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Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement

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Introduction

Reproducibility is the touchstone of the scientific method and one of the strongest norms of the research community.[1] In order to be accepted as scientific fact, results of an experiment must be reproducible by an independent operator following the description given by the original inventor.[2] The inability of others to reproduce results described in a scientific publication can often ruin a scientist's reputation because the lack of reproducibility or operability of published procedures can be evidence of sloppiness or outright fabrication.[3] One of the formal penalties for publishing unreproducible or inoperable research is a forced retraction of a publication, or at least a correction that accurately describes the published experiment.[4] Occasionally, researchers who author unreproducible experiments can be stripped of their doctoral degrees. However, this remedy is generally limited to cases involving evidence of fraudulent behavior.[5] These penalties underscore the importance of the reproducibility norm in the research community.

Verifiability is closely bound to reproducibility. The concept of verifiability has a long pedigree in the philosophy of science,[6] but, for the purposes of this Article, I will adopt a functional, in-the-trenches definition of verifiability. Simply, verifiability is the ability of a follow-on researcher to confirm that he or she has successfully reproduced the original experiment. In scientific publications that describe syntheses of chemical compounds, for example, the original researcher is typically required to provide enough data to characterize the published compounds.[7] The characterization requirement compels the original researcher to give evidence supporting his or her results and benefits other researchers in the field by empowering them to confirm that they have made the same compound as the pioneering worker.[8] If analytical techniques for positively identifying the compound could not be employed or were not available, the researcher must indicate this deficiency in the publication and describe possible ambiguities in the structure of the compound. The inability to provide data that positively identify a chemical compound can result in the rejection of a publication

during the peer review process.[9] For certain inorganic compounds, for example, the absence of a crystal structure can often bar publication in a prestigious journal because reviewers or editors do not really "believe" the result.[10] The chemistry community enforces the requirement of verifiability by mandating positive characterization of published compounds because it strives to ensure that published research is well-supported and reproducible. The added virtue of verifiability is that it allows follow-on researchers to confirm the identity of a published compound even if they make it by a route different from that described in the original publication. Thus, for example, a chemist can use the available identification data to prove that a compound he or she has synthesized in the laboratory is exactly the same as that extracted from a plant or animal source.[11]

U.S. patent law does not directly mandate reproducibility or verifiability as requirements for patentability, but it does recognize their importance by requiring that the specification of a patent teach others skilled in the art to practice the patented invention.[12] Section 112 of the Patent Act states, in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .[13]

Courts have held that, if a person skilled in the art must engage in "undue experimentation" to make and use the patented invention, the patent would be found invalid for lack of enablement.[14] Under this standard, patents that claim unreproducible or inoperable results are, a fortiori, invalid for lack of enablement, for others skilled in the art cannot practice the invention.[15] One court described the undue experimentation doctrine as a tool for invalidating patents and screening out patent applications disclosing results that are "unpredictable and unreliable."[16] This doctrine is consistent with the disclosure[17] and public notice[18] functions of the patent document. Indeed, inventors who try to patent an unreproducible invention or whose specification[19] is inoperable fail to hold up their end of the bargain inherent in the patent system.[20] A patent containing such a non-enabling disclosure is of very little value to the public.[21] Moreover, if the specification does not provide enough information for follow-on researchers of ordinary skill in the art to verify that what they have made is identical to the claimed product, the notice function of the patent document is not fulfilled.[22] Without adequate indicia of verifiability, follow-on researchers have no way of knowing if they infringe the patent's claims.

There is another, related way in which patent law pays heed to the norm of reproducibility and the concomitant requirements of operability and verifiability. In order for a patent claim to be properly rejected for failing to satisfy the novelty requirements of § 102 of the Patent Act, the potentially anticipatory prior art must contain an enabling disclosure.[23] To determine whether prior art is enabling, courts deploy the undue experimentation inquiry used for ascertaining compliance with the § 112 ¶ 1 enablement requirement.[24] How does this requirement apply in practice to the chemical arts? The Manual of Patent Examining Procedure states that "a reference does not contain an enabling disclosure if attempts at making the compound or composition were unsuccessful before the date of the invention."[25] An applicant can, therefore, counter an examiner's § 102 (novelty) rejection of a claim by producing evidence of trying and

failing to practice (i.e., successfully perform) experiments according to the instructions given in the prior art.[26] Thus, reproducibility and operability bear directly on the determination of whether prior art contains an enabling disclosure.

Of course, patentability requirements differ in many significant respects from those of scientific publications. For one thing, a scientific publication typically has to describe an actually completed experiment, while a patent specification does not. A detailed experimental description followed by "prophetic examples" can satisfy the enablement requirement, even if no laboratory work has taken place.[27] Thus, a polymer chemist can patent a method of polymerizing ethylene with a novel catalyst and include a prophetic example describing, for instance, predicted molecular weight and viscosity characteristics of a polymer that the catalyst is expected to produce. Many commentators have bemoaned these so-called paper patents and the resulting disconnect between scientific and legal norms; some have called for a return to, or at least greater use of, the "working prototype" model of enablement, by which an inventor would have to provide evidence of actual reduction to practice to the United States Patent and Trademark Office (USPTO).[28] Nevertheless, such patent reform may deprive the world of valuable inventions.[29] After all, once it is confirmed that a predicted experiment in a paper patent works as described and produces the claimed results without undue experimentation, the rest of the world will benefit from the disclosure.[30] Indeed, perfect correspondence between the reproducibility norm and the statutory enablement requirement is neither practical nor desirable, and courts have conceded as much.[31] There is a way, however, in which the enablement requirement of patent law can become more closely aligned with the norms of the research community.[32] For patents claiming subject matter that is inherently difficult to characterize and verify, the law should encourage changes in claiming practice that reflect the relatively low enabling value of the disclosure associated with claims to such products. As explained above, some degree of correspondence between reproducibility and patentability is inevitable and necessary if patents are to serve their disclosure and notice functions.[33]

This Article maintains that the enablement requirement of § 112 ¶ 1, as informed by the reproducibility norm, calls for narrower claims to some inventions in the biotechnological arts.[34] In particular, this Article makes the case for more frequent use of process limitations in composition-of-matter (hereinafter, "composition") claims to biological and biochemical inventions. The Court of Appeals for the Federal Circuit (Federal Circuit) has very recently settled a long-standing split of authority between two of its panels, holding in an en banc opinion that process limitations[35] in composition claims count for the purpose of determining infringement.[36] Thus, an accused product has to embody all the elements of a composition claim, including a process or source element if the claim has one, to infringe the claim.[37] Now that composition claims with process limitations have clear legal significance, it is worth considering whether these claims are appropriate for biotechnology inventions where the process of preparing a claimed composition is intimately tied to the invention's reproducibility and operability. For claims to compositions whose properties or structures are highly process- or source-dependent, process or source limitations may provide the most effective avenue to ensure that those skilled in the art are enabled to practice "the full scope of the claimed invention."[38]

In Part I of this Article, I will discuss the primacy of the claim in defining the patentee's legal rights and explain the jurisprudence of product-by-process claims. Part I will also consider the implications of the *Sandoz* decision, which clarified the legal status of claims with

process limitations in infringement analysis and created an apparent divergence between novelty and infringement standards for such claims.[39] Part II will lay out the challenges for reproducibility and verifiability of certain types of inventions in biotechnological arts, particularly biosynthetic proteins. With references to shortcomings of presently available analytical techniques and the problem of follow-on biologics, this Part will consider when and whether adequate enablement of broad composition claims directed to such inventions is possible. This Part will then argue for the appropriateness of a regime that involves more frequent use of process limitations for some inventions of biotechnology, with reference to the well-known case of *Amgen Inc. v. Hoechst Marion Roussel, Inc.*[40] The focus of this Part is to determine whether composition claims with process limitations ensure compliance with the enablement requirement, as examined through the lens of the reproducibility norm. Finally, Part III will consider whether claims with process or source limitations offer too little protection to the patentees, effectively limiting them to claiming actual inventions and nothing more. This Part will also suggest how the USPTO can ensure that patent applicants will use process limitations when they are appropriate.

I. Process Elements as Enforceable Limitations on Patent Claims

A. The Basics of Patent Claims

In U.S. patent law, claims define the scope of legal protection that the federal government grants to the owner or exclusive licensee of a patent.[41] Judge Giles Rich of the Federal Circuit famously wrote that "the name of the game is the claim"[42] and courts have followed this maxim.[43] Some commentators have argued that courts may engage in overzealous interpretive efforts and, in so doing, undermine the primacy of the claim by reading in limitations from the specification.[44] Nevertheless, claims remain the touchstone of USPTO's determinations of patentability and of courts' rulings on validity and infringement because "[t]he language of the claim frames and ultimately resolves all issues of claim interpretation."[45]

The types of patent claims that one encounters roughly reflect very general requirements of the Patent Act, which sets out patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . . ."[46] Preambles of claims mirror these statutory categories, as one frequently encounters process claims ("a method for . . . "; "a process for . . ."), machine or device claims ("an apparatus for . . ."; "a device comprising . . ."), and composition claims ("a mixture comprising . . ."; "a compound having the formula . . ."). The preamble is followed by claim elements or limitations,[47] which delimit the scope of the claim so that it satisfies statutory novelty,[48] non-obviousness,[49] and disclosure[50] requirements. An example is helpful to illustrate how limitations work: In a claim that reads, "a mixture comprising from about 80% to about 95% by weight of polyethylene and from about 5% to about 20% by weight of atactic polypropylene," the amounts and identities of polymers that make up the mixture are the claim limitations. Because "[a] claim covers an accused device if the device embodies every limitation of the claim,"[51] a mixture that comprises 87% polyethylene and 13% atactic polypropylene literally infringes our fictitious claim. A mixture that comprises 85% polyethylene, 10% atactic polypropylene, and 5% some other substance also infringes. In contrast, a mixture that comprises 50% polyethylene and 50% atactic polypropylene does not infringe. Also not infringing are mixtures that comprise 87% polyethylene and 13% polybutylene or 87%

polyethylene and 13% isotactic polypropylene, since these compositions do not embody both polyethylene and atactic polyproplyene limitations of the claim.

Chemical and biological inventions are typically claimed as compositions, processes, or both. For example, a synthetic chemist who makes a previously unknown molecule X can likely obtain claims for both "a compound having formula X" and "a process for synthesizing the compound having formula X." Composition claims are considered to be much more powerful than process claims because such claims may severely limit the ability of follow-on researchers to design around the patented invention.[52] Thus, one can avoid infringing a process claim on a molecule by inventing a different process for preparing the same molecule, but the same strategy will not work for avoiding infringement of a composition claim. The owner of a patent with composition claims can assert the patent against an inventor who makes the molecule by another process, even if the follow-on process is much more efficient.[53] For example, the owners of an original patent on polypropylene, who claimed "normally solid polypropylene," successfully asserted their claims against subsequent researchers who synthesized the polymer by methods that significantly improved on the methods used by the patentees.[54] In addition to a robust right to exclude generally provided by composition claims,[55] patentees also favor such claims because their infringement is typically easier to detect than that of process claims.[56]

B. Process Limitations on Composition Claims and the Sandoz Decision

Given the potentially very broad coverage afforded to composition claims, determination of appropriate limitations for this type of a claim is particularly important. As indicated in the polyethylene/polypropylene example above, one kind of a composition claim limitation goes to the constituent parts of the composition. Yet another kind of a limitation can be based on physical or structural characteristics of the composition, such as glass transition (or melting) temperature or crystallinity of a polymer. For example, a claim may read, "*crystalline* polypropylene *having glass transition temperature of 130 °C or higher*" (physical limitations in italics). Functional limitations (e.g., "polyethylene *capable of being molded into a rigid container*") can also be used, although courts have sometimes been suspicious of claims containing only functional limitations.[57]

A special, rather controversial, type of a limitation that sometimes occurs in composition claims is a process limitation, which refers to the product by a process by which it was made; analogously, a source limitation refers to the product by a source from which it was derived.[58] A composition claim with a process limitation has the general form "a material *prepared by a process comprising the steps of . . .*" or "product X *obtained by process Y*."[59] Similarly, a composition claim with a source limitation has the form "product X *obtained from source Z*." While these kinds of claims are considered "pure" product-by-process claims (when no physical, structural, or other types of limitations are used at all),[60] one also encounters claims of the form "product X having property M obtained by process Y" or "product X having property N obtained from source Z."[61]

Until very recently, there was a split of authority in the Federal Circuit as to whether process elements are legally effective for the purpose of determining patent infringement. That is, it was unclear if product X prepared by process Z literally infringes the claim to "product X obtainable by process Y." One line of authority stemmed from *Scripps Clinic & Research Foundation v. Genentech, Inc.*,[62] which had held that the factual scenario described above warrants a finding of infringement. The fundamental rationale for the *Scripps* decision is

predicated on the maxim that "claims must be construed the same way for validity and for infringement."[63] Since it is well established that a composition claim to a known product prepared by a new process is invalid under § 102 of the Patent Act,[64] the infringement-validity maxim leads to the result, achieved by the *Scripps* panel, that process elements should not limit the scope of a claim to a novel product. That is, because process elements cannot impart novelty to a composition claim directed to a known product, the *Scripps* panel reasoned that such elements, when they are directed to a novel product, should not constrain the reach of the composition claim in infringement analysis. *Scripps* held: "[T]he correct reading of product-by-process claims is that they are not limited to product prepared by the process set forth in the claims."[65]

