."[58] Amgen marketed and sold a commercial embodiment of the patented erythropoietin (known as Epogen®), and sought to stop HMR from commercializing a competitive EPO product.[59] Claim 3 of the '080 patent is as follows:

> A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6.*[60]

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[52] *Id.* at 1351, 1356.

[53] *Id.* at 1353.

[54] *Id.* at 1354.

[55] *Id.* at 1349. In a clarifying letter to the district court judge, Schering added that it could not even "advance sufficient evidence to allow a reasonable jury to conclude that Amgen's consensus interferon is equivalent" to the subtype-1 of interferon of the alpha type. Schering Corp. v. Amgen, Inc. (Schering II), 35 F. Supp. 2d 375, 376 (D. Del. 1999), *aff'd*, 222 F.3d 1347 (Fed. Cir. 2000).

[56] 314 F.3d 1313 (Fed. Cir. 2003) [hereinafter *Amgen I*], *cert. denied*, 550 U.S. 953 (2007).

[57] *Id.* at 1319.

[58] *Id.*

[59] *Id.*

[60] *Id.* at 1342–43 (emphasis added). It is not likely that the words "non-naturally occurring" are alone sufficient to remove this claim from an attack under 35 U.S.C. § 101. This claim may no longer be eligible after *Myriad Genetics*. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2114–15, 2120 (2013).

Figure 6 of the '080 patent shows an EPO of 166 amino acids, ending in an arginine.[61] At the time the Amgen '080 patent was drafted and filed, it was believed by the scientific community that the mature EPO DNA sequence had 166 amino acids, and this belief is shown in Figure 6. Later research demonstrated that the full sequence was actually 165 amino acids; the arginine is cleaved off prior to the protein's secretion from the cell.[62]

The Federal Circuit affirmed the holding of the district court that the accused product of 165 AAs does not literally infringe claim 3 of the '080 patent, stating that, "read properly in light of the term 'comprising' this means that the claimed glycoprotein must have—at minimum—all 166 amino acids shown in Figure 6."[63]

The district court concluded that Amgen had proven by a preponderance of the evidence that the accused EPO having 165 amino acids satisfied the function-way-result test, in that HMR's missing arginine residue does not affect the *in vivo* biological activity of its EPO product.[64] It held that the products were equivalent.[65] The Federal Circuit, however, remanded to investigate a possible estoppel during the prosecution.[66] It turns out that, in order to overcome a double patenting rejection, the applicant had added Figure 6 into the claim.[67] In a follow-on decision a few years later, *Amgen Inc. v. Hoechst Marion Roussel, Inc.* ("*Amgen II*"),[68] the Federal Circuit held that Amgen was indeed estopped from asserting that the EPOs having 165 AAs and 166 AAs were equivalent.[69] It found that the EPO with 165 amino acids was a foreseeable equivalent at the filing date, that the patentee did not rebut the presumption of surrender of the 165 amino acid equivalent, and that the patentee's failure to claim the 165 amino acid EPO equivalent could not be excused.[70]

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[61] U.S. Patent No. 5,621,080 fig.6 (filed June 6, 1995); *accord Amgen I*, 314 F.3d at 1343 (emphasis added).

[62] *Amgen I*, 314 F.3d at 1343.

[63] *Id.* at 1345.

[64] *Id.* at 1344.

[65] *Id.* at 1320.

[66] *Id.*

[67] *Id.* at 1345.

[68] 457 F.3d 1293 (Fed. Cir. 2006) [hereinafter *Amgen II*], *cert. denied*, 550 U.S. 953 (2007).

[69] *Id.* at 1314.

[70] *Id.* at 1293. The *Amgen v. HMR* family of decisions is very similar in their ultimate outcome to a 1990 case, *Hormone Research Found. v. Genentech, Inc.*, 904 F.2d 1558 (Fed. Cir. 1990), where the patent claim made reference to a figure showing a specific sequence of human growth hormone, and the accused, after arising—and different—sequence was found neither to infringe literally nor (again, due to an estoppel) under the DoE. *See id.* at 1569.

Sidebar: *Amgen II* is in tension with *AbbVie Deutschland*

In *Amgen I* the court construed the claim term "mature EPO" to be limited to an EPO of 166 amino acids.[71] It did not invalidate the claim (as it couldn't under *Hogan*) for failure to describe the later-discovered form of 165 amino acids.[72] Yet in its later ruling in *Amgen II*, the court held that Amgen was estopped from reading its claim under the DoE on the form of 165 amino acids.[73] The court explained that, among other things, the estoppel arose because the EPO of 165 amino acids was reasonably foreseeable.[74] *AbbVie Deutschland* suggests that failure to describe foreseeable embodiments can lead to invalidity of the entire claim for lack of written description ("WD").[75] If a reasonably foreseeable embodiment such as the 165 amino acid EPO is not described, the claim might be invalidated. Yet in *Amgen I* the claim survived, albeit narrowly interpreted.[76] Can we reconcile these decisions?

There are two possible explanations for the different results. One is that the reasonable foreseeability of the EPO of 165 amino acids came up at the stage of application of the claim under the DoE, not in the context of invalidity. The conclusion would be that, while failure to describe a foreseeable embodiment is fatal to claim validity (*AbbVie Deutschland*), it is not fatal if it is only one factor when deciding whether to use equitable principles under the DoE (*Amgen II*). Perhaps another explanation lies in the intervening years between the decisions, 2003 and 2014. The WD requirement for a genus claim in biotechnology has expanded dramatically from before *Regents of the University of California v. Eli Lilly*,[77] where WD was rarely used to find generic claims invalid for failure to describe a representative number of embodiments,[78] to *AbbVie Deutschland* where, if one has any hope of sustaining the validity of a genus of foreseeable yet unpredictable embodiments, the burden has now become to reduce to practice as many embodiments as possible.[79] Perhaps today the claims in *Amgen I* would also be held invalid.

[71] *Amgen I*, 314 F.3d at 1343.

[72] *Id.* at 1335.

[73] *Amgen II*, 457 F.3d at 1310.

[74] *Id.* at 1313.

[75] AbbVie Deutschland GMBH v. Janssen Biotech, Inc., 759 F.3d 1285, 1294 (Fed. Cir. 2014).

[76] *See Amgen I*, 314 F.3d at 1313.

[77] 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

[78] *Id.* at 1575.

[79] *See AbbVie Deutschland*, 759 F.3d 1285.

d. BiogenIDEC v. GlaxoSmithKline LLC[80] *and Anti-CD20 Antibodies*

This was an appeal from a lower court decision that claim 1 of Biogen IDEC's U.S. patent 7,682,612, which is for a method of treating chronic lymphocytic leukemia ("CLL"), including the limitation ". . .administering an anti-CD20 antibody. . . ," was not infringed by the use of GSK's antibody Arzerra® ("Arzerra").[81] The claim was based on the invention of using, as therapy, an anti-CD20 antibody, Rituxan® ("Rituxan," also known as rituximab), which, at the filing date, was known to bind the antigen CD20 that appeared on the cell membranes of lymphoma cells.[82] It was later discovered that Rituxan bound to just one of at least two different epitopes on CD20, the one now known as the "large loop"; no other epitope was known at the filing date or described in the specification.[83] During prosecution of the patent application, Biogen IDEC, confronted with a rejection under 35 U.S.C. § 112, 1st paragraph, that their specification did not enable the use of all antibodies against CD20, responded in a manner that was later held by the court to have acquiesced to the examiner's characterization of their antibodies as being those that bound the *same epitope* as Rituxan.[84] The accused Arzerra is also an anti-CD20 antibody but it binds to a different epitope, the so-called "small loop" epitope, discovered after the filing date.[85] While Biogen IDEC relied on their broad claim language, "anti-CD20 antibody," for alleging literal infringement, the lower court held that anti-CD20 meant "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," basing its conclusion on prosecution history disclaimer.[86]

On appeal, Biogen IDEC argued (to no avail) that they had "never explicitly referred to any particular 'epitope'—and because CD20 was only thought to have one epitope at the time the patent application was filed—the applicants

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[80] Biogen Idec, Inc. v. GlaxoSmithKline LLC, 713 F.3d 1090, 1092 (Fed. Cir. 2013).

[81] Claim 1 reads as follows (emphasis added): "A method for treating chronic lymphocytic leukemia [CLL] in a human patient, comprising administering *an anti-CD20 antibody* to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody." U.S. Patent No. 7,682,612 (filed Nov. 9, 1999) (emphasis added). This claim would likely survive a challenge under *Mayo v. Prometheus* in that it does not pre-empt a law of nature. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

[82] *BiogenIdec*, 713 F.3d at 1092; *accord* '612 patent.

[83] *BiogenIdec*, 713 F.3d at 1093.

[84] Biogen Idec, Inc. v. GlaxoSmithKline LLC, No. 10-CV-00608 BEN (BGS), 2011 U.S. Dist. LEXIS 120043 at *36 (S.D. Cal. Oct. 17, 2011).

[85] *BiogenIDEC*, 713 F.3d at 1094.

[86] *Id.* at 1094. We will use "disclaimer" synonymously with "disavowal."

were merely referring to specificity and affinity in their general sense."[87] A divided court (with Judge Plager dissenting) reasoned that, because Biogen IDEC limited their claims to what the examiner believed was enabled (antibodies binding to the same epitope as Rituxan and similar ones), the claim scope was limited to those enabled antibodies.[88] The court construed the term "anti-CD20 antibody" as narrowly drawn to antibodies binding the large loop epitope known at the filing date, but did not extend it to the after-discovered small loop epitope.[89] This narrow construction prevented the patent holders from proving literal infringement by Arzerra.[90]

Nothing is said in the lower or appellate court decisions about the DoE.[91] Since Biogen IDEC conceded non-infringement under the narrow claim construction,[92] the implication is that they could not prove infringement under the DoE.

Having discussed cases of unknowing patent holders where the claims were construed narrowly and held not literally infringed, we now turn to those cases (still of unknowing holders) where the claims were construed broadly and held literally infringed.

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[87] *Id.* at 1096.

[88] *Id.* The court noted that Biogen IDEC never directly challenged the examiner's use of "epitope," saying that:

> [T]he applicants in this case . . . simply discussed specificity and affinity with regard to the disclosure of the '612 patent, which was narrowly limited to Rituxan®, rituximab, and 2B8-MX-DTPA. The disclaimer of antibodies that do not have a similar affinity and specificity for the specific epitope to which Rituxan® binds was clear and unmistakable. Accordingly, the district court properly limited the scope of the claim term, 'anti-CD20 antibody,' based on prosecution history disclaimer.

Id. at 1096–97 (citations omitted).

[89] *See id.*

[90] *See id.* at 1097.

[91] *See generally BiogenIDEC*, 713 F.3d 1090 (Fed. Cir. 2013); *see generally Biogen Idec, Inc.*, No. 10-CV-00608 BEN (BGS), 2011 U.S. Dist. LEXIS 120043 (S.D. Cal. Oct. 17, 2011).

[92] *BiogenIDEC*, 713 F.3d at 1096.

2. Claims Construed Broadly and Literally Infringed . . . in Principle[93]

a. U.S. Steel Corp. v. Phillips Petroleum Co.[94] *and Crystalline Polypropylene*

This case is based on Phillips's '851 patent dealing with polypropylene products. The patent claim read "Normally solid polypropylene, consisting essentially of recurring propylene units, having a substantial crystalline polypropylene content."[95] Phillips had filed its patent application in 1956 as a CIP to a previous 1953 application.[96] The 1953 application described tacky solid polymerized olefins and a propylene polymer with substantial crystalline content yet relatively low molecular weight and low viscosity ranges.[97] U.S. Steel sold a crystalline polymer of higher molecular weight and higher viscosity that had not been known until 1954.[98] The court held that in 1953 Phillips was an unknowing holder, and that Phillips's patent was not invalid for lack of novelty over the intervening art.[99]

The Federal Circuit construed the '851 claim generically and held that the later polymer of U.S. Steel infringed literally.[100] The court interpreted the claim to dominate the later-arising high weight/viscosity polymer.[101]

U.S. Steel urged reversal of the lower court, arguing that, notwithstanding literal infringement, it would be inequitable to find infringement.[102] U.S. Steel invoked the Reverse DoE, arguing that its polymer was far removed in principle from the polymer described by Phillips in their 1953 specification.[103] The Federal Circuit disagreed that the claimed and later products were far removed in principle.[104] The court focused not on the improved weight and viscosity characteristics of the later polymer, but on the high crystallinity it shared with the earlier one described and claimed in the '851 patent:

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[93] The cases in this section deal with after-arising technologies; they will be discussed in some detail because they carry the core of one solution to the problem of after-discovered embodiments: equity.

