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Does Size Matter? Nanoscale Particle Size as an Indicator of Inherency in Nanopharmaceutical Patent Validity

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DOES SIZE MATTER? NANOSCALE PARTICLE SIZE AS AN INDICATOR OF INHERENCY IN NANOPHARMACEUTICAL PATENT VALIDITY

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ABSTRACT

Scientific and technological advances in nanopharmaceuticals bring the doctrine of inherent obviousness to a head. On the one hand, nanotechnology promises to offer novel ways to target and treat traditionally incurable diseases by operating at a scale that is comparable to the scales that most biological systems use. On the other hand, nanotechnology inventions that result in improved pharmacokinetic properties are susceptible to validity challenges based on inherent obviousness.

Inherency and obviousness are two independently recognized and well-understood principles in United States patent law. Inherency refers to a claimed limitation or feature that is either necessarily present in, or the natural result of, the features expressly disclosed by the prior art. Obviousness, in contrast, refers to whether the claimed invention as a whole was readily apparent in the prior art based on a combination of references. Because inherency turns on whether something was necessarily present in the prior art at some earlier time, the analysis implicates hindsight. But because obviousness turns on

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what would have been obvious to a person having ordinary skill in the art at the time the invention was made, the analysis forbids hindsight.

Despite the seemingly mutual exclusivity between inherency and obviousness, the two principles have been increasingly applied together in the context of pharmaceutical and biotechnology inventions. Patent challengers frequently rely on the argument that improved pharmaceutical concentration and bioavailability at the target site is implicit in prior art teachings concerning how pharmaceutical particles behave at decreased sizes despite the novelty of the particle's size alone. Rather than engage in an arbitrary analysis focusing on how unexpected some pharmacokinetic response is, courts and the USPTO should eradicate the concept of inherent obviousness in its entirety.

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INTRODUCTION

Within the last thirty years, nanotechnology has emerged as a viable approach to overcome historically insurmountable technological deficits apparent in a variety of traditional scientific applications.[1] Nanotechnology refers to the design, production, or modification of structures, devices, or systems at the nanoscale (<100 nm).[2] Recently, nanotechnology has been used to investigate how structures engineered with nanomaterials interact with biological systems, like the human body.[3] Accordingly, nanotechnology, when applied as clinical nanomedicine, offers a promising approach for treating, diagnosing, or preventing historically untreatable diseases through the design and development of pharmaceutical nanoparticles (nanopharmaceuticals) to drive targeted drug delivery.[4] When compared to conventional drug delivery, nanoparticle-mediated drug delivery increases pharmaceutical concentrations in targeted cells relative to non-targeted cells, thereby decreasing symptoms of unfavorable side effects associated with the administered drug.[5] That said, nanotechnology's promising impact in clinical medicine collides with patentability challenges at the commercialization stage, where the process of converting basic nanopharmaceutical research into commercially viable products has been "difficult."[6] Despite this

1. Alexandre Albanese, Peter S. Tang & Warren C. W. Chan, *The Effect of Nanoparticle Size, Shape, and Surface Chemistry on Biological Systems*, 14 ANN. REV. BIOMEDICAL ENG'G 1, 2 (2012). Nanotechnology research focuses on the association between nanomaterial properties (optical, electrical, and magnetic) "with respect to their size, shape, and surface chemistry." *Id.*

2. *Id.*

3. *Id.*

4. *See id.*; *see also* Domenico Cassano, Salvador Pocoví-Martínez & Valerio Voliani, *Ultrasmall-in-Nano Approach: Enabling the Translation of Metal Nanomaterials to Clinics*, 29 BIOCONJUGATE CHEMISTRY 4, 4 (2018). Nanomedicine is the application of nanotechnology in the medical context. *Id.* For example, some of these medical applications include small-scale drugs in the form of nanoparticles or medical devices in the form of cell-repairing nanorobots. *See id.*; *see also* Jordan Paradise, *Claiming Nanotechnology: Improving USPTO Efforts at Classification of Emerging Nano-Enabled Pharmaceutical Technologies*, 10 NW. J. TECH. & INTELL. PROP. 169, 169 (2012).

5. *See* Raj Bawa, Srikumaran Melethil, William J. Simmons & Drew Harris, *Nanopharmaceuticals: Patenting Issues and FDA Regulatory Challenges*, 5 SCITECH LAW., no. 2, Fall 2008, at 1, 2. *See generally* Albanese et al., *supra* note 1.