Another line of authority stemmed from *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*,[66] which had held that, if an accused infringer of a composition claim with a process limitation can show that the product was made by a different process, then no finding of infringement is warranted. The fundamental rationale for *Atlantic Thermoplastics* is that "infringement requires the presence of every claim limitation or its equivalent" in the accused device or product, and that the *Scripps* decision has the undesirable effect of reading out a claim limitation.[67] The Federal Circuit initially refused to hear the *Atlantic Thermoplastics* case en banc to resolve the apparent conflict between the *Scripps* and *Atlantic Thermoplastics* panels, leaving district courts with the choice of which line of authority to follow.[68] After 17 years of uncertainty, the *Abbott Laboratories v. Sandoz, Inc.* decision explicitly overruled *Scripps* and affirmed *Atlantic Thermoplastics*, holding that process elements in composition claims are effective as limitations in infringement analysis.[69]

In *Sandoz*, the Federal Circuit heard a consolidated appeal of two district court rulings that concerned brand-generic litigation based on the generic manufacturers' Abbreviated New Drug Applications (ANDAs).[70] The lawsuits implicated Abbott's patent on a crystalline form of a chemical compound called cefdinir, a broad-spectrum antibiotic marketed under the brand name Omnicef®,[71] and accused products made by two different generics manufacturers. The first ruling, from the Eastern District of Virginia,[72] was a declaratory judgment action ending in summary judgment finding that defendants did not infringe Abbott's patent, and the second, from the Northern District of Illinois,[73] was a denial of a motion for a preliminary injunction based on the claim construction that led to the first ruling. Abbott appealed both rulings and challenged the claim construction that limited the scope of asserted cefdinir composition claims to a specific crystalline form (Crystal A) of cefdinir, which is a polymorphic compound (i.e., it can crystallize in several different forms).[74] The accused infringers manufactured a different crystalline form of cefdinir, Crystal B. A Federal Circuit panel affirmed the claim construction of the Eastern District of Virginia and upheld its summary judgment ruling of non-infringement; likewise, the panel upheld the Northern District of Illinois' denial of a preliminary injunction.[75] Although this was not necessary to resolve the controversy, the court decided *sua sponte* to use the case as an opportunity to lay down a definitive rule for proper interpretation of composition claims with process limitations in the en banc part of the opinion.[76]

The claims in the '507 patent that contain processes limitations deal with chemical subject matter.[77] All three independent claims (Claims 1, 2, and 5) are directed to a product called "crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)"; the terms after the word "crystalline" represent the systematic

chemical name for cefdinir.[78] One additional limitation in Claim 1 is simply a listing of peaks in the powder X-ray diffraction (PXRD) spectrum of a specific crystalline polymorph of cefdinir, Crystal A.[79] Claims 2 and 5, however, include process limitations that the court addressed in the en banc ruling. The subject matter of Claim 2 is directed to cefdinir "obtainable by acidifying the solution containing [the chemical precursor to cefdinir] at room temperature or under warming."[80] Claim 5 is directed to cefdinir "obtainable by dissolving [the chemical precursor to cefdinir] in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand."[81] Claims 3 and 4 depend from Claim 2, and are therefore subject to the same analysis as Claim 2.

Before addressing the *Sandoz* analysis of process limitations in detail, it is helpful to explain why the patentees likely chose to draft the claims in this format. As it turns out, the patentees held another patent on cefdinir,[82] but the claims of the earlier patent did not specify the crystallinity properties of the compound. Thus, crystallinity of the cefdinir claimed in the '507 patent apparently helped bolster the argument for novelty and non-obviousness of the subject matter of the patent. The patentees did face a non-final obviousness (§ 103) rejection of the claims of the '507 patent, with the examiner arguing that "different forms of the same compounds are presumptively non-patentable."[83] The applicants, however, countered by arguing that "the crystalline form is unknown, unobvious, and productive of unexpected advantageous results."[84] The applicants emphasized that "utility of [the] crystalline product is *not* the same as the utility of the amorphous product of [the earlier patent]," including increased potency and purity of the crystalline cedfinir relative to the amorphous cefdinir disclosed in the prior art.[85] The patentees also pointed out that the "*method of preparation* of the crystalline form of the presently claimed compounds is not considered the heart of the present invention. The crystalline form of the compound represents the inventive concept thereof, and it is clear that [the earlier patent] does not anticipate or suggest said crystalline form."[86] Curiously, however, the application as originally filed also included claims to methods of synthesizing cefdinir (Claims 6–9) that paralleled the composition Claims 2–5.[87] In the examiner interview, the examiner maintained the view that "claims 6–9 were substantial duplicates of 2–5 and that cancellation of claims 6–9 would render the case allowable."[88]

The en banc court did not reach the question of novelty or non-obviousness of Claims 2–5, since the accused generic drug manufacturers focused their defense on non-infringement (which, as noted above,[89] was successful even without resorting to the analysis of process limitations). The court, with Judge Rader writing for the majority, instead went on to clarify the infringement analysis of product claims with process limitations and, relying on various Supreme Court, Circuit Court, and Court of Customs and Patent Appeals precedents, held that "the Eastern District of Virginia correctly construed the process limitations beginning with 'obtainable by' in claims 2–5 as limiting the asserted claims to products made by those process steps."[90] Ultimately, the rationale of the en banc majority was similar to that of the *Atlantic Thermoplastics* panel, whose opinion was also authored by Judge Rader, as the court held that the *Scripps* rule led to the impermissible result of reading limitations out of claims.[91] Judge Newman filed a scathing 20-page dissent (with Judges Lourie and Mayer joining) with her own assessment of the precedents cited by the majority, and argued that applicants who are unable to claim a novel and non-obvious product using structural or physical limitations should not be forced to seek composition claims weakened by process limitations.[92] The dissent's rationale was similar to that of *Scripps*, which Judge Newman wrote,[93] as well as to her dissent from the

denial of the rehearing en banc of *Atlantic Thermoplastics*.[94] In addition to noting that the *Sandoz* holding violated the infringement-validity maxim,[95] she argued against the majority's rejection of the rule of necessity, which had given patentees full composition claim protections when they did not have enough information about their products to draft claims with structural limitations.[96] Another potential problem of the en banc holding, as noted by Judge Newman, was that process-related phrases that merely serve a definitional purpose may be read as limitations, resulting in unwarranted narrowing of claim scope.[97]

Judge Lourie filed a separate dissent that characterized the Supreme Court cases cited by the majority, some of which reached back into the Nineteenth Century, as simply inapposite given the difficulty of analogizing them to modern-day factual patterns involving complex chemical and biotechnological inventions.[98] However, it must be added that the court did not rely exclusively on very old cases. For example, the majority cited *Warner-Jenkinson*, a relatively recent Supreme Court decision dealing with the doctrine of equivalents, for the proposition that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention."[99]

C. Why Use Process Limitations After Sandoz?

Given the apparently diminished level of protection afforded by composition claims with process limitations (arguably after *Atlantic Thermoplastics* and certainly after *Sandoz*), it is worth returning to the question of why patentees may want to use such limitations at all. According to Judge Newman, process-type limitations have been used in three general types of scenarios. The first is a situation "where the product is new and unobvious, but is not capable of independent definition."[100] These circumstances force the use of what Judge Newman called "true" product-by-process claims, where the process limitation is the primary and perhaps the only limitation.[101] The second scenario arises "when the product is old or obvious, but the process is new."[102] In this case, the claim is best treated as a pure process claim masking as a product claim, with no protection at all afforded to the product. Finally, Judge Newman identified a third set of circumstances, "when the product is new and unobvious, but has a process-based limitation."[103] This characterization implies that there are non-process-based limitations in this type of a claim; the claim, however, also includes process elements, which may serve a definitional or a descriptive purpose, or may be necessary for patentability.

Judge Newman's dissent from the rehearing en banc did not say much about this third type of a claim, but it is perhaps the most interesting of the three. While structural or other limitations can be present in this hybrid claim, these limitations, by themselves, are somehow deficient, and additional process-based limitations become necessary. If one excludes sloppy claim drafting, some logical reasons for introducing such limitations may involve improved prospects for meeting novelty, non-obviousness, and/or disclosure requirements, and perhaps even attaining a claim that affords broader coverage than a corresponding claim with a highly restrictive structural limitation. In both such cases, it stands to reason that process elements should have the full legal force of a claim limitation, restricting claim scope in infringement analysis.

In this light, it is instructive to examine the patent-in-suit in *Sandoz*, because process limitations in two of the claims of that patent could have been plausibly introduced to improve both prospects for patentability and to increase scope of claim coverage relative to an analogous structurally-limited claim. Independent Claims 2 and 5, which contain process limitations, also

include structural limitations—the claims, after all, are to "crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)." The chemical name of cefdinir refers to a precise, structurally well-defined chemical entity, which is limited by the type and arrangement of atoms that make up the cefdinir molecule; "crystalline" further physically limits cefdinir to a specific morphology. In the prior art patent, the same chemical compound was disclosed and claimed (in Claim 2), but no physical property, such as crystallinity or amorphousness, was described in the specification or in the claim.[104]

It is likely that the patentees were concerned that, if they were to try for a claim in the latter patent that read "Crystalline cefdinir, period," the USPTO would consider it anticipated or obvious in view of the prior art disclosure of the genus of "cefdinir." While precedent exists that disclosure of a genus does not necessarily render a species within the genus anticipated and/or obvious,[105] it is unlikely that the patentees would have been able to convince the examiner that the entire "crystalline cefdinir" subgenus of "cefdinir," and not just the species that they actually claimed, is patentable given the generic cefdinir disclosure in the earlier patent. After all, given the research they have done, the patentees could plausibly argue only that two specific crystalline forms of cefdinir (Crystal A and Crystal B), which they describe in the specification, offer unexpected potency and stability properties.[106] The patentees had no evidence that other crystalline forms of cefdinir even existed, let alone had any beneficial utilities. So, presumably to avoid a § 102 or § 103 rejection, the patentees saw fit to limit the "crystalline cefdinir" genus to those species produced by the two specific processes recited in Claims 2 and 5.[107] In addition, in Claim 1, the patentees limited the "crystalline cefdinir" genus to a species with a particular PXRD signature.[108]

It is not difficult to see that Claims 2 and 5 potentially afford greater scope than Claim 1. After all, the PXRD data in Claim 1 clearly excludes Crystal B and explicitly limits the claim to Crystal A because the claimed PXRD signature corresponds uniquely to Crystal A of cefdinir.[109] In contrast, it is possible (and the patentees so argued in the district court proceedings) that both Crystal A and Crystal B, and maybe other cefdinir crystal morphologies, are covered by Claims 2 and 5, which have process limitations but do not constrain the morphology of the claimed material to a unique crystal type. If it turned out to be very difficult to produce crystalline forms of cefdinir by other processes, Claims 2 and 5 would have been more powerful than Claim 1, in spite of their process limitations! Of course, this issue became moot when the Federal Circuit affirmed the district court's claim construction that limited the scope of Claims 2 and 5 to only the Crystal A form in view of a restrictive definition in the specification; the accused generics manufacturers produced form B.[110] Nevertheless, it is at least conceivable, in light of the prosecution history of the '507 patent, that process limitations can be favorable to patentees in terms of imparting novelty or non-obviousness to claims, and potentially providing broader claim scope relative to highly restrictive structural limitations.

While the above analysis illustrates that composition claims with process limitations can be useful for complying with novelty and non-obviousness requirements, this Article argues that such limitations can also help patent applicants comply with the enablement requirement of § 112 ¶ 1. While applicants can often satisfy disclosure requirements by submitting a sufficiently detailed specification, an equally valid and sometimes the only strategy for avoiding an enablement rejection by the USPTO, or a ruling of invalidity for lack of enablement in litigation, is to narrow the scope of the claims.[111] Indeed, narrowing of claims is appropriate where the specification simply cannot support a broad composition claim so as to ensure

enablement of the "full scope of the invention."[112] In particular, the third type of composition claim with process limitations identified by Judge Newman,[113] which contains some structural and some process-based limitations, is uniquely appropriate for claiming certain products of biotechnology.