[94] 865 F.2d 1247 (Fed. Cir. 1989).

[95] *Id.* at 1249.

[96] *Id.*

[97] *Id.* at 1249–50.

[98] *Id.* at 1248.

[99] *Id.* at 1253.

[100] *Id.* at 1247–48

[101] *Id.* The Defendants admitted that their products were "literally embraced" by the independent claim of the '851 patent, so the lower court carried out no analysis under the DoE. Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 1345–46 (D. Del. 1987).

[102] *See U.S. Steel Corp*, 865 F.2d at 1253.

[103] *Id.*

[104] *Id.*

"[E]vidence of record establishes that crystallinity gives polypropylene the properties of tensile strength, stiffness, and hardness, and . . . defendants concede that [Plaintiffs] were the first to teach crystallinity,"[105] adding that the principle of high crystallinity was "unchanged in the accused product."[106] In shifting the focus from the undisclosed (and un-disclosable) higher weight/viscosity embodiments to the earlier disclosed high crystalline content, the court reframed the inquiry.[107] High crystalline content was *the* fundamental invention claimed in Philips's patent, and there was no dispute that the polymer of U.S Steel was highly crystalline.[108]

b. Scripps Clinic & Research Foundation v. Genentech, Inc.[109] *and Factor VIII:C*

The court here dealt with a claim by Scripps to coagulation Factor VIII:C, described in the specification as having been purified from plasma.[110] The claim, however, was not limited to any method of preparation.[111] It was to the product *per se*, and was asserted against an after-arising similar molecule with the same name, but made recombinantly by Genentech.[112]

The Federal Circuit refused Genentech's request to read process-of-making limitations from the specification into the claim, and construed it as a product claim, untethered to any method of making.[113] The court recognized that the naturally-derived and the accused recombinantly-made materials were made by different methods but, given its interpretation of the claim as a product, held the claim to be broad enough to literally capture the after-developed recombinant Factor VIII:C.[114]

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[105] *Id.* at 1252.

[106] *Id.* at 1253 n.9.

[107] *See id.* at 1251.

[108] *See id.* at 1249.

[109] 927 F.2d 1565 (Fed. Cir. 1991).

[110] *Id.* at 1568.

[111] *See id.* at 1570.

[112] *Id.* at 1580. Scripps's claim 24 is as follows: "A human VIII:C preparation having a potency in the range of 134 to 1172 units per ml, and being substantially free of VIII:RP." *Id.* at 1570. While this claim was written more than 20 years before *Myriad Genetics*, it has several elements that might save it from a challenge for lack of eligibility. Of particular importance is the phrase "potency in the range of 134 to 1172 units per ml, and being substantially free of VIII:RP." *Id.* This phrase distances the claimed Factor VIII:C from the natural product by defining its high purity. The question, according to the USPTO, would be whether the resulting preparation is "markedly different" from the Factor VIII:C occurring in nature. *See* Chenghua Luo & Jorge Goldstein, *Patenting Purified Natural Products by Specific Activity: Eligibility and Enablement*, 9 BNA Life Sciences L. & Industry Rep. 633 (2015).

[113] *Scripps Clinic*, 927 F.2d at 1583.

[114] *Id.* at 1583–84.

The court then remanded the case to the lower court to investigate, under the Reverse DoE, whether the natural and recombinant materials were "so far changed in principle" that it would be inequitable to find the latter to be infringing a claim to the former.[115] Among the questions to be addressed by the lower court would be the properties of plasma-derived and recombinantly produced VIII:C, and any differences between VIII:C from plasma and VIII:C obtained by recombinant techniques.[116] The case settled without reaching trial.[117]

c. Stanford University v. Roche Molecular Systems[118] *and Antiretroviral Agents*

This California District Court decision shows that sometimes biotech patent holders can obtain a claim construction in the lower court that is broad enough to capture later-arising embodiments. The claim here was for a method of evaluating the effectiveness of anti HIV therapy using "antiretroviral agents."[119]

Agreeing with Stanford, the lower court took the issue of temporal claim construction head on. It found the claim term "antiretroviral agent" to be generic, even though the only such agents on the 1992 filing date were reverse transcription inhibitors.[120] It held that the claim captured Roche's after-arising protease inhibitors, whose use was invented in 1995–1996.[121] Roche's argument that "antiretroviral agent" should be defined as antiretroviral agents available

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[115] *Id.* at 1581.

[116] *Id.*

[117] Shaoyi Liao, *Resolving the Dilemmas Between the Patent Law and Biotechnology: An Analysis of Three Recent Biotechnology Patent Cases*, 11 Santa Clara High Tech. L.J. 229, 244 n.126 (1995).

[118] Bd. of Trs. of Leland Stanford Junior Univ. v. Roche Molecular Sys., Inc. (Stanford II), 563 F. Supp. 2d 1016 (N.D. Cal. 2008).

[119] *Id.* at 1021. The claim is as follows:

> A method of evaluating the effectiveness of anti-HIV therapy of a patient comprising (i) collecting a plasma sample from an HIV-infected patient who is being treated with *an antiretroviral agent*; (ii) amplifying the HIV-encoding nucleic acid in the plasma sample using HIV primers in about 30 cycles of PCR; and (iii) measuring the HIV RNA copy number using the product of the PCR, in which an HIV RNA copy number greater than about 500 per 200 µl of plasma correlates positively with the conclusion that the antiretroviral agent is therapeutically ineffective.

Id. (emphasis added). The format of this claim looks eerily similar to that in *Mayo v. Prometheus*. The claim in *Mayo v. Prometheus* was to a method of evaluating if the dosage of an administered drug was to be modified up or down depending on the levels of its metabolite. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1290–91 (2012). The Supreme Court ruled that claim invalid under 35 U.S.C. § 101. *Id.* at 1305. The therapeutic evaluation claim in *Stanford II* may be similarly vulnerable to such challenge.

[120] *Stanford II*, 563 F. Supp. 2d at 1029.

[121] *Id.*

to doctors for the treatment of AIDS/HIV infected patients in 1992, was rejected.[122] The claim term was held to read on a *category* of agents, not just on reverse transcription inhibitors.[123] The court was not asked and did not undertake any analysis under the Reverse DoE.[124]

d. Roche Palo Alto LLC v. Apotex, Inc.[125] *and Micelles*

In this case, the Federal Circuit analyzed an allegation by Roche that Apotex infringed its '493 patent, directed to a drug formulation.[126] The claimed formulation contains a number of ingredients designed to alleviate the symptoms and causes of eye inflammation.[127] The formulation comprises four ingredients, among them "O_{40}," an ethoxylated alkyl phenol stabilizer.[128] The O_{40} is present in "a stabilizing amount between 0.001% and 1.0% wt/vol."[129]

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[122] *Id.* at 1034.

[123] The court distinguished *Schering v. Amgen* by stating that, in contrast to Weissmann, in *Stanford II*, Stanford did not intend to limit the term "antiretroviral agents" to "known and available technologies." The court also added that there is no evidence that the categorical term, antiretroviral agents, was ever used to refer only to agents that inhibit reverse transcription. *See Stanford II*, 563 F. Supp. 2d at 1034.

[124] *See generally id.* Stanford's success was fleeting. A year after the favorable holding on claim construction for Stanford, the lower court held the claim invalid based on obviousness. *See Stanford II*, 563 F. Supp. 2d at 1016. The aftermath of the case became even more complicated. The Federal Circuit vacated the obviousness determination and remanded with instructions to dismiss the action for lack of standing. Bd. of Trs. of Leland Stanford Junior Univ. v. Roche Molecular Sys., Inc. (Stanford III), 583 F.3d 832, 848 (Fed. Cir. 2009). The Supreme Court affirmed the lack of standing in Bd. of Trs. of Leland Stanford Junior Univ. v. Roche Molecular Sys., Inc. (Stanford IV), 131 S. Ct. 2188 (2011).

[125] 531 F.3d 1372 (Fed. Cir. 2008).

[126] *Id.* at 1376.

[127] *Id.* at 1374.

[128] *Id.*

[129] *Id.* at 1375. Claim 1 is as follows:

> An opthalmologically acceptable nonsteroidal anti-inflammatory drug formulation, comprising:
>
> [1]an opthamologically [sic] acceptable nonsteroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001 % and 10.00% wt/vol;
>
> [2] a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol;
>
> [3] an ethoxylated alkyl phenol that conforms generally to the formula: $C_8H_{17}C_6H_4(OCH_2\text{-}CH_2)_n$ OH where *n* has an average value of 40 [O_{40}] *in a stabilizing amount between 0.001% and 1.0% wt/vol*; and

While Apotex's formulation contained smaller amounts of O_{40} than those exemplified in the '493 patent, these amounts were still within the claimed range, so its formulation literally infringed.[130]

Apotex asserted that its formulation performed in a substantially different way than Roche's claimed invention.[131] Apotex asserted that the *principle* of the Roche invention was the formation of micelles by $O_{40.}$[132] These prevent the active ingredients from reacting with one another in a way that would otherwise reduce the formulation's effectiveness. The reasoning went that the concentration of O_{40} in Apotex's product was too low to form micelles, and therefore its formulation performed the same function in a substantially different way.[133] The argument did not persuade the Federal Circuit, which found that Apotex failed to establish the principle of the invention.[134] The primary rationale for this decision was that Apotex could not reference any support for "micelle formation" as the principle of the Roche invention; "micelle formation" was not discussed anywhere in the '493 patent or the prosecution history.[135] Although Apotex argued that a person of skill would recognize the importance of micelles, the court found that Apotex could not adequately show support for micelle formation as the principle of the invention, and therefore could not make out a case of non-infringement using the Reverse DoE.[136]

* * *

Let us now make some sense of the case law. We will try and elicit some basic rules on the problem of capturing future embodiments. We will see how the most recent cases fit into, clarify, or challenge such rules. We will then propose a legal framework that may help patent holders in their understandable attempts to capture after-discovered embodiments in rapidly moving biotechnologies.

II. Analysis: The Case Law on Future Embodiments

Table 1 below summarizes our detailed analyses of the case law. At a glance, the Table sets forth the broad differences in results obtained by knowing and unknowing patent holders, in terms of validity, literal infringement,

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[4] an aqueous vehicle q.s. to 100%.

Id. at 1375 (emphasis added).

130 *See id.* at 1377.

131 *Id.* at 1378.

132 *See id.*

133 *Id.*

134 *Id.*

135 *Id.* at 1378–79.

136 *Id.* at 1378.

Table 1

Knowing Patent Holders: Invalidity

Case	Literal Infringement	Infringement under the DoE	Comments
The *Plant Cases* and Vegetable Cells	. . . by monocot cells: Not reached	Not reached, in that there was no surviving claim limited to dicot vegetable cells	Claims invalid for lack of enablement
Chiron v. Genentech and Monoclonal Antibodies to HER2	. . . by humanized antibodies: Stipulated as infringed	Not reached, in that the claim was construed to read literally on the accused antibody	Claims lack enablement in one of the priority applications, thus invalid as anticipated by intervening prior art
AbbVie Deutschland and Antibodies to IL-12	. . . by Stelara, a V_H5-type antibody: Not reached	Not reached, in that there was no surviving claim limited to the properly described subgenus of V_H3-type antibodies	Claims invalid for lack of written description

Unknowing Patent Holders: No Invalidity—Narrow Claim Construction

Case	Literal Infringement	Change in Results due to Reverse DoE?	Comments
Genentech v. Wellcome and Tissue Plasminogen Activator	. . . by FE1X t-PA: No, due to narrow claim construction	No, as a matter of fact, given the substantially different results achieved by the accused FE1X t-PA	
Schering v. Amgen and Alpha-type Interferon	. . . by consensus of IFN alpha-types: No, due to narrow claim construction	No, due to concession by patent holder	
Amgen v. HMR and Erythropoietin	. . . by EPO of 165 AAs: No, due to narrow claim construction	No, due to estoppel by amendment to overcome ODP	
BiogenIDEC v. GlaxoSmithKline and Anti-CD20 Antibodies	. . .by anti-CD20 to the small loop: No; narrow claim construction due to disavowal by argument	Not discussed	

Unknowing Patent Holders: No Invalidity—Broad Claim Construction

Case	Literal Infringement	Change in Results due to Reverse DoE?	Comments
U.S. Steel v. Phillips and Crystalline Polypropylene	. . . by high weight/high viscosity polypropylene: Yes	Reverse DoE pled as defense but, *held,* still infringed, since claimed and accused products do not differ in principle	
Scripps v. Genentech and Factor VIII:C	. . . by recombinant Factor VIII:C: Yes	Remanded for determination under Reverse DoE, but case settled	
Roche Palo Alto v. Apotex and Micelles	. . . by very low concentrations of O_{40}: Yes	Reverse DoE pled but, *held*, claim still infringed since principle of invention not proven	
Stanford v. Roche and Antiretroviral Agents.	. . . by later invented protease inhibitors: Yes	Reverse DoE not pled	

infringement under the DoE, or avoidance of infringement under the Reverse DoE.