6. Raj Bawa, M.S., Ph.D., FAAN, *Nanotechnology Patent Proliferation and the Crisis at the U.S. Patent Office*, 17 ALB. L.J. SCI. & TECH. 699, 719 (2007).

difficulty, however, viable commercialization depends on securing valid patent protection first.[7]

Patent law—one of the "most obscure legal disciplines"—sits on the front line of modern drug development.[8] To be patentable, an invention must be novel as well as useful, nonobvious, and compliant with patentability statutory requirements.[9] This fundamental principle of patent law favors patent validity unless the claimed invention covers unpatentable subject matter or has been previously disclosed by one or more prior art references.[10] Prior art references, however, need not disclose every limitation of the claimed invention.[11] Rather, prior art that fails to explicitly disclose the claimed invention nevertheless precludes patentability when a feature of the claimed invention

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7. Bawa et al., *supra* note 5, at 5.

8. *Id.* at 3.

9. 35 U.S.C. §§ 102, 103. The relevant portions of 35 U.S.C. § 102 provide:

> (a) NOVELTY; PRIOR ART.—A person shall be entitled to a patent unless—
> (1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or
> (2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

§ 102.

The relevant portions of 35 U.S.C. §103 provide:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

§ 103.

10. Bawa et al., *supra* note 5, at 3–4. Prior art is any evidence that tends to indicate the claimed invention is already publicly known. *What Is Prior Art?*, EUR. PAT. OFF., https://www.epo.org/learning/materials/inventors-handbook/novelty/prior-art.html [https://perma.cc/X5DY-V6CR]. Prior art need not be a tangible product because many inventions never become products; however, there might be evidence of that invention. *See id.* Common examples of prior art include previous patent applications, scientific articles, or a prior sale of the claimed invention. *See* U.S. PAT. & TRADEMARK OFF., MANUAL OF PATENT EXAMINING PROCEDURE § 2152, at 2100-356 (rev. 9th ed. 2020) (citations omitted); *see also* Michael Goldman, Georgia Evans & Andrew Zappia, *Inherent Anticipation in the Pharmaceutical and Biotechnology Industries*, 5 COLD SPRING HARBOUR PERSPS. MED. 1, 2–3 (2015), http://perspectivesinmedicine.cshlp.org/content/5/8/a021006.full.pdf [https://perma.cc/R9ET-GVWR].

11. *See* §§ 102, 103.

necessarily flows from the prior art.[12] Nanopharmaceuticals present a unique patentability challenge because a decrease in particle size significantly impacts the compound's molecular properties, like biologic distribution (or biodistribution); however, whether the resultant molecular properties necessarily flow from the larger version of that compound remains unclear.[13] Yet with no clear direction from the Federal Circuit, pharmaceutical companies and research institutions are left wondering whether modifying particle size at the nanoscale renders inherent the biological effects resulting from a decrease in size.[14]

Companies either seeking a nanotechnology patent or attempting to enforce a nanotechnology patent share a common problem: patent uncertainty.[15] One obstacle to enforcing nanotechnology and nanopharmaceutical patents, in general, concerns whether a claimed limitation of a nanoparticle composition necessarily flows from, or is inherently present in, the prior art.[16] Although courts generally agree that properties resulting from a decrease in particle size are inherent, at a minimum, courts should cautiously apply the inherency doctrine when evaluating the validity of nanopharmaceutical patents.

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12. Goldman et al., *supra* note 10, at 3. For example, if the prior art product (or composition), "in its normal and usual operation would necessarily perform" the claimed method, then the prior device teaches the claimed method. U.S. PAT. & TRADEMARK OFF., *supra* note 10, § 2112.02, at 2100-140. Further, if the invention claims a method of producing positron-emitting rubidium-82 for use in positron emission tomography (PET) scans by encouraging electron capture (which subsequently overcomes any subject matter eligibility hurdle), a prior disclosure of strontium-82 for use in PET scans will likely bar patentability even if that disclosure is silent as to electron capture because strontium-82 naturally produces rubidium-82 after decaying by electron capture; thus, rendering the electron capture limitation necessarily or inherently present in the prior art. *See, e.g.*, BRACCO DIAGNOSTICS, CARDIOGEN-82 RUBIDIUM RB 82 GENERATOR (2000), http://www.nuclearonline.org/PI/Cardiogen.pdf [https://perma.cc/7UNJ-GTHN].

13. *See* Albanese et al., *supra* note 1, at 8; *see also* Par Pharm., Inc., v. TWi Pharms., Inc., 773 F.3d 1186, 1186 (Fed. Cir. 2014).