II. Process Limitations for Products of Biotechnology

A. Chemical Composition Claim as an Infinite Genus of Processes

In order to demonstrate that process limitations appropriately constrain the scope of claims directed to certain kinds of inventions, it is instructive to consider the difference between relatively small molecules claimed in pharmaceutical inventions on the one hand, and large molecules claimed in biotechnological inventions on the other. Small-molecule chemicals, such as those used in pharmaceutical applications, have precisely defined structures, usually included in claims as a chemical drawing or a name that follows the rules of systematic nomenclature, as seen above with cefdinir.[114] Chemical drawings or names, in themselves, contain a wealth of information about the molecule, including its precise atomic composition, molecular weight, and connectivity of atoms that can be ascertained by various techniques. Given this structural precision, the identity of molecules produced in two different laboratories can be confirmed using established analytical methods such as nuclear magnetic resonance spectroscopy, mass spectrometry, and elemental analysis.[115] If the disclosure provides data that tends to establish the structure and composition of the claimed molecule, or if the data can be obtained and interpreted in a routine manner by those skilled in the chemical arts, follow-on researchers can readily confirm the reproducibility and operability of the claimed invention. At the very least, armed with the depicted chemical structure or a systematic chemical name, along with the data for verifying the structure, follow-on researchers can check if the chemical patent complies with the § 101 requirement of operable utility—that is, if the invention actually works.[116]

Verifiability of chemical structures, however, has legal implications beyond simply allowing follow-on researchers to confirm that the invention is operable. Recall that § 112 requires not only that the patentee teach how to make the claimed invention, but also how to use it.[117] Therefore, enablement of the "full scope of the claimed invention" necessarily constitutes enablement of "how to use" the invention across the full scope of the claim for at least one utility asserted in the patent.[118] In order for a claim to comply with the "how to use" prong of the enablement requirement, the specification must teach those of ordinary skill in the art how to select useful and operable embodiments of the claim without undue experimentation.[119]

One way to understand a claim to "molecule X" is to view it as an infinite genus comprising the species "molecule X obtained by process A," "molecule X obtained by process B," "molecule X produced by process C," and so on.[120] Generally, a composition claim to a chemical compound is granted even if only one process for making it is described in the specification.[121] While patent law can often be suspicious of claims to a genus when only one species is disclosed,[122] courts and the USPTO do not raise the issue of "enablement of the full genus of processes" for composition claims directed to chemical compounds that are structurally well-defined. Claims of the type "molecule X" usually do not face such challenges because the genus "molecule X obtained by process A, B, C, etc." is not so "diverse and

complicated"[123] as to lead an examiner to doubt whether one of ordinary skill in the art can "practice the invention across the entire scope of the claim."[124] Given the advanced state of analytical techniques for confirming structures of molecules, follow-on researchers need possess only ordinary skill to verify that molecule X that they obtained by process B is the same as the claimed "molecule X" that was produced by process A disclosed in the patent's specification. Having confirmed the identity of the molecule, follow-on researchers can be reasonably confident that a copy of the patented molecule, even if made by a process different from that described in the original disclosure, will have the same utilities as those asserted in the original patent.[125] In this way, disclosure of the structure of molecule X, along with a recitation of its utility, helps teach follow-on researchers how to use the claimed invention across the infinite genus of possible processes that produce molecule X.[126] The expected identity of utilities of identical chemical compounds, regardless of the process by which they were made, has the salutary effect of spurring after-arising technologies involving improved methods for making desired molecules.[127] Knowing, for example, that a patented compound that is made in limited amounts by extraction from an exotic plant source is expected to have the same utilities as a structurally identical compound that is synthesized in the laboratory,[128] researchers who read the patent claiming the compound will be encouraged to prepare it on a large scale by a fully synthetic method.[129]

B. Issues with Enablement of Biotechnological Inventions

The enablement landscape is quite different for biotechnological products that function as drugs, such as proteins made by recombinant deoxyribonucleic acid (DNA) techniques.[130] Before addressing the differences between biosynthetic proteins and small-molecule pharmaceuticals, however, it is worth noting the similarities. In a landmark 1991 case dealing with biotechnology patents, the Federal Circuit correctly noted that "a gene is a chemical compound, albeit a complex one" in the context of determining when an invention was conceived for the purpose of determining priority.[131] This statement also applies to proteins, which are very large and complex chemical compounds. The critical differences between pharmaceuticals and proteins, relevant for evaluating enablement of claims to the two types of chemical compounds, relate to the state of the art for characterizing and verifying structures of the latter.

First, as already noted, proteins are generally much larger than organic molecules that serve as active ingredients of pharmaceutical drugs.[132] For example, paroxetine, a well-known small-molecule pharmaceutical drug marketed under the brand name Paxil®, has the molecular weight of 329.4 grams per mole in its free-base form,[133] while growth hormone, a protein and a biological drug, has the molecular weight of approximately 22,000 grams per mole in one of its forms.[134] What this means in practice is that the latter has many more atoms than the former, which leads to uncertainties about the connectivity of the atoms and the three-dimensional structure of the protein. Large size and complexity of proteins makes it difficult for pioneering inventors, as well as for follow-on researchers who may pursue a different process for making the material, to to characterize its structure given the current state of analytical tools available for protein analysis.[135] Second, and perhaps more important, is the fact that recombinant proteins are, by definition, made using the machinery of living organisms. Cell lines from sources such as bacteria or mammalian organs are engineered (by a process called transfection, which entails introduction of recombinant DNA that "codes" for the desired protein into the

cell) to synthesize the desired protein.[136] Because each cell line is unique, the structure and behavior of the final protein product is highly dependent on the specific cell line used to synthesize it.[137] Size and complexity of proteins and the unpredictable nature of their cell-mediated production implicate the problems of verifiability and reproducibility discussed in the Introduction.[138] An article on regulation of the drugs of biotechnology aptly describes these problems:

> Because of the differences in production and size between biologics and chemical drugs, as well as the unique cellular source of biologics, it is nearly impossible to make truly identical copies of a protein using two different production cell lines. . . . This diversity is present to an even greater degree between cell lines from different living organisms, such as bacteria, mammalian organs, yeast, and other sources. . . . The complexity of the biologic molecule, its sensitivity to production, and the challenges associated with characterization result in its being defined primarily in terms of its manufacturing method.[139]

This state of affairs presents two significant problems for follow-on researchers who wish to take advantage of the teachings of a patent that includes a broad composition claim to a recombinant protein (i.e., a protein made using recombinant DNA). First, because currently available analytical techniques may not always allow one to determine structures of large proteins with precision, follow-on researchers sometimes cannot verify, even after extensive experimentation, if they have reproduced the experiment and made the patented composition.[140] Second, because of the high degree of process dependence in the cell-mediated synthesis of biologics, it is quite possible that an attempt to make the patented protein by a different method will yield a product that lacks the asserted utility of the claimed invention.[141]

Difficulties in reproducing biological processes, such as cell-mediated syntheses of large proteins, largely explain why it has taken a long time to for Congress to pass biosimilars legislation.[142] Indeed, the contours of the Pathway for Biosimilars Act that was recently signed into law[143] are very different from those of the legal regime for the approval of generics of small-molecule drugs, given the need to monitor immunogenic response and efficacy of follow-on products after they are introduced in the marketplace.[144] Because of the limitations of analytical techniques in determining protein structure and the unpredictability of behavior of biosynthetic products, the FDA cannot be sure that follow-on biologic drugs will have the same clinical properties and safety profiles as the branded, patented products. "[A]s of today, the FDA has not determined how interchangeability can be established for complex proteins. Different large protein products, with similar molecular compositions may behave differently in people and substitution of one for another may result in serious health outcomes."[145]

Of course, standards of compliance with FDA regulations are not coextensive with the patent law's enablement requirement.[146] Yet process-related differences in the behavior of biotechnological inventions motivate further investigation into whether specifications can adequately support broad protein composition claims across the full scope of processes for making the claimed subject matter. In particular, given the potential differences in utilities of protein products made by different processes, it is worth analyzing under what circumstances such claims can satisfy the "how to use" prong of the enablement requirement.[147]

C. Toward Process Limitations in Biotechnological Inventions

Difficulties in determining precise structures of proteins, as detailed above in Part II.B, provide the initial motivation for proposing that process limitations are appropriate in claims to protein compositions. As the *Sandoz* court noted, "if an inventor invents a product whose structure is either not fully known or too complex to analyze . . . this court clarifies that the inventor is absolutely free to use process steps to define this product."[148] Furthermore, to support generic claims in arts that are considered unpredictable, such as chemistry and biochemistry, patent law generally requires a description of more than one working species of the genus.[149] As the MPEP puts it, "in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims . . . . [In unpredictable arts], it is not obvious from the disclosure of one species, what other species will work."[150]

This principle is related to the holding of the venerable *Incandescent Lamp Patent* case, where a patent was held invalid because disclosed species of materials for use as light bulb filaments did not support the claimed genus of "carbonized fibrous or textile material."[151] The claim was not enabled because many species within the genus were not useful as filaments, and the claimed genus as a whole did not seem to have a unifying property that allowed species within it to be useful for their asserted purpose.[152] Stated another way, the disclosed species, even though they were members of the genus "carbonized fibrous or textile material," could not support the inductive step of concluding that other members of the genus would have the desired utility.[153] This failing was illustrated by the struggles of one follow-on researcher, Thomas Edison, to get other members of the claimed genus to work as filaments for incandescent light bulbs.[154] In modern terms, Edison could not select operative embodiments of the disputed claim without undue experimentation.[155]

Similar to the molecular chemistry example discussed above in Part II.A, the relevant "process" genus of biosynthetic proteins is "Protein X obtained by process A, B, C, etc." Since biotechnological inventions are unpredictable in the sense that a different process that appears to produce the claimed product actually may not yield a material of the same utility as the claimed material,[156] it is not clear that a specification that discloses a single process for making Protein X enables those skilled in the art to practice and use the claimed invention across the full range of possible processes for making Protein X. Of course, it is settled law that a patent cannot be held invalid for lack of enablement of after-arising technology, because enablement is measured at the time of the filing and one cannot enable something that is not yet known.[157] But if several processes for preparing materials that fall within the claimed composition are known at the time of the filing, it is reasonable that the applicant be required to disclose more than one process for producing the claimed product that exhibits the utilities asserted in the specification, given that proteins synthesized by different methods can have unpredictably different properties. If the applicant does not or cannot make the requisite showing, the composition claim to the protein product should include a process limitation or else risk rejection or an invalidity judgment for lack of enablement.[158]

D. The *Amgen v. Hoechst* Case

One of the patents[159] at issue in the well-known case of *Amgen Inc. v. Hoechst Marion Roussel, Inc.*[160] illustrates how a composition claim to a protein may not be fully enabled across

the range of possible preparative processes. For example, one of the independent claims of the patent reads as follows:

"3. 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."[161]

At first glance, the structure of the claimed protein, erythropoietin (EPO), appears to be defined precisely, which suggests that we should treat it no differently than claims to small molecules where, as we saw, no process limitations are warranted. After all, proteins consist of building blocks called amino acids, so the sequence of amino acids (as listed in Figure 6 of the '080 patent), which gives both the identity and the order of these building blocks, provides a precise and verifiable structural description of the molecule.[162] This characterization is misleading, however. The claimed protein is a "glycoprotein," which means that some of the amino acid building blocks of the protein have various oligosaccharide moieties (i.e., sugar, or carbohydrate, molecule fragments) attached to them.[163] Therefore, Claim 3 really reads on a large number of compositions that include the claimed amino acid sequence decorated with varying numbers, types, and locations of sugar substituents, collectively described as "glycosylation."[164] A protein's glycosylation is extremely difficult to control in the course of its cell-mediated production, but it can make all the difference in the clinical and diagnostic utilities of the protein, which are the utilities asserted in the '080 patent.[165]

Furthermore, it is very difficult to determine the location of sugar substituents in a glycoprotein.[166] While techniques for analyzing glycosylation are improving, the best one could do at the time the application for the '080 patent was filed was to figure out the aggregate amount of the various types of oligosaccharides attached to the protein, but not necessarily their locations.[167] Difficulties with reproducibility and verifiability have made this area of science extremely challenging; high degree of process dependence in glycoprotein synthesis is one of the reasons why a follow-on biological drug manufacturer cannot use the regulatory route available to generic drug manufactures to get its product approved by the FDA.[168] Because structure and bioactivity of EPO is highly-process dependent, it is worth inquiring further whether how-to-use enablement of Claim 3 of the '080 patent necessitates demonstration of the asserted utility (or utilities) of claimed EPO made with more than one process known at the time of the filing.[169]

Before the enablement issue is addressed, however, the rest of Claim 3 deserves mention. This claim includes two limitations other than the amino acid sequence (which, as we saw above, only begins to tell the structural story of EPO): the preambular phrase "non-naturally occurring" and the functional "biological activity" element. In evaluating the accused infringer's § 112 invalidity challenge to Claim 3, the court refused to read "non-naturally occurring" as any kind of a process or source limitation, saying simply that the recitation of "non-naturally occurring" helped the claim meet the § 101 subject matter eligibility requirements (since naturally occurring EPO would not be patentable subject matter unless it was isolated from a natural source and purified).[170]

But one wonders if the phrase "non-naturally occurring" should have had more teeth as a limitation. "Non-naturally occurring" implies a laboratory synthesis rather than isolation from a natural source; in the '080 patent, that laboratory synthesis involved transfection of host cells with exogenous, or "foreign" DNA,[171] which the specification portrays as "uniquely

characteriz[ing]" the invention.[172] In reviewing the district court's claim construction, the Federal Circuit did not make much of the "uniquely characterized" phrase, saying only that the plain language of the claim did not limit it to the transfection method.[173] In his dissent, Judge Clevenger made perhaps *too much* of that phrase; he argued that transfection by exogenous DNA is a "necessary element" of the claimed invention and its absence from the independent claims should have led to a holding of invalidity for lack of enablement.[174] Lack of enablement for failure to recite a necessary claim element is a rarely invoked doctrine, which appears to be used only when the patentee unequivocally says in the specification that the patent will not work without it.[175]