Broadly viewed, in the case of *knowing* patent holders, the courts have held claims invalid and, in the case of *unknowing* holders, the courts have construed claims narrowly and held them not literally infringed by after-discovered embodiments. We are now curious to evaluate three deeper questions: (1) whether equity has played any role in helping the *knowing* holders (who lost broad claims to invalidity) assert narrower surviving claims under the DoE; (2) whether *unknowing* holders (whose claims were held not to have been literally infringed) have succeeded in asserting their narrowly construed claims under the DoE; and, (3) what were the winning strategies used by *unknowing* patent holders who were able to obtain broad construction and literal infringement of their claims.

But before we analyze these questions, let us address a threshold issue—as a cautionary tale. A review of the case law reveals that, regardless of whether they are knowing or not, if patent holders are *inattentive*, they will hurt their chances of success at infringement.

A. Inattentive vs. Vigilant Patent Holders

Had the patent holders in *Schering v. Amgen* and *Chiron v. Genentech* been more vigilant, they might have been able to avoid some of the problems they encountered in the courts. These inattentive holders brought many of the claim construction or invalidation problems unto themselves.

In *Schering v. Amgen* (where the patent holder was unknowing), Weissmann's claims to IFN-alpha were so narrowly construed (to IFN-alpha-1) that they did not read on the interferons of the Amgen consensus of "alpha types."[137] While this drastic result was closely reasoned by the court, the case may well have gone the other way had Schering (Biogen's licensee) avoided some self-inflicted damage. Weissmann did not immediately sequence the deposited inserts he had isolated (which, he originally agreed, all encoded for IFN-alpha-1).[138] Throughout the many years of the license between Biogen and Schering, no one else sequenced these inserts.[139] The inserts were presented to the lower court as encoding the alpha-1 subtype.[140] The court interpreted the claims as limited to the alpha-1 subtype and no other, and ruled that the claims were not infringed.[141] Yet after the *Markman* hearing, Schering explained to the

[137] *Schering IV*, 222 F.3d 1347, 1351–54 (Fed. Cir. 2000).

[138] *See* Schering Corp. v. Amgen, Inc. (Schering III), 25 F. Supp. 2d 293, 299 (D. Del. 1998).

[139] *See id.* at 299–300.

[140] *Id.* at 299.

[141] *See* Schering Corp. v. Amgen, Inc. (Schering I), 18 F. Supp. 2d 372, 393 (D. Del. 1998).

court that, upon closer inspection, they had discovered that there was indeed another subtype of alpha in the DSM deposits: IFN-alpha-14.[142] The lower court refused to admit the evidence, and the Federal Circuit affirmed, giving short shrift to the Schering plea and stating:

> After possessing Dr. Weissmann's deposits for nearly 18 years, Schering nonetheless pled that recent tests had discerned that insert 4c (one of the samples deposited at the time of Dr. Weissmann's original application) codes for IFN-α-14. . . . "Under these facts, it is impossible to conclude that Schering exercised due diligence to discover that the 4c insert DNA allegedly codes on IFN-α-14."[143]

Had the evidence of IFN-alpha-14 been presented earlier, it might have shown that Weissmann had indeed isolated and used more than just the alpha-1 subtype. This might have shown that the concept of "alpha-type" was descriptive of a *category* that included more than one subtype. Schering, with a claim construction that was more generic than one limited to the alpha-1 subtype, might have won the case on literal infringement. The consensus interferon of Amgen (which was made by picking several different subtypes of alpha[144]) might even have included sequences from both 1 and 14. Even if it had not, it is clear that the Amgen consensus benefitted from the contribution of more than just the alpha-1 subtype. Alas, none of this was considered. The inattentiveness of the patent holder ended the matter.

A similar result is seen in *Chiron v. Genentech* (where the patent holder was knowing). From 1984 to 1995 the Chiron inventors filed three CIP applications.[145] Every time they filed a new one they added deposits of *murine* antibodies.[146] By 1986, the same month they filed their second CIP application, a publication appeared describing antibody humanization technology.[147] Yet the second CIP application did not mention humanization technologies.[148] This failure proved fatal to their case. Had they been more vigilant and followed the literature (and understood the case law on nascent technology, *Genentech, Inc. v. Novo Nordisk, A/S*[149]) they would have supplemented their second CIP with disclosure of humanization technology. The priority date of the second CIP would not have failed, the intervening prior art would not have been fatal, and they might have won their litigation.

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[142] *Schering III*, 25 F. Supp. 2d at 298.

[143] *Schering IV*, 222 F.3d at 1354 (quoting *Schering III*, 25 F. Supp. 2d 293, 299 (D. Del. 1998)).

[144] *Id.* at 1351.

[145] Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1251 (Fed. Cir. 2004).

[146] *Id.* at 1251–52.

[147] *Id.* at 1251.

[148] *Id.* at 1252.

[149] 108 F.3d 1361 (Fed. Cir. 1997).

Contrast these cases with *BiogenIDEC*, where we think that the applicants were as vigilant as was reasonable under the circumstances, yet were penalized with narrow claim constructions.[150] We believe that the *BiogenIDEC* court incorrectly decided that, during prosecution, Biogen IDEC disavowed epitopes other than the large loop of CD-20.[151] Since the claims in *BiogenIDEC* were not held invalid under 35 U.S.C. § 112, 1st paragraph, for failure of the specification to describe the unknown small loop of CD-20,[152] the holder in *BiogenIDEC* should equally not be seen as having disclaimed unknown, yet-to-be-discovered, additional loops. In contrast with *Chiron* (where the holders had control over whether they kept up with the literature) or *Schering* (where the holders had control over whether to promptly sequence their deposited sequences), the holder in *BiogenIDEC* was not to blame for ignoring facts *over which he had no control.* The question the court should have asked is this: how is it possible to knowingly disclaim something that is not known to exist? The answer is that it is not possible. Even if, as the majority of the court concluded, a disclaimer of the small loop of CD20 was created,[153] the court should have interpreted the disclaimer as applying only to embodiments *known to exist at the time.* It is not logical to conclude that an applicant purposefully will disclaim *future* embodiments unknown to anybody.

The court should take a page from the *Hogan* book. Under *Hogan* and its progeny, an unknowing patent holder is not penalized with claim invalidity for not describing and enabling embodiments that have not yet been discovered, and which she cannot be charged with knowing.[154] Similarly, an unknowing (and faultless) holder should not be penalized with a narrow claim interpretation if it is clear only with hindsight that she disclaimed embodiments that had not yet been discovered, and which she (or anyone else) cannot be charged with knowing. Yet in *BiogenIDEC*, the narrowly construed claims were literally avoided by an unknown later-discovered embodiment of antibodies to the small CD20 loop. This, in our view, is an unjust result.

[150] *BiogenIDEC*, 713 F.3d 1090, 1097 (Fed. Cir. 2013).

[151] *See id.* at 1096–97.

[152] *See id.*

[153] *Id.* Judge Plager wrote a lengthy and carefully reasoned dissent in *BiogenIDEC*, which disagreed that a disclaimer had, in fact, occurred. *See id.* at 1098–1101.

[154] *See* Goldstein, *supra* note 18, at 1960.

Sidebar: Comparing *Schering* and *BiogenIDEC*

We believe that, given the earlier holding in *Schering v. Amgen*, the much-debated prosecution disavowal of anything but large loop CD20 epitopes was not as important to the outcome as the *BiogenIDEC* court held.[155]

Schering v. Amgen, which was not even cited in *BiogenIDEC*, seems to be on point. The words of the *Schering* court explaining their narrow claim construction come back to remind us of the harsh decision: "To grant broader coverage [that is, broader than IFN of the alpha-1 subtype] would reward Dr. Weissmann for inventions he did not make."[156] These words could readily be applied to the situation in *BiogenIDEC*: To grant broader coverage to White and her co-inventors of the '612 patent, that is, broader than antibodies to the large loop of CD20, would reward them for inventions they did not make. This reading of the decisions leads to the obvious conclusion that, in light of *Schering,* it was not necessary for the court in *BiogenIDEC* to rely on disavowal. Even without the disavowal, the court, following its own precedent, could have construed the claim term "CD20" narrowly and concluded no literal infringement by the GSK antibody. The holding in *BiogenIDEC* may well have gone the same way regardless of what was said at the USPTO by Biogen IDEC to overcome their rejection for lack of enablement.

Perhaps the *BiogenIDEC* court took the easy way out and did not address the hard question of the case: whether equity demanded that the Biogen IDEC inventors be given a broader interpretation of the claim. Perhaps if the legal analyses had not been cut short by the presence of the dubious disavowal, the court would have reached the issue addressed in this Article: whether unknowing inventors of groundbreaking products or methods, inventions which open up a whole new field of research and commerce, are entitled to dominate after-discovered embodiments that embody their invention.[157]

[155] *See BIogenIDEC*, 713 F.3d at 1096–97.

[156] *Schering IV*, 222 F.3d 1347, 1354 (Fed. Cir. 2000).

[157] A similar question can be asked of Weissmann and his groundbreaking isolation of the genes for IFN-alpha. Setting aside the self-inflicted wound of not timely sequencing all DSM inserts, shouldn't the court have provided a more generous interpretation of "IFN-alpha type" than that limited to "alpha subtype-1"?

B. The Role of Equity and the Principle of the Invention

Let us now focus on the role of equity. We ask if any of the knowing patent holders who lost their broadest claims due to lack of enablement or written description (*Plant Cases*, *Chiron*, and *AbbVie Deutschland*[158]), or any of the unknowing ones whose claims were construed narrowly (*Genentech, Inc. v. Wellcome Foundation*, *Schering v. Amgen*, *Amgen v. HMR*, and *BiogenIDEC*[159]), successfully pled infringement of surviving claims under the DoE. The short answer for both groups is, no. However, when we evaluate these decisions together with those where literal infringers attempted to defend against liability by pleading the Reverse DoE (*U.S. Steel*, *Scripps*, and *Roche Palo Alto*[160]), we see a common theme, regardless of which side the pleader is on. Whether it is the patent holder or the literal infringer who pleads equity under the DoE or the Reverse DoE, the common theme is the use by the courts of the equitable concept of the *principle of the invention*.[161] By evaluating the principle of the invention, it is possible to glimpse a potential solution to the problem of capturing after-discovered embodiments in biotech patents.

The concept of the principle of the invention is the keystone to both the DoE and the Reverse DoE sides of the equity bridge.[162] Historically, the three-part test, a mainstay of present DoE case law, is in fact rooted in "the principle of the invention," and is a more direct way of elucidating it.[163] And, non-literally infringing products that reproduce the principle of the invention will be captured under this doctrine.[164]

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[158] See *AbbVie Deutschland*, 759 F.3d 1285, 1305 (Fed. Cir. 2014); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1263 (Fed. Cir. 2004); Plant Genetic Sys. v. DeKalb Genetics Corp., 315 F.3d 1335, 1341 (Fed. Cir. 2003).

[159] *BiogenIDEC*, 713 F.3d 1090; *Amgen I*, 314 F.3d 1313 (Fed. Cir. 2003); *Schering IV*, 222 F.3d 1347; *Wellcome Found.*, 29 F.3d 1555 (Fed. Cir. 1994).

[160] Roche Palo Alto LLC v. Apotex Inc., 531 F.3d 1372, 1376 (Fed. Cir. 2008); Scripps Clinic & Research Found. V. Genentech, Inc., 927 F.2d 1565, 1580 (Fed. Cir. 1991); U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1249 (Fed. Cir. 1989).

[161] *Roche Palo Alto*, 531 F.3d at 1377–78.

[162] *See id.*

[163] *See* Gray v. James, 10 F. Cas. 1015, 1016 (D. Pa. 1817) ("[W]here the [accused and the claimed] machines are substantially the same, and operate in the same manner, to produce the same result, they must be *in principle* the same." (emphasis added)); *see also* Winans v. Denmead, 56 U.S. 330, 343 (1854) ("[T]he patentee, having described his invention, and shown *its principles*, and claimed it in that form which most perfectly embodies it, is, in contemplation of law, deemed to claim every form in which his invention may be copied, unless he manifests an intention to disclaim some of those forms." (emphasis added)).