14. Bawa, *supra* note 6, at 728–29. The Federal Circuit, otherwise known as the United States Court of Appeals for the Federal Circuit, is the only appellate level court with jurisdiction to hear patent case appeals, other than the Supreme Court. *Court Jurisdiction*, U.S. CT. OF APPEALS FOR THE FED. CIR., http://www.cafc.uscourts.gov/the-court/court-jurisdiction [https://perma.cc/Y6FK-EF2M]. In *Par Pharmaceutical, Inc. v. TWi Pharmaceuticals., Inc.*, the Federal Circuit laid out the proper analysis for evaluating inherent obviousness under 35 U.S.C. § 103 but remanded the case back to the district court for a ruling. *TWi Pharms., Inc.*, 773 F.3d at 1193–94, 1200.

15. *See* Bawa et al., *supra* note 5, at 4; *see also* Bawa, *supra* note 6, at 730. This uncertainty arises as a result of overly broad pharmaceutical patent claims, that leave pharmaceutical companies unsure of how far the scope of their patent claims extends. Bawa, *supra* note 6, at 730.

16. *TWi Pharms., Inc.*, 773 F.3d at 1195–96.

This Note proceeds in the following three parts. First, Part I provides a general introduction to the structure and function of nanopharmaceuticals and the law governing their patentability.[17] Second, Part II investigates and analyzes the current state of U.S. case law concerning nanopharmaceutical patent challenges based on inherency.[18] Finally, Part III proposes that courts should rethink the inherency standard as it applies to nanopharmaceutical patents—or eliminate it altogether.[19]

I. BACKGROUND

Nanotechnology is "the design, characterization, production and application of structures, devices and systems" by modifying shape and size of matter at the nanoscale.[20] Because nanotechnology simply refers to manipulating matter on an atomic, molecular, or supramolecular scale, the application of nanotechnology within each respective scientific field is equally diverse.[21] Accordingly, nanotechnology defined by size encompasses a naturally broad range of scientific fields and disciplines, including molecular biology, surface science, electrical engineering, semiconductor physics, and more.[22] One application of nanotechnology—namely, nanomedicine—refers to the medical application of nanotechnology.[23]

17. *See infra* Part I.

18. *See infra* Part II.

19. *See infra* Part III.

20. Albanese et al., *supra* note 1; But what constitutes nanoscale depends on the source. Cephalon, Inc. v. Abraxis Bioscience, LLC, 618 F. App'x 663, 665 (Fed. Cir. 2015) ("1000 nanometers"); Paradise, *supra* note 4, at 193 ("[U]nder 100 nm.").

21. *Nanotechnology*, CTRS. FOR DISEASE CONTROL & PREVENTION, NAT'L INST. FOR OCCUPATIONAL SAFETY & HEALTH (NIOSH), https://www.cdc.gov/niosh/topics/nanotech/default.html [https://perma.cc/HK3C-2Y7L] (Mar. 27, 2020); *see also* W. JONES & C. N. R. RAO, SUPRAMOLECULAR ORGANIZATION AND MATERIALS DESIGN 34–35 (2002). The supramolecular scale refers to an area of chemistry concerning chemical systems composed of a discrete number of molecules. *See id.* A molecule is "an electrically neutral group of two or more atoms held together by [a] chemical bond[]" or bonds. *2.6: Atoms and Molecules– Real and Relevant*, CHEMISTRY LIBRETEXTS, https://chem.libretexts.org/Courses/Sacramento_City_College/SCC%3A_CHEM_330_-_Adventures_in_Chemistry_(Alviar-Agnew)/02%3A_Atoms/2.06%3A_Atoms_and_Molecules-_Real_and_Relevant [https://perma.cc/C2LX-JXAW] (Sept. 24, 2021).

22. *See Nanotechnology*, *supra* note 21.

23. ROBERT A. FREITAS, NANOMEDICINE, VOLUME I: BASIC CAPABILITIES 1, 25–26 (1999), http://kriorus.ru/sites/kriorus/files/nanomed/NANOMEDI.PDF [https://perma.cc/D65R-2AQT].

Nanomedicine encompasses a broad application of nanotechnology via the design and development of nanomaterials, biological devices, nanoelectric biosensors, and biological machines.[24] Recent trends in experimental nanomedicine have focused on examining the interaction between nanomaterials and biological systems, thereby paving the way for novel developments in targeted drug delivery through nanoparticles.[25]

The "unique" and "far-ranging properties" attributed to nanoparticles have already facilitated major breakthroughs in the pharmaceutical industry, which raked in $16 billion on nanomedicine sales in 2015 alone.[26] But success comes at a high price. Because of the high-risk, high-reward nature of the pharmaceutical industry—which is characterized by exceedingly high research and development (R&D) costs, lengthy clinical trials and data generation periods, and intense competition among pharmaceutical market participants—patents are a key ingredient for commercial success due to their promise for market exclusivity.[27]

The possibility for commercial success with nanopharmaceutical and nanoparticle-mediated drug delivery systems inspired an influx of patent applications at the United States Patent and Trademark Office

24. *See* Francisco T.T. Cavalcante, Italo R. de A. Falcão, José E. da S. Souza, Thales G. Rocha, Isamayra G. de Sousa, Antônio L. G. Cavalcante, André L. B. de Oliveira, Maria C. M. de Sousa & José C.S. dos Santos, *Designing of Nanomaterials-Based Enzymatic Biosensors: Synthesis, Properties, and Applications*, 2 ELECTROCHEM 149, 152 (2021).