Judge Clevenger's second argument, directed to another patent at issue in the case and based on the rationale of *In re Vaeck*,[176] more closely addresses the enablement problem of Claim 3 of the '080 patent. In *Vaeck*, the patentees claimed, in relevant part, a "chimeric gene capable of being expressed in Cyanobacteria cells,"[177] but the working examples in the specification taught only a single strain of cyanobacteria where the claimed expression took place.[178] The court, speaking through Judge Rich, held that "there is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria."[179] The court made much of the fact that cyanobacteria are in fact divided into multiple genera, are a "diverse and poorly understood group of microorganisms," and are generally unpredictable in their gene expression behavior given how little is known about them.[180] Therefore, disclosure of only one species of cyanobacteria, and a mere mention of a few other species and genera of the organism, did not entitle the patentees to claiming genes expressed in the whole universe of cyanobacteria.[181]

Analogously, Claim 3 of the '080 patent implicitly claims the genus of all possible methods for making "non-naturally occurring EPO," limited only by its amino acid sequence and the biological function of "causing bone marrow cells to increase production of reticulocytes and red blood cells." At the time of the filing, several methods for making "non-naturally occurring" EPO were available, including the transfection method that the patentee perfected and the chemical synthesis method mentioned repeatedly in the specification of the '080 patent.[182] In actuality, the patentee disclosed only chemical syntheses of fragments of the full amino acid sequence of the EPO (which exhibit no asserted biological activity) rather than the entire sequence.[183] The patentee, therefore, really taught only one "species" of at least two possible processes for making EPO, the transfection process.[184]

Although his argument for non-enablement of the '080 patent was primarily based on the theory that the claims at issue did not recite an essential element, Judge Clevenger indicated his general discomfort with the disclosure of only one method to support a broad composition claim in a related patent at the outset of his *Amgen* dissent: he was skeptical of whether "*one* means of producing synthetic EPO, namely exogenous DNA expression [or transfection] entitles [the patentee] to claim *all* EPO produced by mammalian cells in culture."[185] Similarly, disclosure of one method for producing "non-naturally occurring EPO" should not have entitled the patentee to broadly claim, as he did in the '080 patent, the amino acid sequence with the various possible glycosylation patterns and corresponding differences in utility and performance that variations in glycosylation can cause. Crucially, this position is strengthened by the realization, likely true now and certainly true at the time of the filing of the '080 patent, that the art of protein synthesis was (and is) highly unpredictable and the correspondence in structure between EPOs made by transfection (as disclosed in the '080 patent) and those made

by other methods (like those made by the accused infringer in the *Amgen* case, for example)[186] is very difficult to show. Indeed, due to the unpredictability of the field and the limitations of the synthetic and analytical arts, a person skilled in the art would understand that different methods for synthesizing EPOs that fall within Claim 3 of the '080 patent may not yield clinically and diagnostically useful materials without undue experimentation (though they may technically "cause bone marrow cells to increase the production of reticulocytes or red blood cells," as the claim requires).[187] The district court did not grapple with this issue: "[B]ecause the asserted claims were to 'compositions' rather than 'processes,' 'the specification need teach only one mode of making and using a claimed composition.'"[188] The appellate panel also thought that one method was enough: "Amgen also described and enabled at least one method of producing EPO that was . . . 'non-naturally occurring' . . . : the genetic manipulation of CHO and COS-1 cells."[189]

The district court and the Federal Circuit applied traditional small-molecule law to the biotechnology problem at hand,[190] holding that a description of one method of making the claimed protein is sufficient to support a broad composition claim to the protein.[191] While the district court's statement is certainly correct in regard to small-molecule chemicals of precisely defined structure, it is less supportable when applied to large proteins at issue in the *Amgen* case. In the biotechnological arts, where the structure of a product and its utility are intimately connected to the method of its production, disclosure of one method in support of a broad composition claim likely does not meet the "reasonable correlation"[192] and "undue experimentation"[193] standards of enablement. Indeed, these standards were not met by Claim 3 of the '080 patent, which claimed the universe of non-naturally occurring EPOs of unknown utility, containing an untold number of glycosylation patterns, without any process limitations. The Federal Circuit should have reversed the district court and held the claim invalid for lack of enablement under § 112 ¶ 1.

E. Rescuing Claim Validity with Process Limitations

Since the patentee did not have enough information to limit the structure of EPO in Claim 3 by pinning down locations and types of glycosyl moieties on the amino acids of the protein, a process limitation would have been a logical alternative for narrowing the claim so that it would meet the enablement requirement. Indeed, such limitations are useful precisely when the structure of the product is not fully known.[194] Perhaps realizing that his disclosure did not support broad composition claims, the applicant originally drafted key claims of the application that became the '080 patent with process limitations.[195] Of course, the applicant then tried for something more, and the rest is history.[196]

Interestingly, an Amgen patent from the same family as the '080 patent has a dependent claim with the kind of a process limitation that would also be appropriate for the '080 patent:

"3. A non-naturally occurring glycoprotein product *of the expression in a mammalian host cell of an exogenous DNA sequence* comprising a DNA sequence encoding human erythropoietin, said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells."[197]

Note that the claim does not have the traditional process or source limitation phrasing, such as "obtained by" or "derived from." The emphasized portion, however, does serve as a pair of process elements, the first limiting the source of the glycoprotein to "a mammalian host cell" and the second limiting the triggering of cell expression (i.e., synthesis) of EPO to "an

endogenous DNA sequence," which captures the transfection process. To be sure, the glycoprotein described in the claim is not immune to structural unpredictability arising from process- or source-based variations. Glycosylation of the claimed material is still dependent on the type of host cell used to express it, for example. Nevertheless, the two limitations in this claim make the correlation between disclosure and scope of the claim reproduced above significantly more reasonable than that in Claim 3 of the '080 patent. For example, the specification of the '993 patent (which is the same as that of the '080 patent, as the two have the same parent application) discloses EPO made by transfection of at least two types of mammalian host cells: COS-1 (from kidney cells of the African green monkey carrying the SV40 genome) and CHO (from Chinese hamster ovary).[198] There is no guarantee, of course, that EPO that falls within the scope of the above claim, but is made from host cells other than COS-1 or CHO, will have the utilities of the EPO disclosed in the examples of the '933 patent. The patentee's demonstration of production of useful EPO in two widely used cell lines from two different mammalian species, however, makes a strong case for the enablement of the claim. As for the "expression . . . of an exogenous DNA sequence" limitation, it is appropriate, as argued above,[199] because the patentee disclosed only one process for making the structurally unpredictable glycoprotein.[200]

Thus, taking a cue from the patentee, one may revise Claim 3 of the '080 patent to say the following:

A non-naturally occurring erythropoietin glycoprotein *derived by an expression of an exogenous DNA sequence in a mammalian host cell* 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.

This formulation, with the source and process limitations emphasized, ensures that the claim has a reasonable correlation to the specification, which principally discloses the transfection method for producing EPO. Of course, were the patentee able to obtain and disclose additional structural information on the EPO that he had made, including locations and types of glycosyl groups on the various amino acids of the EPO, he would have been free to draft composition claims with only structural limitations.[201] The follow-on researcher, then, could set out to make the claimed structures by the same or different process and, in the course of doing so, confirm or disconfirm the operability and utility of the claimed invention. In the absence of particularized structural information, however, the patentee would have to show more than one method of making the claimed composition and confirm the utility of the claimed material made by the two or more methods in order to obtain a valid composition claim unencumbered by process limitations.

III. Required Process Limitations and Their Consequences

A. Enforcement of Process Limitations

The USPTO cannot require patent applicants to draft claims with specific types of limitations. Patent examiners can, however, encourage patentees to use such limitations by issuing Office Actions rejecting certain composition claims without process limitations for lack of enablement.[202] A proper analysis by an examiner would first consider the claim's structural, physical, and other limitations and determine the level of structural precision at which the product is described in the claim. The EPO of Claim 3 of the '080 patent, for example, was

described precisely at the level of its amino acid sequence but not at the level of glycosylation. If the subject matter of the claim lacks structural precision (such as uncertain positioning of glycosyl groups in glycoproteins), the examiner may then consider the claimed product as a genus of processes for making it, if it is known in the art that process variations can lead to uncertainties in the structure and utilities of the claimed product. Once the product is cast as a genus of processes, the examiner would proceed with the standard enablement inquiry to see if the disclosure supports the full product genus (i.e., composition claim that is not limited by a process). How many processes for making the claimed product are described in the specification? Are the disclosed processes sufficiently different, such as fully chemical and recombinant methods for making EPO, as to be representative of the full product genus, free of process limitations? Do products made by the different processes have the utilities asserted in the patent? Would undue experimentation be required to select processes for making useful embodiments of the product?

If the examiner determines that a composition claim free of process limitations is not adequately supported by the specification, he or she should reject the claim as failing to meet the enablement requirement of § 112 ¶ 1. The applicant can then amend the claim by introducing appropriate process, structural, or physical limitations. For products whose structure cannot be determined precisely, process limitations may be the only choice for ensuring that the claim meets the enablement requirement.

B. Potential Consequences of Enforcing Process Limitations

Clearly, process limitations would reduce the level of protection available to patentees in the biotechnological arts, but whether or not such diminished protection would discourage or encourage innovation is a difficult question. At the very least, commentators have identified a tradeoff between too much and too little protection; as Merges and Nelson noted in a classic paper, "every potential inventor is also a potential infringer . . . [A] 'strengthening' of property rights will not always increase incentives to invent; it may do so for some pioneers, but it will also greatly increase an improver's chances of becoming enmeshed in litigation."[203] What seems clear, however, is that patentees can retain a meaningful level of protection with claims that include process limitations.

Consider a recent Federal Circuit case, decided several months after *Sandoz*, again dealing with Amgen's biotechnology products.[204] In *Hoffman-La Roche*, one of the claims asserted by Amgen was Claim 3 of the '933 patent, discussed extensively in Part II.E. The accused product, called MIRCERA®, was made with "EPO produced in and purified from mammalian cells,"[205] which was further modified with polyethylene glycol (PEG). The Federal Circuit affirmed the district court's summary denial of Judgment as a Matter of Law (JMOL) to Hoffman-La Roche on the issue of non-infringement of Claim 3, thereby sustaining a jury verdict of infringement, because "MIRCERA® embodies the human EPO and source limitations of the asserted claims."[206] The "mammalian host cell" source limitation of Claim 3[207] did not weaken the claim to the point that Amgen could not win an infringement lawsuit. The researchers of Hoffman-La Roche, a leading pharmaceutical company and a competitor of Amgen,[208] made a product that fell within the scope of Claim 3 of Amgen's well-known '933 patent on EPO, source or process limitations notwithstanding.

Claim 3 of the '933 patent and related claims also survived an invalidity challenge in the same case, based on a prior publication by Eugene Goldwasser and co-workers,[209] which

disclosed EPO produced from human urine.[210] Hoffman-La Roche argued that the "derived . . . in a mammalian host cell" limitation was the only limitation of Claim 3 that was not disclosed by Goldwasser. Because "a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitation,"[211] Hoffman-La Roche asserted that Goldwasser's urinary EPO anticipated Claim 3 of the '933 patent.[212] The court, however, pointed to expert testimony in the trial record, which demonstrated that Amgen's recombinant EPO differed *structurally* from the urinary EPO disclosed in the prior art.[213] The Federal Circuit agreed with the district court and Amgen's experts in that "the source limitation imparts both novel structure and function onto EPO"[214] and upheld the novelty of the disputed claim. This move is worth noting. Even though the claim at issue lacks a novelty-imparting structural limitation, external evidence was admitted to show that a process limitation corresponds to a structural difference between the claimed material and the prior art, thereby rendering the claimed material novel. Acknowledgement that the structure and function of a prior art EPO was difficult to reproduce and verify, so that the change in the process apparently created a different structure (yet one that was not and probably could not be captured in a structural limitation), rescued the validity of the claim from an anticipation challenge.[215]

The *Hoffman-La Roche* decision shows that process limitations can be an important tool in the hands of patent applicants. If potential structural limitations are difficult to pin down or appear to be overly restrictive, a process limitation can be introduced as a proxy for a novel structure and help establish the patentability of a claim over the prior art.[216] Indeed, the unique status of composition claims with process limitations, reflected in the fact that such claims are not subject to the maxim "that which infringes if later anticipates if earlier,"[217] may help make up for the reduced level protection of such claims relative to "pure" composition claims. As the Federal Circuit noted in *Hoffman-La Roche*, "an accused product may meet each limitation in a claim, but not possess features imparted by a process limitation that might distinguish the claimed invention from the prior art."[218]

A related issue to consider is whether enforcement of the enablement requirement through process limitations affects the analysis of whether prior art is sufficiently enabling as to be anticipatory.[219] In analyzing cases on enablement by prior art, the Federal Circuit noted: "The disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."[220] In biotechnological arts, it is likely that prior art would almost always have to describe a method of making the disclosed product and provide adequate identifying data in order to be enabling, since, as discussed above in Part II.B, structure and identity of biotechnological products can be highly process-dependent and difficult to ascertain.[221] Furthermore, as *Hoffman-La Roche* suggests, an applicant can defeat the charge of anticipation by submitting evidence of structural differences between the claimed product and the material disclosed in prior art.[222] Such an approach has the salutary effect of rewarding applicants who perform laboratory experiments rather submit mere paper patent applications.[223] It is important to note, however, that this Article does not propose heightened enablement or "working prototype" requirements for biotechnological arts. Rather, the Article argues for restricting claims to certain process-dependent inventions to ensure commensurability between claim scope and disclosure that is understood to be a part of the enablement requirement in patent law.[224]

Conclusion

The proposal described in this Article is controversial. It is unquestionable that process limitations would weaken the level of protection available to patentees who invent in the field of biotechnology. Nevertheless, the arguments advanced herein are meant to stay firmly within the confines of the enablement doctrine as it has been developed from foundational cases such as the *Incandescent Lamp Patent* case to modern decisions such as *In re Fisher*, *In re Wands*, and *In re Vaeck*. The key insight of this Article is to treat processes as another form of species into which a generic claim can be decomposed. Recognition that every product claim is really a genus of processes adds another dimension to the space in which the unpredictability of the art can play a role. The Article shows the importance of evaluating the genus of processes for making a claimed product in the context of the enablement inquiry, as performed through the underlying analyses of whether claim breadth is in "reasonable correlation" to the disclosures of the specification and of whether the specification teaches those skilled in the art to practice the subject matter of the invention without "undue experimentation." In addition, the Article advances a workable proposal for encouraging changes in claiming practice that can help foster compliance with the enablement requirement of § 112 ¶ 1.