[164] *See Gray*, 10 F. Cas. at 1016.

Application of the DoE in biotechnology patents, however, has been rare and has met with mixed success.[165] One general reason is that the DoE is in tension with the notice requirement.[166] The courts worry greatly (and justifiably) about predictable rules of claim construction.[167] These rules are the fundamentals of the notice requirement: to the public at large and to potential infringers in particular. These constituencies need to know with high a degree of certainty, and without waiting for a judicial ruling, whether their planned commercial activities will or not be patent infringement. Invoking equity in decisions of infringement undermines emphasis on strict rules of claim interpretation.

A more specific issue in applying the DoE in biotechnology is the difficulty in proving that two biological products, one claimed, the other accused, perform "in substantially the same manner." Biology, even at this date, is still a black-box science, especially when it comes to understanding the mechanisms of action of biological substances, such as IFN, EPO, t-PA or anti-CD20 antibodies. These are substances that rapidly bind and unbind from receptors inside or outside the cell and, in the process, trigger or stop metabolic cascades. The difficulty in applying a three-way test developed for 19th century mechanical inventions to 21st century biotechnology materials has not escaped the court.[168]

With these considerations in mind, let us explore the role of equity in giving relief to inventors who have used claim terminology that, because of after-discovered embodiments, has gone from specific at filing to generic at infringement.[169]

1. Patent Holder Pleading the DoE

One result that stands out from Table 1 is that, in neither of the two *Plant Cases*, *Plant Genetic Sys. v. DeKalb Genetics Corp*.[170] or *Monsanto Co. v. Syngenta Seeds, Inc.*,[171] nor in *AbbVie Deutschland* did the *knowing* patent holders plead relief under the DoE.[172] In *Plant Genetic Sys.* and in *Monsanto*, a narrower claim

[165] *See, e.g.*, Genentech, Inc. v. Wellcome Found., 29 F.3d 1555, 1569 (Fed. Cir. 1994).

[166] *See, e.g.*, Warner-Jenkinson Co. v. Hilton Davis Chem., 520 U.S. 17, 28–29 (1997).

[167] *See* Gart v. Logitech, Inc., 254 F.3d 1334, 1339–43 (Fed. Cir. 2001).

[168] See, for example, Judge Lourie's concurring opinion in *Genentech v. Wellcome*, which we have discussed above. *See Wellcome Found.*, 29 F.3d at 1570.

[169] Applying the DoE to capture after-arising technologies has been discussed in Christopher A. Cotropia, "*After-Arising" Technologies and Tailoring Patent Scope*, 61 N.Y.U. Ann. Surv. Am. L. 151 (2005).

[170] 315 F.3d 1335, 1339, 1345 (Fed. Cir. 2003).

[171] 503 F.3d 1352, 1360–61 (Fed. Cir. 2007).

[172] *See AbbVie Deutschland*, 759 F.3d 1285, 1290 (Fed. Cir. 2014); *Plant Genetic Sys.*, 315 F.3d at 1339, 1345, *Monsanto*, 503 F.3d at 1360–61. We have already seen that the patent holder and the defendant in *Chiron Corp. v. Genentech, Inc.* stipulated to a broad

to dicotyledonous plant cells would have survived the invalidity challenge for lack of enablement of monocots.[173] In *AbbVie Deutschland*, a narrower claim to the 300 representative antibodies of the V_H3-type would also have survived the invalidity challenge for lack of written description.[174] There were no such claims, and their absence precluded any pleading under the DoE. While the DoE necessitates a factual inquiry based on the function-way-result test, these cases never had a chance to get to that stage—whatever the ultimate outcome.[175]

In the category of *unknowing* patent holders, *Genentech v. Wellcome*/t-PA, *Schering v. Amgen*/alpha-type IFN, *Amgen v. HMR*/EPO, or *BiogenIDEC*/anti-CD20 antibodies, the claims avoided invalidity attacks.[176] However, the claims were construed narrowly to avoid literal infringement.[177] The DoE was invoked in *Genentech v. Wellcome*, where the court evaluated the facts and found no equivalent infringement.[178] This seems like a just result. A decision based on scientific facts, concluding that two biological molecules with different structures (t-PA and FE1X t-PA) and differing half lives in the blood are not equivalent, is as fair a result as anyone can expect and hope for from our courts.

The DoE was not even addressed by the court in *Schering v. Amgen*.[179] The court may have been willing to at least explore the factual equivalency between the claimed alpha-1 subtype interferon and Amgen's consensus of several subtypes of the alpha type. Yet in the letter sent to the lower court,

claim construction, making unnecessary any analysis under the DoE. 363 F.3d 1247, 1252 (Fed. Cir. 2004). Had the claim survived the invalidity attack over intervening prior art, it would have been literally infringed.

[173] *Plant Genetic Sys.*, 315 F.3d at 1341; *see also Monsanto*, 503 F.3d at 1361–62.

[174] *See* Goldstein, *supra* note 18.

[175] *See Monsanto Co.*, 503 F.3d at 1356. At the time of this writing, there is no VH3-type product of AbbVie to *clinically* compare to Stelara. One of the antibodies described in the AbbVie specification, J695 (known as briakinumab), has not been approved anywhere. Non-clinical comparisons could perhaps have been carried out.

[176] *BiogenIDEC*, 713 F.3d 1090, 1094, 1096–97 (Fed. Cir. 2013); *Amgen II*, 457 F.3d 1293, 1296–97 (Fed. Cir. 2006); *Schering IV*, 222 F.3d 1347, 1349, 1355–56 (Fed. Cir. 2006); Genentech, Inc. v. Wellcome Found., 29 F.3d 1555, 1559–60, 1563–65 (Fed. Cir. 1994). The court in *Genentech, Inc. v. Wellcome Founation.* was quite forgiving of claim invalidity; it interpreted the claim term "t-PA" in a narrow fashion, precisely so as *not* to invalidate the patent. 29 F.3d at 1559–60, 1563–65.

[177] *BiogenIDEC*, 713 F.3d at 1094, 1096–97; *Amgen II*, 457 F.3d at 1296–97; *Schering IV*, 222 F.3d at 1349, 1355–56; *Wellcome Found.*, 29 F.3d at 1559–60, 1563–65.

[178] *Wellcome Found.*, 29 F.3d at 1566–67.

[179] *Schering IV*, 222 F.3d at 1355–56.

Schering conceded infringement of the narrowly construed claim, whether literal or under the DoE.[180]

In *Amgen v. HMR* and in *BiogenIDEC*, application of the DoE was further frustrated by two defenses that are also ubiquitous in biotechnology: amendment-based estoppels and argument-based disavowals.[181]

a. Amendment-Based Estoppels

Amendment-based Estoppels ("ABEs") are common in the prosecution of biotechnology applications, because, since the 2002 decision in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*,[182] estoppels arise no matter the substantive nature of the rejection from the USPTO.[183] After *Festo*, amendments or arguments in response to rejections under 35 U.S.C. § 112, 1st paragraph, give rise to estoppels.[184] Because rejections for lack of enablement or written description are among the most common ones for biotechnology claims,[185] a biotechnology patent applicant is fortunate if he has not created any ABEs during the passage of his application through the USPTO.

Amgen v. HMR illustrates how ABE eliminates most, if not all, possibilities of relief for a patent holder, who, in the mistaken belief that her newly discovered protein has a certain amino acid sequence, places the sequence into the claim in response to a rejection by the USPTO.[186] Once the amendment has been made (as in overcoming an ODP rejection), it will block an equitable plea that the owner should not be penalized for discovering *after the filing date* that the amino acid sequence was incorrect—even by one terminal amino acid that has no effect on the basic biology of the protein.

b. Argument–Based Disavowals

The argument-based disavowal in *BiogenIDEC* should not have created an estoppel broad enough to bar application of the DoE. Crucially, BiogenIDEC

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[180] *Id.* at 1349.

[181] *BiogenIDEC*, 713 F.3d at 1094–97; *Amgen II*, 457 F.3d at 1308, 1314–16.

[182] 535 U.S. 722 (2002), *cert. denied*, 553 U.S. 1093 (2008).

[183] *Id.* at 723–24. Before 2002 estoppels most often resulted from amendments or arguments made to overcome prior art. *See* Exhibit Supply Co. v. Ace Patents Corp., 315 U.S. 126, 133–34 (1942).

[184] *Festo Corp.*, 535 U.S. at 737. The *Festo* Court stated:

> A patentee who narrows a claim as a condition for obtaining a patent disavows his claim to the broader subject matter, whether the amendment was made to avoid the prior art or to comply with § 112. We must regard the patentee as having conceded an inability to claim the broader subject matter or at least as having abandoned his right to appeal a rejection. In either case estoppel may apply.

Id.

[185] *See id.* at 736–37.

[186] *Amgen I*, 314 F.3d 1313, 1352 (Fed. Cir. 2003).

did not amend any claims during the prosecution.[187] The Federal Circuit has taken a more lenient approach to argument-based disavowal than to amendment-based estoppel. This view is confirmed in *Conoco, Inc. v. Energy & Environmental International, L.C.*,[188] and *Cordis Corp. v. Medtronic Ave, Inc.*[189]

Notably, the court in *Cordis* refers to "arguments made to distinguish prior art references."[190] The arguments made by Biogen IDEC during prosecution were not made to distinguish prior art references, but to overcome a rejection for lack of enablement.[191] This suggests a less drastic view of the argument-based disavowal than occurred in *BiogenIDEC*. We are at least justified from *Conoco* and *Cordis* to propose that arguments used to overcome an enablement rejection (without accompanying claim amendments) should not create an absolute estoppel to the DoE during litigation *over after-discovered embodiments*. Since the question of estoppel comes up at the time of deciding infringement,[192] the court at that point in time has the benefit of placing the prosecution argument in context. The obvious innocence of a patent holder, who could not have had any knowledge during prosecution that a term (like "CD20") used specifically would come to acquire a generic meaning later in time, should play a major role in a more equitable decision under the DoE. We don't even have to ignore the disavowal: even if the disavowal results in a narrow interpretation of the claim for *literal* infringement purposes, it should not estop access to the DoE. Equity is invoked to alleviate precisely such injustice.[193] Even if the claims in *BiogenIDEC* were construed narrowly

[187] *BiogenIDEC*, 713 F.3d 1090, 1095–96 (Fed. Cir. 2013).

[188] 460 F.3d 1349 (Fed. Cir. 2006) ("Unlike amendment-based estoppel, we do not presume a patentee's arguments to surrender an entire field of equivalents through simple arguments and explanations to the patent examiner.").

[189] 511 F.3d 1157, 1177 (Fed. Cir. 2008) ("[A]n applicant can make a binding disavowal of claim scope in the course of prosecuting the patent, *through arguments made to distinguish prior art references.* Such argument-based disavowals will be found, however, only if they constitute clear and unmistakable surrenders of subject matter." (emphasis added)). Judge Plager in a dissent in *BiogenIDEC* disagreed that the disavowal of anything but the large loop epitope of CD-20 was "clear and unmistakable." *BiogenIDEC*, 713 F.3d at 1098. It is ironic that two judges concluded that something was "clear and unmistakable" and a third judge concluded that it was not. Since the court's opinion in *BiogenIDEC* was split 2-1, the disavowal could not have been so "unmistakable." Had Judge Plager convinced one more of his colleagues that the disavowal was far from clear, BiogenIDEC might have succeeded in proving literal infringement, a result that seems just.

[190] *Cordis*, 511 F.3d at 1177.

[191] *BiogenIDEC*, 713 F.3d at 1094.

[192] *See Conoco, Inc.*, 460 F.3d at 1364.

[193] *Id.* at 1363.

due to the disavowal,[194] the question of whether GSK's Arzerra and Biogen IDEC's Rituxan were *factually* equivalent (under the three-way test) in the treatment of CLL should at least have come up.

From this analysis of equitable considerations, we are led to conclude that, unless an unknowing patent holder survives prosecution without amendment-based estoppels or clear disavowals, capturing after-discovered embodiments through the DoE is an elusive endeavor. At the very least, in a situation where an argument-based disavowal of a yet unknown and undiscovered embodiment is innocently made, the court should provide access to the DoE. This possibility would give some equitable relief to those, who, by the very fact that they are pioneers, are unable to see the generic scope of what they have achieved until, years later, their competitors show it to the world and—through clever designing—commercialize an equivalent with impunity. Actually, the problem for our unknowing patent holder is worse. A competitor wanting to avoid the holder's claims will likely experiment long enough to find a biological molecule that is *not* an equivalent as a matter of fact. This is apparently what happened with the accused FE1X t-PA in *Genentech v. Wellcome*, where at least a pleading under the DoE came up and was resolved.[195] FE1X t-PA had far superior half-life in blood than human t-PA and was held not to be equivalent to t-PA.[196]

Thus, even without ABEs or disavowals, it is likely that a patent holder in biotechnology will not come out ahead invoking the DoE to capture after-discovered embodiments. His best chance at fairness is to convince the court to a broad interpretation of his claims *ab initio,* and to demonstrate literal infringement, setting aside any likely improved properties of his competitor's product. Let us look at the cases where this happened, and the role that equity played in the final outcome.