Several Federal Circuit decisions of the past two decades have shown discomfort with broad claims of biotechnology.[225] One judicial innovation for invalidating broad biotechnology patents is the application of the written description requirement to originally filed claims.[226] Although this line of cases has been vigorously criticized by a number of scholars,[227] the Federal Circuit has recently affirmed the existence of the written description requirement and its potential application to originally filed claims in an en banc decision.[228] Another approach for cabining the claims directed to the subject matter of biotechnology is to limit the scope of the claims to embodiments known at the time of the filing,[229] but this proposal runs into conflict with the venerable doctrine of allowing the patentee to capture some of the upside from unforeseeable after-arising technologies that fall within the literal scope of its claims.[230] Finally, some commentators have suggested doing away with the doctrine that treats "natural extracts" as patentable subject matter.[231] Such a prohibition, however, contravenes well-established caselaw,[232] and, in any case, probably would not apply to synthetic proteins made using engineered cells.

In contrast, the approach outlined herein relies on the enablement doctrine, which is less controversial than the written description doctrine,[233] attempts to achieve consistency with recent Federal Circuit case law dealing with the enablement requirement,[234] and applies the holding of a recent case that clarified the status of process limitations in infringement analysis.[235] Moreover, the approach of this Article is consistent with the doctrine that claims may be invalid for lack of enablement if they read on a large number of inoperative embodiments.[236] Most importantly, however, this Article strives to help make the enablement doctrine of patent law more consonant with the research community's requirements of operability and verifiability, which themselves are based on the fundamental norm of reproducibility.

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1. MICHAEL C. H. MCKUBRE, THE IMPORTANCE OF REPLICATION, in ICCF-14 INTERNATIONAL CONFERENCE ON CONDENSED MATTER NUCLEAR SCIENCE 1 (2008) (internal quotations omitted).

2. IUPAC COMPENDIUM OF CHEMICAL TERMINOLOGY 567 (2d ed. 1997).

3. *See, e.g.*, Kenneth Chang, *Columbia Chemistry Professor Is Retracting 4 More Papers*, N.Y. TIMES, June 15, 2006.

4. *See* Chang, *supra* note 3.

5. *See generally* EUGENIE SAMUEL REICH, PLASTIC FANTASTIC: HOW THE BIGGEST FRAUD IN PHYSICS SHOOK THE SCIENTIFIC WORLD (2009).

6. *See, e.g.*, Rudolph Carnap, *Testability and Meaning*, in READINGS IN PHILOSOPHY OF SCIENCE (Herbert Feigl & May Brodbeck eds., 1953).

7. *See, e.g.*, *Guidelines for Characterization of Inorganic and Organometallic Compounds*, J. AM. CHEM. SOC'Y , http://pubs.acs.org/page/jacsat/submission/inorg_
character.html ("Only in exceptional circumstances will a paper be published in which none of the new compounds reported has been isolated and fully characterized.").

8. *See* J. AM. CHEM. SOC'Y , *Ethical Guidelines to Publication of Chemical Research*, *in* J. AM. CHEM. SOC'Y PUBS. 1, 2 (2006), *available at* http://pubs.acs.org/userimages/
ContentEditor/1218054468605/ ethics.pdf ("An author's central obligation is to present an accurate account of the research performed" and that "[a] primary research report should contain sufficient detail . . . to permit the author's peers to repeat the work.").

9. *See id.*

10. J. AM. CHEM. SOC'Y , *supra* note 8 ("In many cases, X-ray diffraction may provide the most unambiguous characterization of [inorganic compounds] . . . .").

11. *See* Frank E. Koehn & Guy T. Carter, *The Evolving Role of Natural Products in Drug Discovery*, 4 NAT. REVS. DRUG DISCOVERY 206 (2005); *see also infra* note 129 and accompanying text.

12. 35 U.S.C. § 112 (2008).

13. *Id.* Note that enablement is determined as of the time of the filing. *See* MANUAL OF PATENT EXAMINING PROCEDURE (8th ed. Rev. 7, July 2008) [hereinafter "MPEP"] § 2164.01 ("Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, *when filed*, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.") (emphasis added).

14. *See, e.g.*, Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re* Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). A number of underlying factual inquiries, including (1) the quantity of experimentation necessary, (2) the amount of direction or guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the invention, and (8) the breadth of the claims, are made in order to conclude whether the experimentation is undue. *See In re* Wands, 858 F.2d 731, 735, 736–37 (Fed. Cir. 1988).

15. On these facts, the USPTO may also reject claims under 35 U.S.C. § 101 as lacking operable utility. *See, e.g.*, *In re* Swartz, 232 F.3d 862 (Fed. Cir. 2000). Note that a rejection of a claim for lack of enablement under 35 U.S.C. § 112 ¶ 1 can be a corollary of a § 101 operable utility rejection. *See* MPEP §§ 2107.02, 2164.07.

16. *Wands*, 858 F.2d at 735.

17. *See* Subhashini Chandrasekharan, Sapka Kumar, Cory M. Valley & Arti Rai, *Proprietary Science, Open Science and the Role of Patent Disclosure: The Case of Zinc-Finger Proteins*, 27 NAT. BIOTECHNOLOGY 140, 142–43 (2009); Jeanne C. Fromer, *Patent Disclosure*, 94 IOWA L. REV. 539, 553 (2009) ("The accepted understanding in patent policy and doctrine is that disclosure of a patented invention to the public—and its dedication to the public after the expiration of the patent term—is part of a quid pro quo the patentee must provide to gain the broad patent right.") (citations omitted); *see also* Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 150–51 (1989). *But see* Timothy R. Holbrook, *Possession in Patent Law*, 59 S.M.U. L. REV. 123 (2006) (arguing that the patent document serves primarily to show that the inventor has possession of the claimed invention).

18. *See* Tun-Jen Chiang, *Fixing Patent Boundaries*, 108 MICH. L. REV. 523, 529 (2010) (discussing "the public notice function of claims"); Kelly A. Casey, *Patent Hermeneutics: Form and Substance in Claim Construction,* 59 FLA. L. REV. 333 (2007); Clarisa Long, *Patent Signals*, 69 U. CHI. L. REV. 625 (2002); *see also* Holbrook, *supra* note 17, at 149–50.

19. Technically, "specification" refers to both the claims and the written description of the patent. However, use of the term "specification" to refer to the part of the patent document other than the claims is now common, and I use "specification" in this sense.

20. *See* Orin S. Kerr, *Rethinking Patent Law in the Administrative State*, 42 WM. & MARY L. REV. 127 (2000).

21. Perhaps, however, such a patent has some limited value in informing the public of what does not work.

22. For general accounts of fundamental difficulties encountered in ascertaining what claims mean, *see* Dan L. Burk & Mark A. Lemley, *Fence Posts or Sign Posts? Rethinking Patent Claim Construction*, 157 U. PA. L. REV. 1743 (2009); Jeffrey A.

Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY TECH. L.J. 1141 (2008); Mark A. Lemley, *The Changing Meaning of Patent Claim Terms*, 104 MICH. L. REV. 101 (2005). *See also supssra* note 18.

23. *See* United States v. Adams, 383 U.S. 39, 50 (1966) ("An inoperable invention or one which fails to achieve its intended result does not negative novelty."); PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). Courts have applied the "undue experimentation" standard to enablement by anticipatory art. *See, e.g.*, Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003).

24. *See supra* note 23. To be sure, the standards for enablement under § 112 and enablement by anticipatory prior art under § 102 are not identical. For example, the potentially anticipatory reference does not have to disclose any utility in order to be enabling for the purposes of anticipation. *See* Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1326 (Fed. Cir. 2005) (stating that "a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102").

25. MPEP § 2121.02.

26. *See, e.g.*, *In re* Wiggins, 488 F.2d 538 (C.C.P.A. 1973). The applicant may convey information about trying and failing to reproduce prior art experiments to the USPTO in a "Rule 132" affidavit. 37 C.F.R. § 1.132 (West 2010). For an example of a Rule 132 affidavit, see U.S. Pat. App. No. 11/867,587, *Amendment and Request for Reconsideration after Non-Final Rejection*, at 28–33 (filed July 14, 2009).

27. *See* Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984).

28. *See, e.g.*, Christopher A. Harkins, *Fending off Paper Patents and Patent Trolls: A Novel "Cold Fusion" Defense Because Changing Times Demand It*, 17 ALB. L.J. SCI. & TECH. 407 (2007); Sean B. Seymore, *Heightened Enablement in the Unpredictable Arts*, 56 UCLA L. REV. 127 (2008).

29. A more prosaic reason to oppose such reform is that it may not lead to cost-effective use of the USPTO's resources. *See generally* Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U. L. REV. 1495 (2001).

30. One commentator suggested a procedural change in the prosecution of paper patents, arguing that patentees who draft claims supported by prophetic examples must bear the burden of demonstrating enablement. *See* Seymore, *supra* note 28, at 156 ("While the lack of working examples would not absolutely preclude patentability, in order to rebut the prima facie case, the applicant would have to show that the specification provides some technique which enables the scope of protection sought by the claims, unless such knowledge is reasonably accessible to the PHOSITA.") (citation omitted). As the law stands now, the burden is on the USPTO to demonstrate lack of enablement, even for paper patents. *See id.*

31. *See* Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1212 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991) ("What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible.") While this statement refers to the best mode requirement of § 112 ¶ 1, it can apply with equal force to the enablement requirement.

32. Courts have looked to research norms for guidance in other areas of patent law. For example, in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), the Federal Circuit relied partly on the research community's expectations to hold that, for a claimed compound whose asserted utility lies on in a pharmaceutical setting, *in vitro* testing is sufficient to satisfy substantial utility requirements of § 101. "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes *the expectation of further research and development*." *Id.* at 1569 (emphasis added). There is an active debate in legal academia on what role scientific norms should play in patent law. *See* ROBIN COOPER FELDMAN, THE ROLE OF SCIENCE IN LAW (2009); Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177 (1987); F. Scott Kieff, *Facilitating Scientific Research: Intellectual Property Rights and the Norms of Science: A Response to Rai & Eisenberg*, 95 NW. U. L. REV. 691 (2001); Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U. L. REV. 77 (1999). Of course, an important part of this debate, not addressed here, is that the research community is not homogeneous, encompassing, for example, academic and industrial research communities. Nevertheless, the goals of reproducibility, operability, and verifiability are shared by all scientists.

33. *See supra* notes 12–24.

34. While claims can generally be supported with an adequate specification in order to comply with the enablement requirement, the Supreme Court has recognized that the problem can often reside in the claim itself. Thus, some overly broad claims simply cannot be supported by the specification to overcome the challenge of invalidity:

While the cases more often have dealt with efforts to resort to specifications to expand claims, it is clear that the latter fail equally to perform their function as a measure of the grant when they overclaim the invention. When they do so to the point of invalidity and are free from ambiguity which might justify resort to the specifications, we agree with the District Court that they are not to be saved because the latter are less inclusive.

Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 336 U.S. 271, 277 (1949); *see also infra* Part II.

35. *See infra* Part I.B for a definition and discussion of process limitations.

36. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1291 (Fed. Cir. 2009) (en banc).

37. Courts have generally placed both process and source elements in the same category. *See, e.g.*, Amgen Inc. v. F. Hoffman-LaRoche, Ltd., 580 F.3d 1340, 1369–70 (Fed. Cir. 2009) (citing *Sandoz* for its holding on "process terms" and using the case to analyze "source limitations" in one of the patents-in-suit). Note that I use "element" to refer to parts of a claim whose legal status is unclear (e.g., process elements pre-*Sandoz*), and "limitation" to refer to claim elements that have legal force in infringement analysis.