2. Infringer Pleading the Reverse DoE

In *U.S. Steel*/high crystallinity, *Scripps v. Genentech*/Factor VIII:C, and *Roche Palo Alto v. Apotex*/micelles, the generic interpretation of the claims led to findings of literal infringement.[197] None of these cases involve situations where a claim term started off as a species at filing only to end as a category

[194] *BiogenIDEC*, 713 F.3d at 1094. Or, as noted above (in analogy with the decision in *Schering v. Amgen*) were construed narrowly to not credit the inventors with inventions they did not make.

[195] Genentech, Inc. v. Wellcome Found., 29 F.3d 1555, 1557 (Fed. Cir. 1994).

[196] *Id.* at 1569.

[197] Roche Palo Alto LLC v. Apotex Inc., 531 F.3d 1372, 1378 (Fed. Cir. 2008); Scripps Clinic & Research Found. V. Genentech, Inc., 927 F.2d 1565, 1580 (Fed. Cir. 1991); U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1253 (Fed. Cir. 1989).

at infringement.[198] Nevertheless, they provide insight, especially because the accused infringer pled equity under the Reverse DoE.[199] The equitable pushback from the accused infringer (as its proactive use by a patent holder) is based on the concept of the *principle of the invention*.[200] In two of the cases, the court evaluated the principle as either a set of physico-chemical properties (*Scripps*[201] or as a fundamental contribution (*U.S. Steel*),[202] and in the third (*Roche Palo Alto*) it refused to deal with the principle at all because it was not expressly set forth.[203]

a. The Principle as a Set of Properties: Scripps and Factor VIII:C

Based on classic tenets of claim interpretation, the claim term "Factor VIII:C" in *Scripps* was interpreted to literally encompass the same factor by whatever method made, such as recombinant methods developed years later.[204] The accused infringer, Genentech, pleaded the Reverse DoE, arguing that, while literal, the infringement was not actual, in that the two products being

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[198] *Roche Palo Alto*, 531 F.3d at 1378; *Scripps*, 927 F.2d at 1580; *U.S. Steel Corp.*, 865 F.2d at 1253.

[199] *See Roche Palo Alto*, 531 F.3d at 1376–79; *Scripps*, 927 F.2d at 1580–81; *U.S. Steel*, 865 F.2d at 1249, 1253.

[200] *See Graver Tank*, 339 U.S. at 608–09; *Scripps*, 927 F.2d at 1581.

[201] *See Scripps*, 927 F.2d at 1581.

[202] *See U.S. Steel*, 865 F.2d at 1253.

[203] *See Roche Palo Alto*, 531 F.3d at 1377–79. In this Article we use the concept of "principle of the invention" following the reasoning of the court in *U.S. Steel*, which is based on the equitable analysis underpinning the DoE and the Reverse DoE. 865 F.2d at 1253. There is another meaning of "the principle," which has been proposed by Professor Liivak. Oskar Liivak, *Finding Invention*, 40 Fla. St. U. L. Rev. 57 (2012). Liivak's concept of "principle" is defined by "determining the structural features that are common to all of the disclosed embodiments." *Id.* at 80. This concept of "principle" seems to be similar if not identical with the judicial concept of generic written description. *See, e.g.*, Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997) ("A description of a genus of cDNAs may be achieved by . . . *a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added)). In this paper we do not equate the concept of principle of the invention with that of generic written description.

[204] *See Scripps*, 927 F.2d at 1580–81. The 1991 holding in *Scripps* is a harbinger of the 2003 decision in Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003). As we have seen, the *Amgen* court affirmed the long standing rule that a product claim (an EPO composition) need be enabled at the filing date by only one method of making it (e.g., using exogenous EPO genes), and will not be found invalid for failure to enable or describe other, later developed, methods (e.g., using endogenous EPO genes). *See id.* at 1331–32, 1355. *Amgen* and *Scripps* share the same basic ruling: Later developed methods of producing a product will not detract from generic construction of the product claim. *See id.* at 1355; *Scripps* 927 F.2d at 1580.

compared were far removed in principle.[205] The court in *Scripps* remanded to find out if the factor isolated from plasma was or not *in principle* the same factor as that made recombinantly.[206] The court commented that, if the specific activities and purity achievable by recombinant technology exceeded those available by isolation from plasma, then "depending on the specific facts of similarities and differences," these would be sufficient grounds for finding that the principles were different and would equitably negate actual infringement.[207] Seen from the opposite perspective, if the patent holder could prove that the specific activities and purities of the two products were not that different from each other, then actual infringement would be confirmed.[208]

It is refreshing to note the willingness of the Federal Circuit in *Scripps* to entertain an investigation of "the principle" based on readily-measurable physico- and bio-chemical properties of the two proteins. The court did not ask for an investigation or understanding of any fundamental contributions (as in *U.S. Steel*, below) or of any *scientific* principles.[209] The court simply wanted to see comparative data and understand the differences, if any. This is an excellent analysis, because it equates "the principle" with a collection of measurable properties. Such an approach would lead patent holders to compare the properties between the one product they isolated and patented, and those of after-discovered products that belong in the same category. This would be a generous yet measured approach to the question of capturing after-discovered bio-technologies with claims whose terminology has gone from specific at filing to generic at infringement.

b. The Principle as a Contribution: U.S. Steel and Crystallinity

The court in *U.S. Steel* focused on the invention of a fundamental property by Phillips Petroleum: high crystallinity.[210] In refocusing the inquiry from the improved properties of the accused polymer to the fundamental property of crystallinity common to the claimed and accused polymers, the court went to a deeper level of abstraction, transcended the specifically higher levels of molecular weight/high viscosity of the U.S. Steel polymer, and confirmed literal infringement.[211] The Federal Circuit recognized the difficulties in seeking the

[205] *See Scripps*, 927 F.2d at 1580–81.

[206] *Id.* at 1581.

[207] *Id.*

[208] *See id.* at 1580–81.

[209] *See id.* at 1581.

[210] *See* Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 1286–87 (D. Del. 1987).

[211] *See* U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1250, 1253 (Fed. Cir. 1989).

"principle" of an invention when the claims are to chemical compounds;[212] it praised the lower court for working this issue around the Reverse DoE:

> The reverse doctrine of equivalents can in some cases be seen as conceptually and linguistically difficult to apply when the claim is drawn to chemical compounds or compositions. The doctrine speaks of performance of a "function" in a substantially different "way." The district court here did not face that difficulty, having focused on *the "principle" of the contribution made by the inventor and found it unchanged in the accused product.*[213]

In this analysis, "the principle" is equated with the *contribution* made by the inventor, and whether it is or is not unchanged in the accused product.[214] The court also explained that, in order to evaluate if the contribution was or was not unchanged, it would be improper to compare the exemplified product with the accused product.[215] This is because the exemplified product went back to a time when the later technology had not yet been developed.[216] The court implied that this would (frequently, if not always) result in a finding of different principles,[217] stating:

> [D]efendants, as they did at trial, compare their product with only that disclosed in the 1953 [the first] application. Defendants' comparison fails, first, because, as they concede, the 1953 specification disclosed polypropylene having substantial crystallinity. Second, as correctly noted by the district court, the claim of the '851 patent issued on Phillips' 1956 [the second] application. We agree with the district court that the principle of the claimed invention . . . "is the production for the first time of crystalline polypropylene." [sic] and that defendants made no change at all in that principle.[218]

This is an even better result for our patent holders that that in *Scripps*. The court in *U.S. Steel* warned against comparing the properties of two products *separated in time*, when the technologies were not yet comparable.[219] Focusing on a fundamental contribution that transcends time is a more powerful tool for the pioneering patent holder.

U.S. Steel remains an outlying success among the precedents dealing with unpredictable technologies, like biotechnology. This is because the litigating parties rarely agree—and the courts rarely are able to conclude—what the "principle of the invention" really is. While both *Scripps* and *U.S. Steel* show the court willing to explore "the principle" in different ways, the exercise is

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[212] *See id.* at 1253.
[213] *See id.* at 1253 n.9 (emphasis added).
[214] *See id.* at 1253.
[215] *See id.*
[216] *See id.* at 1247–48.
[217] *See id.* at 1253.
[218] *Id.* (citation omitted).
[219] *Id.* at 1251.

not always simple. This is exemplified in the next case, *Roche Palo Alto LLC v. Apotex, Inc.*

c. Difficulties with the Principle: Roche Palo Alto LLC v. Apotex, Inc. *and Micelles*

In contrast to *U.S. Steel* and *Scripps*, the Court in *Roche Palo Alto LLC v. Apotex Inc.* was unwilling or unable to define "the principle" at all.[220] The accused infringer in *Roche* proposed "the principle" to be micelle formation, based on the *implicit* understanding of a person of ordinary skill in the art.[221] Perhaps Apotex was correct in its understanding of the *scientific* principle behind the operation of the Roche product and of its own product, but the Federal Circuit refused to adopt this proposition.[222] Hindsight elucidation of the *scientific* principle was insufficient for Apotex to succeed under the Reverse DoE.

It is clear from the cases that the Federal Circuit's invocation of equitable principles, either under the DoE (*Genentech v. Wellcome*/t-PA) or under the Reverse DoE (*Scripps v. Genentech*/Factor VIII:C; *Roche v. Apotex*/micelles; and *U.S Steel*/high crystallinity), involved evaluating "the principle of the invention." Given the court's willingness to entertain such evaluation, should we advise our biotech patent holders (whom we should always assume to be unknowing of yet-to-be-discovered embodiments) to try to elucidate and describe the principle(s) of their inventions at the filing date?[223] While the answer is not free from risk, we think so.

3. A Principle Should be Described in the Specification

We should note first that both decisions of literal infringement where infringers invoked "the principle of the invention" under the Reverse DoE, *U.S. Steel* and *Roche v. Apotex*, favored the patent holders, although for different reasons. The holder in *U.S Steel benefitted from a description* of the principle

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[220] *See* Roche Palo Alto LLC v. Apotex Inc., 531 F.3d 1372, 1378–79 (Fed. Cir. 2008).

[221] *Id.*

[222] *See id.*

[223] In *BiogenIDEC* and in *Schering* the claims were narrowly construed but the holders did not plead equity under the DoE, so we do not know how the court may have resolved the issue of principle. *See generally BiogenIDEC*, 713 F.3d 1090 (Fed. Cir. 2013); *Schering IV*, 222 F.3d 1347 (Fed. Cir. 2000). In other cases, such as in the decision of the lower court in *Stanford v. Roche* (antiretrovirals), the claims were construed broadly based on intrinsic evidence (such as statements in the specification) or extrinsic evidence (such as usage as a category at the filing date, or an admission by Roche, the party opponent), an analysis of a principle was not necessary to achieve infringement. *See Stanford II*, 563 U.S. 776 (2011). The defendant in *Stanford II* raised no reverse DoE plea because the case never reached the stage of infringement determination, and the lower court did not have any opportunity to analyze the concept of a principle. *Id.*

of crystallinity.[224] In contrast, the holder in *Roche benefitted from no description* of the principle of micelle formation.[225] Had Roche understood and described the principle of micelle formation, it might have run the risk of being held to that principle by the court, and it may have lost the case. Thus, description of a principle is not free from risk. Nevertheless, we believe that, if possible, it should be described. Of course, elucidating and explaining what constitutes "the principle" of an invention is a particularly difficult task in biology. This is especially so for the discoverer of a new substance or method of targeting it, who does not realize at the time that he may have discovered a whole category of substances or methods. Nevertheless, the rewards of at least trying to elucidate a principle are high. The prize may be literal infringement and a solid position to defend against a counterattack based on the Reverse DoE.

Weissmann in *Schering*, the inventors in *Amgen v. HMR*, and those in *BiogenIDEC* thought that all they had invented was one embodiment.[226] If Weissmann had described a "principle" or fundamental contribution (such as the underlying genetics of antiviral activity) in discovering the "alpha-type" genes, Schering could have demonstrated that his contribution was unchanged in the accused consensus interferons of Amgen, and that the consensus molecules embodied the principle. If Amgen had described the basic biology of EPO as not being dependent on the final amino acid Arg 166, it might have been able to argue that their contribution remained unchanged in the accused EPO.[227] And, Biogen IDEC could have asked the court to focus on a fundamental principle that was unchanged in Stelara: that binding to CD20 on lymphoma cell membranes helps treat CLL.

Even if it may be difficult to glean a principle or fundamental property from the discovery of one species, the discoverer should routinely suspect that she has hit upon more than one, and make additional efforts to investigate the existence of other species within a possible broader category. Short of asking our unknowing inventors to be seers, we should at least ask them to be as far-sighted as they can when they are preparing their patent specifications. They should assume that the single compound or gene they have just discovered in nature is eventually going to define a category of similar compounds.

In sum, given the advantages of relying on fundamental contributions and principles, we recommend describing a principle in the specification. If a smart

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[224] *See* U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1253 (Fed. Cir. 1989).

[225] *See Roche Palo Alto*, 531 F.3d at 1378–79.

[226] *See BiogenIDEC*, 713 F.3d 1090, 1090 (Fed. Cir. 2013); *Amgen II*, 457 F.3d 1293, 1293 (Fed. Cir. 2006); *Schering IV*, 222 F.3d 1347, 1347 (Fed. Cir. 2000).

[227] Figure 6 (and the claim which incorporated it) then might have been drafted in a more expansive format (with the Arg 166 optionally present or not) and a credible argument could have been made that the accused EPO of 165 amino acids was a literal infringement.

scientist or attorney can understand a principle (e.g. "crystallinity" or "CLL treatment with anti-CD20 antibodies"), they should describe it. Invoking a principle may lead to a broad claim construction, allow the capture of after-discovered embodiments by literal infringement, and defeat a defense under the Reverse DoE. Even if the claim is construed narrowly, the description of a principle may assist in achieving success under the DoE.

Let us now ask what—if any—were the winning strategies used by *unknowing* patent holders that succeeded in obtaining broad construction of their claims at the outset of the case, and thus literal infringement by after-arising embodiments. This is the golden ring of our pursuits. While the answers provide strategic insight to the specific problem of after-*discovered* embodiments in biotechnology, they are far from uniform.

C. Obtaining Broad Claim Construction at the *Markman* Stage[228]

1. The Quest for Literal Infringement

The holders in *U.S. Steel*, *Scripps v. Genentech* and *Roche* succeeded in obtaining rulings of literal infringement at the *Markman* stage.[229] However, none of these precedents directly translates to the main question of this paper, i.e., how to help unknowing patent holders, whose specific filing date terminology has become generic, capture after-discovered biological materials that fall within the genus. None of these cases deals with similar situations. The holders in *U.S. Steel* and in *Roche Palo Alto LLC v. Apotex, Inc.* claimed, respectively, crystalline polymeric substances and drug formulations. The accused infringers commercialized, respectively, the same substance (crystalline polypropylene) and the same drug formulation, albeit with higher viscosities or lower amounts of stabilizers. The infringer in *Scripps v. Genentech* used the same Factor VIII:C substance as claimed, albeit produced by a different method than that described in the patent.[230] In all three cases, the accused substances were the *same* substances or compositions as those claimed. Perhaps they had been improved, but not sufficiently so as to be *new* substances. In contrast, the accused consensus IFN-alpha types in *Schering*, or the antibody against the small CD20 loop in *BiogenIDEC*, were *new* substances, not mere improvements or modifications of claimed ones. Should we therefore conclude that the courts seem unwilling to extend the rules of broad claim construction to dominate new substances or compositions? We do not believe so.

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[228] In *Markman v. Westview Instruments, Inc.* the Supreme Court held that patent claim construction is an issue of law. 517 U.S. 370, 391 (1996). Lower courts routinely hold *Markman* hearings to decide on claim construction ahead of trial.

[229] *See Roche Palo Alto*, 531 F.3d at 1381; Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1584 (Fed. Cir. 1991); *U.S. Steel Corp.*, 865 F.2d at 1253–54.

[230] *Scripps*, 927 F.2d at 1574–75.

In the last case we reviewed in the group of holders who succeeded in obtaining generic claim construction, *Stanford v. Roche*, the later-developed protease inhibitors were new and different substances than (and not mere improvements of) the filing-date reverse transcriptase inhibitors. The crucial distinction in *Stanford v. Roche* was that the lower court interpreted the claim term "antiretroviral agents" to define a *category* of compounds.[231] The ordinary and customary meaning of the term *at the filing date* was that of a category. The court felt reassured in this conclusion by the fact that Roche itself used the term "antiretroviral agent" to describe its own, later developed protease inhibitor-based antiretrovirals.[232] The lower court stated:

> The term in question may be a category, the contents of which expand over time. It is clear that the term "antiretroviral agents" describes a *category of pharmaceuticals* because Roche itself uses the term antiretroviral agents to describe new drug therapies that were unveiled in 1995. It is clear from the publication history and the prolific research being conducted by HIV researchers on protease inhibitors, that a person of ordinary skill in the art would have known that *the category of "antiretroviral agents*" would only expand over time to include these new agents. * * * Since the ordinary and customary meanings of the words are not dependent on time, the court finds no reason to limit the scope of "antiretroviral agents" to those agents available when the patentee applied for the patent. The claims can therefore be construed to cover later developed technology that was unavailable but known at the time of the invention. In sum, even if specific agents were not available in May 1992, the conceptual framework for them had been laid and they were reasonably known to those skilled in the art.[233]

The lesson from *Stanford v. Roche* is that, when the claim term used *at filing* already defines a category of compounds, the court is more likely to interpret the term at infringement time in a generic sense than in a specific one.

Short of presciently using terms of *category* at filing, as in *Stanford v. Roche*, how else could our inventor of what seems like a single new substance, receive a broader claim construction at the *Markman* stage to achieve literal infringement by after-discovered embodiments? We can think of three possible answers, one self-evident and two not so evident.

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[231] *See* Bd. of Trs. of Leland Stanford v. Roche Molecular (Stanford I), 528 F. Supp. 2d 967, 980 (N.D. Cal. 2007).

[232] *Id.*

[233] *Id.* at 980–81 (emphases added). With more dubious logic, the court, noting that the Stanford specification stated the following: "Antiretroviral agent, as used herein, includes any known antiretroviral agent including, but not limited to, dideoxynucleosides," concluded that, "[t]he statement is inclusive and seeks to include, without limiting the scope, agents known at the time. The specific inclusion of known agents presupposes the existence of agents unknown at the time that may also be considered to be antiretroviral agents." *Id.* at 979–80. It is not at all clear how inclusion of *known* dideoxynucleosides implies *unknown* and later-developed protease inhibitors.

The self-evident (and somewhat ironic) answer is to provide as much written description and enablement as necessary for a genus of compounds. The scope of the supporting disclosures in the specification of a patent application, taken together with the prior art, are fundamental guideposts for the availability of broad claims.[234] The more extensive the written description, the broader the claims, and the higher the opportunity for obtaining and sustaining claims that can be literally infringed by later-discovered embodiments, unknown and unforeseeable at the filing date. If an inventor is able to describe the common structure of a genus of biological materials together with a structure-function correlation, the better the chance to obtain and later assert broad claims.

We label this answer ironic, because the inventors of novel substances, their genes or uses, such as IFN or uses of antibodies to CD-20, were, by definition, pioneers in their fields. While their accomplishment in discovering hitherto unknown substances or uses would eventually prove to be groundbreaking, they did not spend any further time searching for additional examples of their inventions, such as other IFNs or other CD-20 epitope loops. They were content (and likely driven by their patent attorneys) to rush to the USPTO and file as soon as possible.[235] Thus, it is not realistic to ask them to slow down with their filings until they have found other examples or (even worse) figured out the common structure underlying a genus of multiple examples. There ought to be alternative answers to the question of obtaining broad claim construction.

We believe that our second and third answers, although not self-evident, may provide a path to broad claim construction at the outset. Our two additional answers are (1) routinely invoking equity at the *Markman* in cases of after-discovered embodiments and/or (2), using a legal or legal-equitable analysis based on 35 U.S.C. § 112, 6th paragraph.

2. Routinely Invoking Equity at the Markman *Stage*

We have seen that the Federal Circuit is not against invoking the "principle of the invention" when applying the DoE or the Reverse DoE. We propose that the evaluation of principle be carried out at the *Markman* stage. Our review of the biotechnology precedents shows that, so far, the results along these lines have been disappointing. The patent holders in *BiogenIDEC* and *Schering*, in pleading for broad claim construction, invoked the principle of the invention, although unsuccessfully.[236] Biogen IDEC phrased it as a "novel

[234] *See, e.g.*, Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

[235] *See id.* at 1351.

[236] *See BiogenIDEC*, 713 F.3d 1090, 1097 (Fed. Cir. 2013); *see also Schering IV*, 222 F.3d 1347, 1356 (Fed. Cir. 2000).

aspect" that they had recognized,[237] but to no avail: the court was so focused on the disavowal issue that the argument on "principle" got lost.[238] The *Schering* court did recognize Weissmann's pioneering work on interferons of the alpha type.[239] The court seemed to understand that Weissmann had opened the door to more than one subtype, but still construed his claims narrowly.[240] As in *BiogenIDEC*, the analysis of claim scope was governed by standard principles of claim construction; the court's attention in *Schering* was focused principally on what was enabled by the DSM deposits.[241] The patent holder did not urge the court to refocus the analysis towards contributions or principles.

The decisions in *BiogenIDEC* and *Schering* illustrate that a discussion of principle does not normally succeed at the stage of claim construction. It does not matter if patent holders explain that it is unfair to construe claims narrowly and thus favor the infringers, who in all likelihood have benefitted from their discovery and have designed their products to literally avoid the claims.[242] Arguments in equity do not routinely come up at the *Markman* stage.[243] Nevertheless, since the court has efficiently used the concept of the principle at the infringement stage[244] and, through decisions like *Scripps*, *U.S. Steel* and *Roche v. Apotex*, has given us useful guidelines on how to go about doing so,[245] we believe that the court should openly look at the equities during claim construction. This is especially so when it is dealing with pioneering patent holders in rapidly developing biotechnologies.

The avoidance of equity at the *Markman* stage is based on the strict separation of law and equity.[246] It presupposes that claim construction is a pure matter of law, and claim application during evaluation of infringement

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[237] *See BiogenIDEC*, 713 F.3d at 1101. This "novel aspect" may be equated to the fundamental contribution of crystallinity invoked in *U.S. Steel Corp. v. Phillips Petroleum Co.* 865 F.2d 1247, 1249 (Fed. Cir. 1989).

[238] *See BiogenIDEC*, 713 F.3d at 1095.

[239] *Schering IV*, 222 F.3d at 1349 ("The '901 patent resulted from the pioneering work of Dr. Charles Weissmann in the fields of immunology and molecular biology in the late 1970s.").

[240] *Id.* at 1353–54.

[241] *Id.*

[242] Andrew B. Dzeguze, *Did* Markman *And* Phillips *Answer The Right Question? A Review of the Fractured State of Claim Construction Law and the Potential Use of Equity to Unify It*, 15 Tex. Intellect. Prop. L.J. 457, 472 (2007).

[243] *Id.* at 488.

[244] *Id.* at 484.

[245] *See* Roche Palo Alto LLC v. Apotex Inc., 531 F.3d 1372, 1377 (Fed. Cir. 2008); Scripps Clinic & Research Found. V. Genentech, Inc., 927 F.2d 1565, 1581 (Fed. Cir. 1991); U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1253 (Fed. Cir. 1989).

[246] Dzeguze, *supra* note 242, at 462.

under the DoE is a pure matter of equity.[247] If things were so simple. The court has not shied away from commingling the two, at times expressly admitting it (see *Texas Instruments v. U.S. International Trade Commission*,[248] below), and at other times not.[249] For example, before finding invalidity, the court in *AbbVie Deutschland* concluded that the claims were broad enough to read on a class of antibodies that included the accused Stelara, but that the specification did not describe the Stelara class.[250] The court did not base this construction on legal principles of intrinsic and extrinsic evidence, but mingled claim construction with claim *application*.[251] The consideration of the accused product implicitly balanced the rights of the patent holder with those of the accused infringer.[252] This is the kind of equitable analysis in which the court engages when it applies (or not) the DoE.