38. Sitrick v. Dreamworks, LLC, 516 F.3d 993, 1000 (Fed. Cir. 2008).

39. *Sandoz*, 566 F.3d at 1291.

40. 314 F.3d 1313 (Fed. Cir. 2003).

41. 35 U.S.C. § 112 (2008) ("The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."); *see also* 35 U.S.C § 154(a) (2008) (describing a patent as "a grant to the patentee, his heirs or assigns, of the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States").

42. Giles Sutherland Rich, *Extent of Protection and Interpretation of Claims – American Perspectives*, 21 INT'L REV. INDUS. PROP. & COPYRIGHT L. 497, 499 (1990).

43. *See, e.g.*, *In re* Hiniker Co., 150 F.3d 1362, 1369 (Fed. Cir. 1998).

44. David Sanker, Note, Phillips v. AWH Corp.: *No Miracles in Claim Construction*, 21 BERKELEY TECH. L.J. 101, 101 (2006) (noting that "the court did not explain how to read claims in light of the specification without importing limitations from the specification into the claims").

45. AbTox, Inc. v. Exitron Corp., 122 F.3d 1019, 1023 (Fed. Cir. 1997) (citing Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996)).

46. 35 U.S.C. § 101 (2008).

47. A preamble itself can, under certain circumstances, serve as a limitation. *See* MPEP § 2111.02.

48. 35 U.S.C. § 102 (2008).

49. 35 U.S.C. § 103 (2008).

50. 35 U.S.C. § 112 (2008). Disclosure requirements are satisfied by the patent document as a whole, i.e., by claims in conjunction with the specification.

51. Carroll Touch, Inc. v. Electro Mechanical Sys., Inc., 15 F.3d 1573, 1576 (Fed. Cir. 1993).

52. *See* Jeanne F. Loring & Cathryn Campbell, *Intellectual Property and Human Embroynic Stem Cell Research*, 311 SCIENCE 1716 (2006).

53. *See generally* Charles W. Adams, *Allocating Patent Rights Between Earlier and Later Inventions*, 54 ST. LOUIS U. L.J. 55 (2009). Of course, a potential infringer can escape liability by modifying the composition by designing around the claim such that the new composition does not fall within the scope of the claim.

54. *See* United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247 (Fed. Cir. 1989). The liability of an improving inventor to the owner of the "dominant" patent is a general feature of patent law, however, and is not limited to composition claims. *See supra* note 53.

55. *See* 35 U.S.C. § 154(a), which describes patents as granting "the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States." Any patent, not just one with composition claims, grants such a right to exclude, but certain types of composition claims are seen as particularly powerful relative to other types of claims, such as process claims. *See* Oskar Liivak, *Maintaining Competition in Copying: Narrowing the Scope of Gene Patents*, 41 U.C. DAVIS L. REV. 177, 201–03, 230–31 (2007); *supra* note 52 and accompanying text. *But see* Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Competition*, 2009 B.C. INTELL. PROP. & TECH. F. 070201, at *45 (2009) (suggesting that claims to certain compositions are particularly susceptible to being designed around).

56. Note, *The Disclosure Function of the Patent System (or Lack Thereof)*, 118 HARV. L. REV. 2007, 2015 (2005).

57. *See, e.g.*, Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993); *see also* Paul M. Janicke, *The Crisis in Patent Coverage: Defining Scope of an Invention by Function*, 8 HARV. J.L. & TECH. 155 (1994).

58. *See supra* note 37.

59. ROGER SCHECHTER & JOHN THOMAS, PRINCIPLES OF PATENT LAW 213–14 (2d ed. 2004).

60. Judge Newman of the Federal Circuit believes that only such pure or "true" product-by-process claims should be called product-by-process claims. *See* Atlantic Thermoplastics Co. v. Faytex Corp., 974 F.2d 1279, 1284 (Fed. Cir. 1992) (Newman, J., dissenting from the denial of rehearing en banc). I generally follow this approach in the Article, calling claims

that have structural limitations in addition to process limitations by a cumbersome, but descriptive moniker "composition claims with process limitations."

61. *See Atlantic Thermoplastics Co.*, 974 F.2d at 1284.

62. 927 F.2d 1565 (Fed. Cir. 1991). For an excellent early account of the *Scripps* case and the 1991 *Amgen v. Chugai* case (see *infra* note 131 and accompanying text), see Michael S. Greenfield, Note, *Recombinant DNA Technology: A Science Struggling with the Patent Law*, 44 STAN. L. REV. 1051, 1093 (1992) (concluding that "[i]nstead of product patents, process claims constitute a more appropriate form of protection for naturally occurring proteins"). For another set of views on these cases, see Bret Field, Note, *Protein Pharmaceuticals: Altering the Scope of Product Patents to Accommodate Recombinant DNA Technology*, 15 HASTINGS COMM. & ENT. L.J. 495 (1993).

63. *Id.* at 1583. This so-called infringement-validity maxim is sometimes stated as follows: "that which would literally infringe if later in time anticipates if earlier." Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001)).

64. *See* Atlantic Thermoplastics Co., Inc. v. Faytex Corp., 970 F.2d 834, 844 (Fed. Cir. 1992) ("An applicant could obtain a process patent for a new, useful, and non-obvious process, but could not claim rights to a product already in the prior art by merely adding a process limitation.").

65. *Scripps*, 927 F.2d at 1583.

66. 970 F.2d 834.

67. *Atlantic Thermoplastics Co., Inc.*, 970 F.2d at 846; *see also* at 838 n.2 (noting that *Scripps* failed to consider Supreme Court precedent). *But see* Atlantic Thermoplastics Co., Inc. v. Faytex Corp., 974 F.2d 1279, 1281 (Fed. Cir. 1992) (Rich, J., dissenting from the denial of rehearing en banc) ("The most egregious act of the *Atlantic* panel . . . is its defiant disregard, for the first time in this court's nearly ten-year history, of its rule that no precedent can be disregarded or overruled save by an *en banc* court, on the stated but feeble ground that the authors of the precedential opinion 'ruled without reference to the Supreme Court's previous cases involving product claims with process limitations.' . . . This is not only insulting to the *Scripps* panel . . . , it is mutiny. It is heresy. It is illegal.").

68. *Atlantic Thermoplastics*, 974 F.2d at 1279. Although *Scripps*, according to Federal Circuit rules, should have been followed as the earlier of the two panel decisions, *see id.* at 1281 ("where there are *conflicting* [panel] precedents, the *earlier* precedent controls") (emphasis in original), some district courts followed *Atlantic Thermoplastics*. For an early case following *Atlantic Thermoplastics*, see *Tropix, Inc. v. Lumigen, Inc.*, 825 F. Supp. 7 (D. Mass. 1993). For a case following *Scripps*, see *Trs. of Columbia Univ. v. Roche Diagnostics GmbH*, 126 F. Supp. 2d 16 (D. Mass. 2000). For attempts to reconcile *Atlantic Thermoplastics* and *Scripps*, see *Atlantic Thermoplastics*, 974 F.2d at 1281–98 (Newman, J., dissenting from the denial of rehearing en banc); Gregory S. Maskel, *Product-by-Process Patent Claim Construction: Resolving the Federal Circuit's Conflicting Precedent*, 17 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 115 (2006).

69. 566 F.3d 1282, 1291 (Fed. Cir. 2009) (en banc).

70. *Id.*; *see* 21 U.S.C. § 355(j) (2008) (detailing the law of ANDAs).

71. U.S. Patent No. 4,935,507 (issued June 19, 1990) ("the '507 patent").

72. Lupin Ltd. v. Abbott Labs., 491 F. Supp. 2d 563 (E.D. Va. 2007).

73. Abbott Labs. v. Sandoz, Inc., 486 F. Supp. 2d 767 (N.D. Ill. 2007).

74. *See* U.S. FOOD AND DRUG ADMINISTRATION, *Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications*, http://www.fda.gov/ohrms/dockets/ac/02/briefing/3900B1_04_Polymorphism.doc (last visited Nov. 26, 2009).

75. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1299 (Fed. Cir. 2009) (en banc).

76. *Id.* at 1294–95.

77. *Cf.* SCHECHTER & THOMAS, *supra* note 59, at 214 (noting that "[product-by-process] claims are most common in chemical practice").

78. '507 patent, col.16, l. 13–34 & 43–50.

79. PXRD is a standard analytical technique used to characterize crystalline compounds, and peaks in a PXRD spectrum represent a "signature" of a specific crystalline form of a chemical compound.

80. '507 patent, col. 16, l. 29–34.

81. '507 patent, col. 16, l. 43–50.

82. U.S. Patent No. 4,559,334 (issued Dec. 17, 1985) ("the '334 patent").

83. U.S. Pat. App. No. 07/229,489, *Examiner's Action (Non-Final Rejection)*, at 2 (filed May 9, 1989).

84. U.S. Pat. App. No. 07/229,489, *Amendment and Request for Reconsideration After Non-Final Rejection*, at 7 (filed Oct. 27, 1989).

85. *Id.* at 4 (emphasis in original). Note that properties of a chemical compound are inseparable from its structure for the purpose of non-obviousness determinations. That is, a compound whose structure is obvious in view of prior art may still be non-obvious under § 103 if it has unexpected properties. *See In re* Papesch, 315 F.2d 381, 391–92 (C.C.P.A. 1963). A claimed compound (here, crystalline cefdinir) may be novel and non-obvious even if falls into a previously disclosed genus. *In re* Baird, 16 F.3d 380, 382 (Fed. Cir. 1994). Here, the prior art patent disclosed (and claimed) cefdinir without any limitations. *See* '334 patent, col. 20, l. 21 (claim 2 encompassing crystalline cefdinir); *see also infra* note 105 and accompanying text.

86. U.S. Pat. App. No. 07/229,489, *Amendment and Request for Reconsideration After Non-Final Rejection*, at 6 (filed Oct. 27, 1989) (emphasis added).

87. U.S. Pat. App. No. 07/229,489, *Original Application*, at 3 (filed Aug. 9, 1988).

88. U.S. Pat. App. No. 07/229,489, *Examiner Interview Summary Record* (Nov. 14, 1989).

89. *See supra* notes 75–76 and accompanying text.

90. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1296 (Fed. Cir. 2009) (en banc). Note that the court did not perceive any legally cognizable difference between the phrases "obtainable by" and "obtained by" – the former was treated as equivalent to the latter in that it introduced a process limitation. *Id.* at 1295.

91. *Abbott Labs.*, 566 F.3d at 1295 ("The process limitations cannot be haphazardly jettisoned for an infringement analysis when they were so important in the patentability analysis."); *see also id.* at 1294 ("Because the inventor chose to claim the product in terms of its process, however, that definition also governs the enforcement of the bounds of the patent right. This court cannot simply ignore as verbiage the only definition supplied by the inventor.").

92. *Id.* at 1299–1320.

93. *See supra* notes 62–63 & 65 and accompanying text.

94. Atlantic Thermoplastics Co., Inc. v. Faytex Corp., 974 F.2d 1279, 1281–98 (Fed. Cir. 1992) (Newman, J., dissenting from the denial of rehearing en banc).

95. *See supra* note 63 and accompanying text.

96. *Sandoz*, 566 F.3d at 1319 ("The purpose of the rule of necessity is to allow inventors of complex new products to obtain the patent scope to which their invention is entitled-the scope of the novel product they invented, no more and no less."). For more on the rule of necessity, *see* Gary Newson, Note, *Product-by-Process Patent Claims: Arguing for a Return to Necessity and a Reduction in the Scope of Protection*, 40 ARIZ. ST. L.J. 327 (2008).

97. *Sandoz*, 566 F.3d at 1310–11 (citing MPEP § 2113). The issue of whether a process-related phrase is definitional or truly limiting as a process element is a matter of claim construction. *See generally* Eric P. Mirabel, *Product-by-Process Claims: A Practical Perspective*, 68 J. PAT. & TRADEMARK OFF. SOC'Y 3 (1986) and the discussion *infra* in Part I.C; *see also infra* note 103.

98. *Sandoz*, 566 F.3d at 1320–21.

99. *Id.* at 1293 (quoting Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 19 (1996)).

100. Atlantic Thermoplastics Co. v. Faytex Corp., 974 F.2d 1279, 1284 (Fed. Cir. 1992) (Newman, J., dissenting from the denial of rehearing en banc).

101. *Id.*

102. *Id.*

103. *Id.* For this third type of claim, the very existence of a process limitation can be a matter of claim construction. For example, verbs like "fluorinated," "molded," and "bonded," can be read as introducing process-based limitations or as describing the structure of the product. For an illuminating analysis of claim construction and other issues in these types of claims, *see* Mirabel, *supra* note 97.

104. '334 patent, col. 20, l. 21.

105. *See In re* Baird, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re* Jones 958 F.2d 347, 350 (Fed. Cir. 1992).

106. *See supra* notes 84–85 and accompanying text.

107. *Cf.* Smithkline Beecham Corp. v. Apotex Corp., 439 F.3d 1312 (Fed. Cir. 2006) (holding that product-by-process claims were anticipated by a patent on the underlying product in spite of an apparent structural difference between the claimed product and the prior art product).