Other commentators have also proposed that equity should play an important role during the *Markman* stage.[253] For example, Professor Dzeguze has argued that claim construction law is "fractured" and that equity should be used to heal it.[254] Dzeguze cites to several Federal Circuit cases where the court has implicitly used equity during claim construction.[255] For example (he notes), the court has indicated that the accused device can and should be consulted as part of the claim construction process.[256] Dzeguze states that this "plainly opens the door to shaping the construction in a manner to benefit one side or the other based on the court's sense of the equities."[257] Dzeguze concludes:

> What [evaluating equities at the *Markman* stage] would allow . . . is the open consideration of things such as the accused infringing device, the inventive process, the economic impact of the invention, and the impressions and views of others in the industry as evidence of the proper scope of the patent. This broadening of the available evidence would ensure that the court was given a complete record to arrive at a construction consistent with the fullest appreciation of the invention's true scope. Effectively, the courts would be left in their familiar role of analyzing competing interests and assessing where necessary, credibility—skills that are highly developed among the lower bench.[258]

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[247] *Id.*

[248] 805 F.2d 1558, 1562 (Fed. Cir. 1986).

[249] Dzeguze, *supra* note 242, at 484.

[250] AbbVie Deutschland GMBH & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1298 (Fed. Cir. 2014).

[251] *Id.* at 1285.

[252] *Id.*

[253] Dzeguze, *supra* note 242, at 472.

[254] *Id.* at 482–83.

[255] *Id.* at 484.

[256] *Id.* at 485. That is precisely what the court did in *AbbVie Deutschland* when it consulted the accused Stelara antibody during claim construction. 759 F.3d at 1292.

[257] Dzeguze, *supra* note 242, at 485.

[258] *Id.* at 488.

We believe that equity should play an important role during construction of biotechnology claims that use words which, while denoting species at the filing date, have become categories at infringement time. The courts should not wait to look into equity at claim application time but should do so as part of the *Markman* exercise. The courts should focus on the fundamental contribution of the inventors—and their patent holders—and weigh competing interests between them and the accused infringers. The courts should ask questions about the accused infringing molecules or methods, the process by which the claimed invention came to be, the impact of the invention on society, and the impressions and views of others in the industry. Invoking *U.S. Steel*, they should further ask if the fundamental contribution remains unchanged in the accused product.[259] If the answer is, yes, the courts should construe the claims broadly and hold that a prima facie case of literal infringement has been made out.

3. 35 U.S.C. § 112, 6th Paragraph and Biotechnology Claims

a. Legal Analysis

Our third answer to the question of broad claim construction at the *Markman* involves *Williamson v. Citrix Online, LLC*,[260] an interesting legal development in the application of 35 U.S.C. § 112, 6th paragraph.[261] The Federal Circuit held in *Williamson* that the absence of the words "means for" does not preclude applying means plus function analysis;[262] there is no longer a strong presumption to that effect.[263] This development may help biotechnology holders achieve a generic interpretation of combination claims. Admittedly, while the biotechnology claims reviewed in this paper are not of the means plus function type, *Williamson* suggests to us that the use of such claims in biotechnology should be explored. This is especially the case when the situation is one where the "means" described in the specification at the filing date has changed by the time of infringement. By then, the "means" used by the accused infringer is usually quite different.

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[259] *See* Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 1253 n.9 (D. Del. 1987).

[260] 770 F.3d 1371 (Fed. Cir. 2014); *see supra* note 14 and accompanying text.

[261] 35 U.S.C. § 112, 6th (2006). The statute states:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Id.

[262] *Williamson*, 770 F.3d at 1379.

[263] *See id.*

Assume that *Schering*'s inventor Weissman had obtained a combination claim as follows: "A pharmaceutical composition that comprises an antivirally-effective amount of an interferon of the alpha type in combination with a pharmaceutically inert carrier."

Under *Williamson*, the term "interferon of the alpha-type" could (and should) be construed to cover the "corresponding . . . material . . . described in the specification and equivalents thereof."[264] The material described in the specification is the DSM deposit made by Weissman, which encoded for interferon alpha, subtype-1. The focus then is on the statutory phrase "and equivalents thereof." The claim construction argument to be made is that the claim term "alpha type" should be construed to cover all manners of alpha interferons that are structurally equivalent to the ones on deposit. The Federal Circuit has used the insubstantial differences test of the DoE when analyzing structural equivalence under § 112, 6th paragraph.[265] The main difference is that, in the case of an analysis under § 112, 6th, the "function-way-result" three-part test becomes a "way-result" two-part test, because the function of the structural equivalent needs to be *identical* to that of the "equivalent thereof."[266] Thus, the structural equivalents of the described IFN-alpha subtype-1 must perform the identical function, in substantially the same manner, to achieve substantially the same result as the subtype-1 on deposit at the DSM.[267] If Weissman can convince the court that the claim should be construed broadly enough to read on several IFN-alpha subtypes, including a consensus of IFN-alpha subtypes, he would come out of *Markman* with a claim that is literally infringed.

b. Equitable Analysis

The Federal Circuit has experience in the use of § 112, 6th paragraph, as applied to after-arising technologies. In *Texas Instruments, Inc. v. U.S. International Trade Commission*,[268] the court addressed the issue of changing means in rapidly developing technologies.[269] The issued claims were to an electronic calculator drafted in means plus function format ("input

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[264] 35 U.S.C. § 112, 6th. Of course an even stronger case for invoking § 112, 6th would be to draft the claim as follows: "A pharmaceutical composition that comprises, in combination: drug means for ameliorating a viral infection by using an antivirally effective amount of an IFN of the alpha type and carrier means for inertly carrying said IFN into a human body." Such a claim is *presumed* to require analysis under § 112, 6th paragraph.

[265] *See, e.g.*, Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc., 145 F.3d 1303, 1309 (Fed. Cir. 1988).

[266] *See, e.g.*, Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1320–21 (Fed. Cir. 1999).

[267] *Id.* at 1320–21.

[268] 805 F.2d 1558 (Fed. Cir. 1986).

[269] *Id.* at 1569.

means . . . electronic means . . . memory means, . . . means for providing a visual display . . . .").[270] The specification contained a detailed description of the preferred means of performing each function of the claims at the filing date.[271] In the seventeen years between the first filing of the patent application and the filing of the complaint with the ITC, each of the means had undergone technological advance.[272] The court expressly admitted that, in looking at after arising technologies, it was commingling law and equity:

> While the scope of patent claims under section 112 paragraph 6, is a legal determination, it is not devoid of equitable considerations, particularly when determining the breadth of "means" claims *on complex and rapidly-evolving technologies*. Thus it has long been recognized, as affirmed in *Graver Tank,* . . . [that]: ". . . Consideration must be given to the purpose for which an *ingredient* is used in a patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform."[273]

The "complex and rapidly-evolving technologies" mentioned by the court are precisely the technologies invented by our pioneering and unknowing biotech inventors, e.g., the first gene for IFN-alpha, or the first anti-CD20 antibody for treatment of CLL.[274] Significantly, the Federal Circuit in *Texas Instruments* cites *Graver Tank*,[275] a Supreme Court case that did not deal with means plus function claims to mechanical inventions, but with run-of-the-mill composition claims drawn to electric welding mixtures.[276] The Supreme Court in *Graver Tank* talks of "ingredients," and their purpose, quality and function.[277] And, we know that the Federal Circuit is no stranger to the special status of rapidly evolving technologies in the biologic realm: it has even formulated a special type of evaluation for the enablement of such technologies, which it called "nascent technologies" in *Genentech, Inc. v. Novo Nordisk, A/S.*[278] Thus, it would not be out of the ordinary for the court to recognize the unique status of rapidly-developing bio-technologies and consider equity under § 112, 6th paragraph, at the *Markman* stage. In comparing the IFN-alpha type deposited

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[270] *Id.* at 1561.

[271] *Id.*

[272] *Id.* at 1561–62.

[273] *Id.* at 1569 (emphasis added) (citation omitted).

[274] *Id.*

[275] *Id.*

[276] Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 610, *reh'g denied*, 340 U.S. 845 (1950). For example, claim 18 of Patent No. 2,043,960 involved in *Graver Tank* was as follows: "A composition for electric welding containing a major proportion of alkaline earth metal silicate. [sic] and being substantially free from uncombined iron oxide and from substances capable of evolving gases under welding conditions." U.S. Patent No. 2,043,960, cl. 18 (filed Oct. 9, 1935).

[277] *Graver Tank*, 339 U.S. at 609.

[278] 108 F.3d 1361 (Fed. Cir. 1997).

at the DSM (which was the alpha-1 subtype) with other alpha subtypes, including a consensus of several subtypes (such as that of Amgen) the Court should compare the "purpose, quality and function" of the described IFN-alpha subtype-1 with the same three qualities of the accused consensus of alpha-types of Amgen. By applying to after-discovered bio-technologies the mix of law and equity it used in *Texas Instruments*,[279] the court might reach the conclusion that infringement has occurred.

In discussing the use of equity in claim construction under 35 USC § 112, 6th paragraph, the Federal Circuit in *Texas Instruments* was aware of the tension between the public notice function of the claims and the interests of "serving the greater interests of justice," stating:

> [Equivalency] constitutes a deviation from the need of the public to know the precise legal limits of patent protection without recourse to judicial ruling. *For the occasional pioneering invention, devoid of significant prior art*—as in the case before us—whose boundaries probe the policy behind the law, there are no immutable rules. We caution that the incentive to innovation that flows from "inventing around" an adversely held patent must be preserved. To the extent that the doctrine of equivalents represents an exception to the requirement that the claims define the metes and bounds of the patent protection, we harken to the wisdom of the Court in *Graver Tank,* that the purpose of the rule is "to temper unsparing logic" and thus to serve *the greater interest of justice.*[280]

We conclude that to "serve the greater interest of justice," the Federal Circuit is quite willing to evaluate equitable considerations when construing claims at the *Markman*, "especially for the occasional pioneering invention."[281] The court here is describing precisely our pioneering biotech inventors. The Federal Circuit is well aware that equity may have to be invoked in doing justice to complex and rapidly moving inventions, including in the chemical and biological arenas.

Conclusions and Practice Tips

Capturing after-discovered embodiments in biotechnology patents is not a straightforward exercise. Our pioneering inventors are charged with knowing the latest state of the art and all of its foreseeable embodiments, or else their generic claims may be invalidated under 35 U.S.C. § 112, 1st paragraph, for lack of written description or enablement. If our inventors (and the art) are unknowing of yet-to-be-discovered embodiments, then it is likely that their claims will be construed narrowly to what they enabled and described at the filing date, and that they will not likely be literally infringed. Our inventors would then be well advised to invoke equity under the DoE for any surviving

[279] *Texas Instruments*, 805 F.2d at 1563, 1569, 1571.
[280] *Id.* at 1572 (emphasis added).
[281] *Id.*

or narrowly construed claims. However, as seems likely, if their competitors have designed improved substances that are not factually equivalent to the originally claimed ones, then the claims will not be infringed under the DoE.[282] Their best strategy then is to try to achieve generic construction of their claims at the outset of the case. They may be able to do this by invoking equity at the *Markman* stage, either directly or by the use of 35 U.S.C. § 112, 6th paragraph.

We next provide some guidance to inventors and their attorneys at the various stages of the patent process, from scientific discovery to litigation. Scientists, patent applicants, and litigators in biotechnology should heed these lessons, and choose and construe their claim terms carefully so that they—like Humpty Dumpty—may be the "masters of their words."[283]

A. At the Drafting Stage

Use generic nomenclature. Biotechnologists should assume that, when they discover a new substance, they have only seen the tip of an iceberg that will reveal its underside as the years go by. It is wise not to draft patent specifications as limited to just one substance, or one epitope, or one type of antibody. Applicants, like the ones in *Stanford v. Roche*, should contemplate a broader category and use appropriate language.[284]

Describe a principle or fundamental contribution. If they are able, inventors and attorneys should search for a principle or fundamental contribution and describe it—or at least invoke it—as the patent holders did in *U.S. Steel*.[285]

Describe prophetically but, if not possible, reduce to practice representative examples. If it is not possible to define a structure-activity correlation to meet the written description requirement, applicants and their attorneys should try to define a genus by describing prophetically as many species within the genus as possible. Sometimes, as in *AbbVie Deutschland*,[286] it is not possible to describe other embodiments prophetically without first reducing them to practice. They should then reduce to practice representative examples in as many categories as foreseeable.

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[282] Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1564 (Fed Cir 1994).

[283] Lewis Carroll, Through the Looking Glass and What Alice Found There 253 (1896) ("'When *I* use a word,' Humpty Dumpty said, in rather a scornful tone, 'it means just what I choose it to mean—neither more nor less.' 'The question is,' said Alice, 'whether you *can* make words mean so many different things.' 'The question is,' said Humpty Dumpty, 'which is to be master—that's all.'").

[284] *See Stanford IV*, 131 S. Ct. 2188, 2192, 2193 (2011).

[285] *See* U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1250 (Fed. Cir. 1989).

[286] *See* AbbVie Deutschland GMBH & Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1301 (Fed. Cir. 2014).

Be creative in the use of § 112, 6th paragraph. Williamson allows arguments under 35 U.S.C. § 112, 6th paragraph, even when the claim does not contain the language "means for."[287] Applicants should include combination claims. By careful use of such claims and arguments, it may be possible to achieve literal infringement of structurally-equivalent biological materials. Furthermore, following the plaintiff's pleas in *Texas Instruments*, holders should argue that equity demands that the court find after-discovered embodiments to be infringements.[288]

Include claims of different scope. Unlike the applicant in *AbbVie Deutschland* (who failed to claim the distinct class of V_H3-type antibodies[289]) include claims of intermediate scope that will hopefully not be invalidated for lack of enablement or written description. Intermediate claims will give the patent holder a chance to invoke the DoE.

B. At the Prosecution Stage

Keep up with the science. While applicants should not worry about the specifics of what is yet to be discovered, they need to be up to date on the literature so that they can be sure that, if new technology has been developed recently, it is incorporated into their specifications. Patent attorneys and their clients need to remain ever vigilant to developments in the literature, as the parties in *Chiron v. Genentech* were not.[290] They should update their provisional specifications and, if necessary, file new CIP applications with additional embodiments so that the USPTO (and eventually a judge) will conclude that they made a generic invention.[291]

Avoid estoppels and disavowals. Applicants do not always have control over the creation of estoppels and disavowals during prosecution. They should obviously try to minimize them by using careful language and/or by expressly disagreeing with an Examiner's overtly narrow interpretation of their claims; that way, they may avoid dubious disavowals, as the applicants in *BiogenIDEC* did not do.[292]

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[287] *See* Williamson v. Citrix Online, LLC, 770 F.3d 1371, 1378 (Fed. Cir. 2014), *superseded by* 792 F.3d 1339 (Fed. Cir. 2015).

[288] *See* Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n, 805 F.2d 1558, 1569 (Fed. Cir. 1986).

[289] *AbbVie Deutschland*, 759 F.3d at 1291, 1302.

[290] *See* Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1251 (Fed. Cir. 2004).

[291] And applicants should immediately correct their nomenclature if they realize that they made a mistake, as the applicants in *Bayer CropScience* failed to do. Bayer CropScience AG v. Dow AgroSciences LLC, 728 F.3d 1324, 1324–25 (Fed. Cir. 2013).

[292] *See BiogenIDEC*, 713 F.3d 1090, 1096 (Fed. Cir. 2013).

C. At the Litigation Stage

Be thorough in pre-litigation diligence. At the onset of the case, the litigators should leave no stone unturned in their attempts to try to argue that the claimed invention is generic. The patent holders in *Schering v. Amgen* failed to do this when they did not instruct that all of the DSM deposits be immediately sequenced;[293] such an action would have demonstrated that Weissmann's invention was more generic than just the alpha-1-subtype.

Distinguish between amendment-based estoppels and argument-based disavowals. If the prosecution history leads to amendment-based estoppels, the holders, as those in *Chiron v. Genentech*, may not have much leeway in arguing for a broad range of equivalents.[294] However, if the history only reveals an argument-based disavowal, the litigators should forcefully argue that equity demands that, similarly to *Hogan* and its progeny,[295] the patent holders not be seen as having disclaimed embodiments that no one knew existed. And even if disavowal exists due to a rejection not based on prior art, and, even if it leads to a narrow claim interpretation for literal infringement purposes, the patent holder, citing *Conoco*, should still argue the DoE.[296]

Argue the principle at the Markman and at the nfringement stages. If the patent applicants have described a principle in their specification, they will have the necessary support when the *Markman* stage comes, or at least when they have to repel an accused infringer's arguments under the Reverse DoE. Demonstrating what the principle of a biotech invention is—and pleading for equity—may not be easy at the *Markman* stage. The situation is ideal, however, when a claim term has become generic over time and is being asserted against an after-discovered embodiment. Following *Texas Instruments*, argue equitable principles at the *Markman* stage, especially in rapidly moving technologies and for unknowing and faultless patent holders, who did not self inflict any wounds.[297] The patent holder should point out that the fundamental principles of the claimed invention and the accused substance or method are the same. She should argue that the accused product embodies unchanged the fundamental contribution of her invention. This succeeded in *U.S. Steel*, it was considered

[293] Schering Corp. v. Amgen, Inc., 222 F.3d 1347, 1354 (Fed. Cir. 2000).

[294] *See* Chiron Corp. v. Genentech, Inc., 266 F. Supp. 2d 1172, 1181, 1186 (E.D. Cal. 2002).

[295] *In re* Hogan, 559 F.2d 595, 601 (C.C.P.A. 1977).

[296] *See* Conoco, Inc. v. Energy & Environmental International, L.C., 460 F.3d 1349, 1363 (Fed. Cir. 2006).

[297] Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n, 805 F.2d 1558, 1569 (Fed. Cir. 1986).

feasible in *Scripps v. Genentech*, and may be a formula for success in the next biotech litigation trying to capture after-discovered embodiments.[298]

Argue the DoE. If the court construes the claim narrowly and not literally infringed, the patent holder should at least argue for a generous DoE, as the holders in *BiogenIDEC* and *Schering* did not do.[299] In framing such an equitable remedy, the litigators should ask the court to weigh the fact that the claim is asserted against a later-discovered embodiment.

* * *

We started this Article with the tale of the 1957 discovery of interferon by Isaacs. We wondered if the courts during infringement litigation would be sympathetic to the fact that these scientists opened a large field of basic research and commercial development. We wondered if the broadly worded claims they obtained in the '222 patent would be construed to capture a category of similar substances or only the one substance they discovered and isolated. Specifically, would the claims capture the commercialization of fish IFN-beta used for veterinary purposes? Applying our practice tips, we are now ready to provide some tentative answers.

First, let us admit that the four claims of the '222 patent are hopelessly invalid under 35 U.S.C. §§ 101 and 102.[300] Instead, let us assume that Isaacs had obtained a method of treatment claim, such as:

> **Claim 1.** A method of treating a viral infection in a subject, which comprises the step of intravenously administering to the subject an isolated and purified form of interferon in an amount sufficient to achieve antiviral activity.

Such a claim is not easily vulnerable to attacks under 35 U.S.C. §§ 101 and 102,[301] and is similar to that in *BiogenIDEC*: both are method-of-treatment claims and both use terms ("interferon," "CD20") that were once believed to be specific to one substance but later turned out to be a category of substances.[302]

Isaacs will face an uphill struggle to have his hypothetical method-of-use claim construed broadly—although the hill is not as steep as one might expect. The specification of the '222 patent makes it clear that Isaacs contemplated that he had discovered a *category* of substances. He described various species, human, monkey, and chicken. He concluded that the common denominator among them was their antiviral activity. Isaacs's usage of the term "interferon"

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[298] U.S. Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1253 (Fed. Cir. 1989); Scripps Clinic & Research Found. V. Genentech, Inc., 927 F.2d 1565, 1581 (Fed. Cir. 1991).

[299] *See BiogenIDEC*, 713 F.3d 1090 (Fed. Cir. 2013); *Schering IV*, 222 F.3d 1347 (Fed. Cir. 2000).

[300] *See supra* note 4 and accompanying text.

[301] 35 U.S.C. §§ 101–102 (2006).

[302] *BiogenIDEC*, 713 F.3d. at 1096.

is like the usage of the term "antiretroviral agents" in *Stanford v. Roche.* They both denote *categories* at the filing date.

And, just like the court in *Stanford v. Roche* distinguished *Schering v. Amgen*,[303] so can Isaacs. Weissmann did not describe more than the subspecies-1 of the alpha species of interferon genes.[304] Weissmann did not contemplate that he had made a generic invention that encompassed more than one subspecies of the alpha-type. In contrast, Isaacs could successfully argue that his invention was generic; he even said so. As long as no amendment-based estoppel or argument-based disavowal occurred during prosecution (as in *HMR v. Amgen* or *BiogenIDEC*)[305] Isaacs could credibly argue that his claim should be construed broadly.[306]

Isaacs should try to convince the court at the claim construction stage to interpret his term "interferon" broadly, based on equity, citing *Texas Instruments* and *Graver Tank*.[307] While his (newly defined) claim is a method and not a means-plus-function claim, 35 U.S.C. § 112, 6th paragraph, does contemplate a "step for performing a specified function";[308] so, following *Williamson*, Isaacs should urge interpretation of the claim under 35 U.S.C. § 112, 6th paragraph.[309] He should also argue at the *Markman* stage that the "specified function" in the claim (i.e., achieving antiviral activity) can be carried out by structurally equivalent molecules. Arguing equity at the *Markman*, Isaacs should explain "the principle" of his invention: the discovery of a class of molecules that share a fundamental property, i.e., antiviral activity, just like Phillips Petroleum, in *U.S. Steel*, discovered the "substantial crystalline content" of their polymers.[310]

Because it turns out that Isaacs discovered what is known today as Type I interferon, he might, in accordance with *Schering v. Amgen*, be limited

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[303] *Stanford I*, 528 F. Supp. 2d 967, 981–82 (N.D. Cal. 2007).

[304] *Id.*

[305] *See Amgen I*, 314 F.3d 1313, 1358 (Fed. Cir. 2003), *cert. denied*, 550 U.S. 953 (2007); *BiogenIDEC*, 713 F.3d at 1097.

[306] We did not review what is clearly the lengthy prosecution history of the '222 patent (from its priority date in 1958 to its issuance in 1972). Surely such review would need to be undertaken when preparing for litigation.

[307] Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n, 805 F.2d 1558, 1569 (Fed. Cir. 1986); Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608, *reh'g denied*, 340 U.S. 845 (1950).

[308] 35 U.S.C. § 112, ¶ 6 (2006).

[309] *See* Williamson v. Citrix Online LLC, 770 F.3d 1371 (Fed. Cir. 2014), *superseded by* 792 F.3d 1339 (Fed. Cir. 2015).

[310] Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 1297, 1354 (D. Del. 1987).

to that particular type.[311] However, the facts for Isaacs are better than those for Weissmann. He could urge the court to be equitable, and construe the hypothetical method claim to capture the use of both classes of Type I interferons, alpha and beta, from whatever animal source. Both alpha and beta interferons share the fundamental property of being antivirals.

In sum, the commercialization of fish beta interferon for antiviral veterinary use might well be a literal infringement of the hypothetical method claim we have created.[312] If the use of claim 1 is construed narrowly (following *Schering* or *BiogenIDEC*),[313] then Isaacs's best hope is to invoke the DoE. He would hope that the facts show that the uses of his human or monkey interferons alpha are equivalent to the use of the fish IFN-beta. Citing *Scripps*, he should be able to compare as many properties of his interferons as needed, side-by-side to the properties of the after-discovered fish interferon.[314] If, after all that, he still loses, based on factual differences between the properties, Isaacs—as Genentech did in their t-PA litigation against Wellcome[315]—should be satisfied that such a result is as just as our court system can give him.

At all times, biotechnologists should keep in the back of their minds that, while they may think they have uncovered a small hill, it might be part of a mountain range still to be discovered. The immortal words of Tom Lehrer seem like a good ending for our legal explorations:

> There's antimony, arsenic, aluminum, selenium,
>
> And hydrogen and oxygen and nitrogen and rhenium,
>
> * * *
>
> And argon, krypton, neon, radon, xenon, zinc, and rhodium,
>
> And chlorine, carbon, cobalt, copper, tungsten, tin, and sodium.
>
> These are the only ones of which the news has come to Harvard,
>
> And there may be many others, but they haven't been discovered.[316]

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[311] *See Schering IV*, 222 F.3d 1347, 1353–54 (Fed. Cir. 2000).

[312] As long as the claim survives an *AbbVie Deutschland* invalidity challenge. *See* AbbVie Deutschland GMBH & Co. v. Janssen Biotech, Inc., 759 F.3d 1285 (Fed. Cir. 2014).

[313] *Schering IV*, 222 F.3d at 1353; *BiogenIDEC*, 713 F.3d 1090, 1095–96 (Fed. Cir. 2013).

[314] Scripps Clinic & Research Found. V. Genentech, Inc., 927 F.2d 1565, 1580–81 (Fed. Cir. 1991).

[315] Genentech, Inc. v. Wellcome Foundation, 29 F.3d 1555, 1569 (Fed Cir 1994).

[316] Thomas Lehrer, *The Elements*, *on* Tom Lehrer in Concert (1959), sung to the tune of Gilbert and Sullivan's "I am the very model of a modern Major-General."