108. *See supra* note 79 and accompanying text.

109. The patentees actually contested this conclusion, but the court found their argument to be without merit. *See* Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1289 (Fed. Cir. 2009).

110. *Id.* at 1289–91.

111. *See* Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 336 U.S. 271, 277 (1949).

112. *See, e.g.*, Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274 (Fed. Cir. 2007).

113. *See supra* note 103 and accompanying text.

114. Of course, chemical patents often claim genera of molecules rather than individual molecules. For simplicity and ease of comparison, I will initially consider the case where a claim is directed only to a single molecule.

115. *See generally* DANIEL C. HARRIS, QUANTITATIVE CHEMICAL ANALYSIS (5th ed. 1998); ROBERT M. SILVERSTEIN, FRANCIS X. WEBSTER & DAVID KIEMLE, SPECTROMETRIC IDENTIFICATION OF ORGANIC COMPOUNDS (7th ed. 2005).

116. *See In re* Swartz, 232 F.3d 862 (Fed. Cir. 2000).

117. 35 U.S.C. § 112 ¶ 1 (2008) ("The specification shall contain a written description of the invention, and of the manner and process of making *and using it*, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and *use the same* . . . .") (emphasis added).

118. For a recent rejection for lack of how-to-use enablement, *see Ex Parte Samuelson*, No. 2008-5927 (B.P.A.I. Feb. 10, 2009) (affirming examiner's rejection of U.S. Pat. App. No. 10/958,452).

119. *See* MPEP § 2164.01(c); *see also* MPEP § 2164.08(b).

120. *See* Lefstin, *supra* note 22, at 1168–81 (showing that all claims have infinite scope).

121. MPEP § 2164.01(b).

122. *See* MPEP § 2164.03.

123. MPEP § 2164.06(b) (discussing the case of *In re* Wright, 999 F.2d 1557 (Fed. Cir. 1993)).

124. SCHECHTER & THOMAS, *supra* note 59, at 186.

125. This identity of utilities is exactly what gives generics manufacturers the assurance that the pursuit of making copies of brand-name pharmaceuticals will yield effective products. Of course, the FDA's requirements for approval of generics require a great deal more from generics manufacturers than simply the proof of structural equivalence to the brand-name product. *See* U.S. FOOD AND DRUG ADMINISTRATION, *Facts and Myths About Generic Drugs*, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last updated Oct. 13, 2009).

126. The fact that a small molecule will generally behave the same way no matter what the process of production is goes to one of the *Wands* factors in the "undue experimentation" inquiry, namely the predictability or unpredictability of the invention. *See supra* note 14. That is, molecule X made by process A will have predictably similar utility (and likely the same utility) as molecule X made by process B. A claim to an infinite genus of processes for making molecule X, therefore, easily satisfies the *Wands* predictability factor.

127. For excellent analyses of the correspondence between the enablement requirement and after-arising technologies, see Kevin Emerson Collins, *Enabling After-Arising Technologies*, 34 J. CORP. L. 1083 (2009); Kevin Emerson Collins, *The Reach of Literal Claim Scope into After-Arising Technology: On Thing Construction and the Meaning of Meaning*, 41 CONN. L. REV. 493 (2008).

128. While structural *similarity* of chemical compounds does not guarantee the same function or utility, *see In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990), structural *identity* generally does, as long as the follow-on product does not have impurities that interfere with its functioning; *see also supra* note 125. *See generally* John R. Thomas, CONG. RESEARCH SERV., RL 33605, *Authorized Generic Pharmaceuticals: Effects on Innovation* 1 (2008).

129. For an interesting example of a composition patent on a natural product, which was later prepared by synthetic routes, *see* U.S. Patent No. 5,840,750 (issued Nov. 24, 1998) (disclosing discodermolide, a powerful antitumor agent extracted from a marine sponge). For examples of methods for making this compound in the laboratory, *see* Jennie B. Nerenberg et al., *Total Synthesis of the Immunosuppressive Agent (-)-Discodermolide*, 115 J. AM. CHEMICAL SOC'Y. 12621 (1993) and Amos Smith III et al., *Total Synthesis of (-)-Discodermolide*, 117 J. AM. CHEMICAL SOC'Y. 12011 (1995). By all accounts, research into making the discodermolide target led to spectacular advances in synthetic organic chemistry. *See* Michael Freemantle, *Scaled-up Synthesis of Discodermolide*, 82 CHEMICAL & ENGINEERING NEWS 33, 33 (2004) (quoting Steven V. Ley, Professor of Chemistry at the University of Cambridge, England, as saying that "[t]he ability to make something at this level of complexity as opposed to extracting it from natural product sources illustrates the power of modern synthetic chemistry.").

130. JEREMY M. BERG ET AL., BIOCHEMISTRY 157–59, 813–35 (5th ed. 2002) (presenting an overview of recombinant DNA technique and an overview of protein synthesis that occurs in the recombinant DNA technique).

131. Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1206 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991).

132. *See* Bryan A. Liang, *Regulating Follow-on Biologics*, 44 HARV. J. ON LEGIS. 363, 369 ("[B]iologics and chemical medicines are tremendously different in size. A biologic with thousands to millions of atoms forming a highly interconnected group of hundreds to thousands of amino acids aggregated into chains and subgroups, is much larger than a chemical drug, which typically consists of just dozens of atoms forming a single molecule.").

133. Rx List Webpage, *The Internet Drug Index*, http://www.rxlist.com/paxil-drug.htm (last visited Nov. 28, 2009).

134. Hans H. Stuting & Ira S. Krull, *Determination of Pituitary and Recombinant Human Growth Hormone Molecular Weights by Modern High-Performance Liquid Chromatography with Low Angle Laser Light Scattering Detection*, 539 J. CHROMATOGRAPHY A 91 (1991); *see also* George E. Chapman et al., *The 20,000 Molecular Weight Variant of Human Growth Hormone: Preparation and Some Physical and Chemical Properties*, 256 J. BIOLOGICAL CHEMISTRY 2395 (1981). As seen from these references, even the very determination of approximate molecular weight of human growth hormone was the product of intensive research efforts, while the molecular weight of paroxetine can be readily calculated from the atomic weights of constituent atoms because its precise structure is known.

135. *See* Liang, *supra* note 132, at 369–71.

136. *See* BERG ET AL., *supra* note 130, for a detailed description of the transfection method.

137. *See* Liang, *supra* note 132, at 370–71.

138. *See supra* notes 1–11 and accompanying text. In contrast, small-molecule pharmaceuticals are made by laboratory techniques that tend to be more readily reproducible, and it is more straightforward to verify their structures.

139. Liang, *supra* note 132, at 370–71.

140. Even as techniques for determining the primary structure of proteins (i.e., connectivity of atoms in a protein) mature, challenges persist for the analysis of secondary (interaction between fragments of the protein molecule), tertiary (three-dimensional form of the protein molecule), and quaternary (interaction between the protein molecules) structure, which can be affected by subtle chemical changes. *See* Yang Zhang, *Progress and Challenges in Protein Structure Prediction*, 18 CURRENT OPINION ON STRUCTURAL BIOLOGY 342 (2008); *see also* Liang, *supra* note 132, at 369 (citing BERG ET AL., *supra* note 130, at 51–63); *supra* note 22 and accompanying text.

141. For example, biological drugs often present the problem of immunogenicity, whereby the immune system reacts adversely to the drug, sometimes with fatal consequences. Immunogenicity can severely limit the usefulness of biologic drugs, particularly in the context of attempts to make follow-on analogs. *See* Liang, *supra* note 132, at 375–78.

142. The relationship between biosimilars and branded biological drugs is analogous to, but not the same as, the relationship between generics and branded pharmaceutical drugs. *See generally* Liang, *supra* note 132.

143. 42 U.S.C § 262 (West 2010); *see also* William J. Simmons, *Biosimilars Pathway: A Far Cry from Hatch-Waxman*, LAW360 (Mar. 30, 2010), http://law360.com/articles/157960.

144. For such provisions in the European biosimilars regulation, see *EMEA Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, available at* http://www.emea.europa.eu/pdfs/human/ biosimilar/4934805en.pdf (last visited Dec. 28, 2009) and *EMEA Guideline on Similar biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues*, *available at* http://www.emea.europa.eu/pdfs/ human/biosimilar/4283205en.pdf (last visited Dec. 28, 2009).

145. Liang, *supra* note 132, at 372–73 (quoting Press Release, FDA, *U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) on Possible International Non-Proprietary Name (INN) Policies for Biosimilars* (Sept. 1, 2006)).

146. MPEP § 2164.05 ("[C]onsiderations made by the FDA for approving clinical trials are different from those made by the USPTO in determining whether a claim is enabled.") (citing Scott v. Finney, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")).

147. *See supra* notes 117–119 and accompanying text.

148. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1294 (Fed. Cir. 2009) (en banc).

149. *See* MPEP § 2164.03.

150. *Id.* (citations omitted); *see also* Bilstad v. Wakapoulos, 386 F.3d 1116, 1125 (Fed. Cir. 2004) ("If the difference between members of the group is such that the person skilled in the art would not readily discern that other members of the genus would perform similarly to the disclosed members, i.e., if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus."). Note, however, that *Bilstad* approached the problem of overclaiming through the written description, rather than enablement, analysis.

151. Consol. Electric Light Co. v. McKeesport Light Co., 159 U.S. 465, 468 (1895).

152. *Id.* at 472. ("[The patentees] made a broad claim for every fibrous or textile material, when in fact an examination of over six thousand vegetable growths showed that none of them possessed the peculiar qualities that fitted them for that

purpose. Was everybody then precluded by this broad claim from making further investigation? We think not."). The Court further noted:

[T]o hold that one who had discovered that a certain fibrous or textile material answered the required purpose should obtain the right to exclude everybody from the whole domain of fibrous and textile materials, and thereby shut out any further efforts to discover a better specimen of that class than the patentee had employed, would be an unwarranted extension of his monopoly, and operate rather to discourage than to promote invention. *Id.* at 476.

153. One author described this problem as the patentee's assertion of a "false inventive genus." Brian P. O'Shaughnessy, *The False Inventive Genus: Developing a New Approach for Analyzing the Sufficiency of Disclosure Within the Unpredictable Arts*, 7 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 147 (1996).

154. *Consol. Electric Light Co.*, 159 U.S. at 472–73 ("The injustice of [upholding the validity of the 'carbonized fibrous or textile material' genus] is manifest in view of the experiments made, and continued for several months, by Mr. Edison and his assistants, among the different species of vegetable growth, for the purpose of ascertaining the one best adapted to an incandescent conductor. Of these he found suitable for his purpose only about three species of bamboo, one species of cane from the valley of the Amazon . . . and one or two species of fibers from the agave family."). The art of making incandescent light bulbs was certainly an unpredictable one in the Nineteenth Century!

155. *See* J. Benjamin Bai, *Enablement Issues Concerning Aggressively Broad Generic Claims*, 7 NW J. TECH. & INTELL. PROP. 1, 3–13 (2008) (putting the *Incandescent Lamp Patent* case in the context of modern enablement law).

156. *See supra* notes 135–145. Utility concerns over broad composition claims have motivated courts to invalidate claims for lack of enablement. For example, the Federal Circuit in Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991), held a biotechnology claim invalid because of "attendant uncertainty as to what utility will be possessed by these [claimed but untested] analogs." *Id.* at 1214; *cf.* MPEP § 2164.08(b) (noting that claims can be rejected for lack of enablement if they read on a "significant numbers of inoperative embodiments . . . when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.").

157. *See In re* Hogan, 559 F.2d 595 (C.C.P.A. 1977). Nevertheless, a recent Federal Circuit decision made it clear that the enablement inquiry is no less lenient for "pioneering" patents than for "routine" patents. *See* Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335 (Fed. Cir. 2003).

158. Of course, the former remedy (introduction of a process limitation) would occur at the patent prosecution stage, while the latter remedy (invalidation) would occur at the litigation stage.

159. U.S. Patent No. 5,621,080 (issued Apr. 15, 1997) ("the '080 patent").

160. 314 F.3d 1313 (Fed. Cir. 2003).

161. *Id.*, col. 38, l. 45–50.

162. BERG ET AL., *supra* note 130, at 813–35.

163. Anne Dell & Howard R. Morris, *Glycoprotein Structure Determination by Mass Spectrometry*, 291 SCIENCE 2351 (2001).

164. *Id.*

165. '080 patent, col. 9, l. 16–21 ("It is consequently projected in the art that the best prospects for fully characterizing mammalian erythropoietin and providing large quantities of it for potential *diagnostic and clinical use* involve successful application of recombinant procedures to effect large scale microbial synthesis of the compound.") (emphasis added). For general background on glycosylation, *see* KURT DRICKAMER & MAUREEN E. TAYLOR, INTRODUCTION TO GLYCOBIOLOGY (2nd ed. 2006).

166. Determining glycosylation was an important barrier in the development of proposed regulatory regimes for the approval quasi-generic versions of biologic drugs. *See, e.g.*, Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(a)(2)(k)(1)(A)-(H) (2007) (noting that characteristics for evaluating biosimilars include: "data on comparability, comparability of principal molecular structure, posttranslational events, infidelity of translation or transcription, amino acid sequence, *polysaccharide repeating units, glycosylated protein product structure*") (emphasis added); *see also* notes 135–145 and accompanying text.

167. '080 patent, col. 32, l. 66 - col. 33, l. 3 ("Preliminary analyses reveal significant heterogeneity in products produced by the expression system, likely to be due to variations in glycosylation of proteins expressed, and relatively high mannose content of the associated carbohydrate.").

168. *See* David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 224 (2005). The relevance of the lack of FDA approval is that it provides evidence of possible lack of utility due to process dependence in glycoprotein biosynthesis. *See supra* note 146 and accompanying text.

169. This is so because it would require undue experimentation for a person of ordinary skill in the art to select the process for making EPO with the asserted utilities. *See supra* notes 117–129 and accompanying text; *see also infra* notes 182–193 and accompanying text.

170. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1329 (Fed. Cir. 2003). ("By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101."). *See also infra* note 232 and accompanying text.

171. *See supra* note 136.

172. '080 patent, col. 10, l. 24.

173. *Amgen*, 314 F.3d at 1326 (noting, in the context of a patent with claims similar to that of the '080 patent, that "[t]he plain meaning of the claims controls here, and they plainly are not so limited"). It is unclear that this analysis would survive the holding of *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315–17 (Fed. Cir. 2005) (en banc) (emphasizing the importance of the specification for ascertaining the meaning of claim terms).

174. *Amgen*, 314 F.3d at 1360 (Clevenger, J., dissenting in part).

175. *In re* Mayhew, 527 F.2d 1229, 1232–33 (C.C.P.A. 1976); MPEP § 2172.01; *cf.* Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479–80 (Fed. Cir. 1998) (proposing what appears to be an "essential element" test to evaluate whether claims met the written description requirement); MPEP § 2164.08(c).

176. *In re* Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

177. *Id.* at 490.

178. *Id.*

179. *Id.* at 495.

180. *Id.* at 496. The court further held that "[t]here must be sufficient disclosure . . . to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed," and that, for such an unpredictable art, "the required level of disclosure will be greater than, for example, the disclosure of an invention involving a 'predictable' factor such as a mechanical or electrical element." *Id.*

181. *Id*.

182. *See, e.g.*, Abstract of the '080 patent ("Disclosed also are chemically synthesized polypeptides disclosing the biochemical and immunological properties of EPO.").

183. '080 patent, col. 35, l. 4–21.

184. The specification of the '080 patent suggests that yet another process for making claimed EPO, affinity purification, was known at the time of the filing: "While polyclonal and monoclonal antibodies as described above provide highly useful materials for use in immunoassays for detection and quantification of erythropoietin and can be useful in the affinity purification of erythropoietin, it appears unlikely that these materials can readily provide for the large scale isolation of quantities of erythropoietin from mammalian sources sufficient for further analysis . . . ." ('080 patent, col. 9, l. 7–12).

185. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1359 (Fed. Cir. 2003) (Clevenger, J., dissenting in part). Note that the shortcoming of Claim 3 is strikingly similar to that of the claims at issue in Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274 (Fed. Cir. 2007), which dealt with the patent where the plaintiff claimed a method that encompassed both mechanical and electronic sensors but said very little about electronic sensors in the specification. The patent was held invalid due to lack of enablement across the full scope of the claimed invention. The court made much of the fact that the electronic sensors, which represented a "distinctly different" embodiment of the invention, were not enabled. *Id.* at 1285; *see also* Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007) (invalidating claims for lack of enablement on similar grounds).

186. *Amgen*, 314 F.3d at 1325.

187. *See supra* notes 163–167. Recall that unpredictability of the art and breadth of the claims are two of the *Wands* factors in the inquiry whether experimentation is undue. *See supra* note 14; *see also supra* note 126 and accompanying text.

188. *Amgen*, 314 F.3d at 1359 (Clevenger, J., dissenting) (quoting Amgen Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 160 (D. Mass. 2001)).

189. *Id.* at 1335.

190. *See* MPEP § 2164.01(b) (noting that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied").

191. *See* Jeffrey A. Lefstin, *The Constitution of Patent law: The Court of Customs and Patent Appeals and the Shape of the Federal Circuit's Jurisprudence*, 43 LOY. L.A. L. REV. 843, 875 (2010) (defining the question presented in *Amgen* as whether "the

disclosure of one method of synthesizing a natural product permit the patentee to claim essentially all synthetic versions of the product").

192. *In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970).

193. *In re* Wands, 858 F.2d 731, 733 (Fed. Cir. 1988).

194. *See supra* note 148 and accompanying text.

195. *Amgen*, 314 F.3d at 1329. Claim 1 as originally filed read as follows: "A purified and isolated polypeptide having part or all of the primary structural conformation and one or more of the biological properties of naturally occurring erythropoietin and *characterized by being the product of prokaryotic or eukaryotic expression of an exogenous DNA sequence*." U.S. Pat. App. No. 08/468,556, *Original Application*, at 97 (filed June 6, 1995) (emphasis added to flag the process element).

196. The applicant made a preliminary amendment, cancelling all the originally filed claims (including the claim reproduced *supra* in note 195) and adding several new claims. The filing was preceded by an examiner interview where it was noted that "[a]pplicant intends to file preliminary amendment. . . . Exr. [examiner] favorably impressed." U.S. Pat. App. No. 08/468,556, *Examiner Interview Summary Record* (Dec. 11, 1996) (Claims A and B accompanying the interview report became Claims 1 and 2 of the '080 patent). Interestingly, the claim that was to become Claim 3 of the '080 patent was not discussed with the examiner but added anyway in the amendment that followed the interview. The applicant's remarks confirm that "[n]o discussion was had during the interview concerning the specific subject matter of newly-submitted claim[] 71," which became Claim 3. *Third Preliminary Amendment and Terminal Disclaimer Pursuant to 37 C.F.R. § 1.321*, at 9 (filed Dec. 20, 1996). All of the claims filed as part of this amendment were allowed without any subsequent substantive amendments or office actions. Claim 3, of course, was the crucial claim in the '080 patent. The prosecution history can be obtained from the USPTO and is also on file with the author.

197. U.S. Patent No. 5,547,933 (issued Aug. 20, 1996) ("the '933 patent") (emphasis added). *See supra* note **Error! Bookmark not defined.** for another example of appropriate process limitation language.

198. '933 patent, col. 10, l. 42 and Examples 6–10.

199. *See supra* Part II.D.

200. Claim 3 of the '933 patent was never asserted in the *Amgen* litigation, of course, because the accused infringer did not use the process in the claim, but relied on a completely different process that involved tricking *endogenous* DNA into making the host cell express (i.e., synthesize) the desired EPO. *Amgen*, 314 F.3d at 1325.

201. Allowing broad composition claims without meaningful structural or process limitations creates a de facto more lenient standard for biotechnological patents relative to chemical patents. *Accord* Natalie A. Lissy, Note, *Patentability of Chemical and Biotechnology Inventions: A Discrepancy in Standards*, 81 WASH. U. L.Q. 1069 (2003).

202. MPEP § 2260.

203. Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 916 (1990). *But see* Edmund W. Kitsch, *Elementary and Persistent Errors in the Economic Analysis of Intellectual Property*, 53 VAND. L. REV. 1727, 1739–40 (2000) (arguing that other commentators have underestimated the importance of patent licensing, which can help inventors avoid litigation).

204. Amgen Inc. v. F. Hoffmann-La Roche Ltd., 580 F.3d 1340 (Fed. Cir. 2009).

205. *Id.* at 1376.

206. *Id.*

207. Source limitations are treated the same way as process limitations by the Federal Circuit. *See supra* note 37 and accompanying text.

208. Kerry A. Dolan, *Diagnosing Amgen*, FORBES, Oct. 25, 2006, *available at* http://www.forbes.com/2006/10/25/leadership-amgen-pharmaceutical-lead-managecz_kd_ 1025amgen.html.

209. Takaji Miyake, Charles K.-H. Kung & Eugene Goldwasser, *Purification of Human Erythropoietin,* 252 J. BIOLOGICAL CHEMISTRY 5558 (1977).

210. Amgen Inc. v. F. Hoffmann-La Roche Ltd., 580 F.3d 1340, 1363–70 (Fed. Cir. 2009).

211. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 n.20 (Fed. Cir. 2003); *see also Hoffmann-La Roche*, 580 F.3d at 1366 (citing Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 373 (1938) (noting that "[i]t has long been the case that an old product is not patentable even if it is made by a new process")); *supra* notes 64–65 and accompanying text.

212. *Hoffman-La Roche*, 580 F.3d at 1364. In addition to appealing the district court's denial of JMOL on the issue of invalidity, Hoffman-La Roche appealed the district court's denial of a new trial, which it sought based on erroneous jury instructions that did not mention the special rule that process limitations cannot impart novelty to a product-by-process claim to an old product. *Id.* at 1368. The Federal Circuit denied this appeal as well because the claim was not anticipated, and the jury instructions were therefore non-prejudicial. *Id.* at 1369.

213. *Id.* at 1367 (referring to expert testimony that showed differences in "carbohydrate composition of recombinant EPO and urinary EPO"). The court cited this evidence in upholding the validity of an EPO claim in another Amgen patent, but the evidence applies with equal force to Claim 3 of the '933 patent. "For purposes of the source limitation, which is what is at issue, there essentially is no difference between [the other claim] . . . and claim 3 of the '933 patent . . . ." *Id.* at 1369.

214. *Id.* at 1365.

215. *Cf. supra* Part II.E.

216. *See also supra* Part I.C.

217. *Hoffmann La-Roche*, 580 F.3d at 1370.

218. *Id.*

219. *See supra* notes 23–24 and accompanying text.

220. Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1055 (Fed. Cir. 2003).

221. *See also supra* Parts II.C & II.D.

222. Such evidence can be submitted to the USPTO via Rule 132 affidavits. *See supra* note 26 and accompanying text.

223. *See* Sean B. Seymore, *The Teaching Function of Patents*, 85 NOTRE DAME L. REV. 621 (2010); Seymore, *Heightened Enablement in the Unpredictable Arts*, *supra* note 30.

224. *Cf.* O'Reilly v. Morse, 56 U.S. 62 (1854); *In re* Moore, 439 F.2d 1232, 1236 (C.C.P.A. 1971) ("The relevant inquiry may be summed up as being whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the claims.").

225. *See, e.g.*, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed. Cir. 2004); Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997); Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361 (Fed. Cir. 1997); Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993); *In re* Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993); *In re* Vaeck, 947 F.2d 488 (Fed. Cir. 1991); Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991).

226. *Rochester*, 358 F.3d 916; *Eli Lilly*, 119 F.3d 1559; *see also* Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316 (Fed. Cir. 2002).

227. *See, e.g.*, Jeffie A. Kopczynski, Note, *A New Era For § 112? Exploring Recent Developments in the Written Description Requirement as Applied to Biotechnology Inventions*, 16 HARV. J.L. & TECH. 229 (2002); Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615 (1998); Karen G. Potter, *Getting Written Description Right in the Biotechnology Arts: A Realist Approach to Patent Scope*, 28 BIOTECHNOLOGY L. REP. 1 (2009); *see also* Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155 (2002) (suggesting that the written description requirement is enforced more rigorously for biotechnology patents than for patents in other areas of technology, particularly software).

228. Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

229. *See* Robin Feldman, *Rethinking Rights in Biospace*, 79 S. CAL. L. REV. 1, 40–41 (2005).

230. *See* United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247 (Fed. Cir. 1989); *In re* Hogan, 559 F.2d 595 (C.C.P.A. 1977).

231. *See, e.g.*, Allen K. Yu, *Why It Might Be Time to Eliminate Genomic Patents, Together with the Natural Extracts Doctrine Supporting Such Patents*, 47 IDEA 659 (2007); *see also* Liivak, *supra* note 55.

232. *See* Diamond v. Chakrabarty, 447 U.S. 303 (1980); Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95 (C.C.S.D.N.Y. 1911). *But see* Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (invalidating patent claims to DNA containing breast cancer susceptibility genes).

233. *See generally* Robin C. Feldman, *The Inventor's Contribution*, 2005 UCLA J.L. & TECH. 6 (2005).

234. *See* Sitrick v. Dreamworks, LLC, 516 F.3d 993, 1000 (Fed. Cir. 2008); Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274 (Fed. Cir. 2007); Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007); Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335 (Fed. Cir. 2003); AK Steel Corp. v. Sollac and Ugine, 344 F.3d 1234 (Fed. Cir. 2003).

235. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1291 (Fed. Cir. 2009) (en banc).

236. MPEP § 2164.08(b); *see also* Atlas Powder Co. v. E.I. Du Pont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984); *In re* Cook, 439 F.2d 730, 735 (C.C.P.A. 1971). For a recent decision invalidating a patent on enablement grounds by employing the inoperative embodiments reasoning, see Pharm. Resources, Inc. v. Roxane Labs., Inc., Nos. 2007-1093, 2007-1134, 253 Fed. Appx. 26, 2007 (Fed. Cir. 2007). In the Article, I approached the question of inoperative embodiments through the lens of the undue experimentation inquiry, insofar as undue experimentation is required to select *operative* embodiments of the disputed claim. *See supra* notes 119 & 155 and accompanying text.