25. *See* Albanese et al., *supra* note 1. Targeted drug delivery reduces overall drug consumption by increasing pharmaceutical concentrations at the targeted intracellular site and subsequently reduces negative side effects because of this overall reduction in drug consumption. *See* Timothy S. Tracy, *Pharmacokinetics*, *in* MODERN PHARMACOLOGY WITH CLINICAL APPLICATIONS 48, 49–52 (Charles R. Craig & Robert E. Stitzel eds., 6th ed. 2004).

26. *See* Paradise, *supra* note 4; *Market Report on Emerging Nanotechnology Now Available*, NAT'L SCI. FOUND. (Feb. 25, 2014), https://www.nsf.gov/news/news_summ.jsp?cntn_id=130586 [https://perma.cc/A7SR-CKM9]; *see also* Cornelia Vasile, *Polymeric Nanomaterials: Recent Developments, Properties and Medical Applications*, *in* POLYMERIC NANOMATERIALS IN NANOTHERAPEUTICS 36 (Cornelia Vasile ed., Elsevier 2018) ("Nanomedicine sales reached $16 billion in 2015, with a minimum of $3.8 billion in nanotechnology R&D invested every year."). For example, Abraxane®, a drug used for the treatment of breast cancer, netted $848 million from sales in 2014 alone. Press Release, Celgene, Celgene Corporation Announces 2015 and Long-Term Financial Outlook and Preliminary 2014 Results (Jan. 12, 2015) (on file with the Georgia State University Law Review).

27. *See* Paradise, *supra* note 4; *see also* Michael Berger, *Nanotechnology Patents and the Future of the Pharma Industry*, NANOWERK (Oct. 12, 2007), https://www.nanowerk.com/spotlight/spotid=2912.php [https://perma.cc/U74Z-KKBU].

(USPTO) that continues in full force to date.[28] Rather than succumb to this influx of nanopharmaceutical patent applications, however, the USPTO did exactly as it does: It granted patents.[29] With no formal classification system to fully encompass novel nanotechnologies, the USPTO granted overly broad patent claims.[30] Broad nanopharmaceutical patent claims coupled with nanotechnology's promise to be the "next frontier" in health care is likely to trigger needless patent litigation because these products are just now beginning to reach commercialization stage.[31] With the added uncertainty that many pharmaceutical companies and research institutions face concerning whether far-reaching claims from earlier patents overlap with theirs, validity disputes are almost certain. The Federal Circuit had a chance to resolve this uncertainty. Yet the Federal Circuit's decision (or lack thereof) in *Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc.*, merely left many companies and universities wondering whether biological effects resulting from modifications in particle size at the nanoscale are inherently disclosed in prior art.[32]

A. Vehicles of Drug Delivery: How Do Nanopharmaceuticals Even Work?

Before the sophisticated structural components of nanoparticles can be appreciated, it is important to first understand how pharmaceuticals exert their biological effect. In any biological system, compound structure determines function, and nanoparticles are no exception to this well-established rule.[33] Nanopharmaceuticals work to increase pharmaceutical bioavailability at their on-site targets by improving pharmacokinetic and pharmacodynamic effects.[34] To produce an effect, a pharmaceutical particle binds to and interacts with specialized

28. *See* Paradise, *supra* note 4, at 191.
29. *See* Bawa et al., *supra* note 5, at 723.
30. *See id.* at 724.
31. *See* Paradise, *supra* note 4, at 169–70.
32. *See generally* Par Pharm., Inc., v. TWi Pharms., Inc., 773 F.3d 1186, 1186 (Fed. Cir. 2014).
33. *See generally* JONES & RAO, *supra* note 21. Shape and size are equally important. *See id.* at 36.
34. *See* ROBERT M. JULIEN, CLAIRE D. ADVOKAT & JOSEPH E. COMATY, A PRIMER OF DRUG ACTION 3–4, 36 (12th ed. 2010).

cellular surface receptors.[35] Particle binding leads to changes in a cell's functional properties, which result in the drug's signature pharmacologic response.[36] The strength of this attachment is determined by how the drug's three-dimensional structure fits with the receptor's three-dimensional site.[37] Importantly, even modest variations in a particle's chemical structure greatly influence the receptor's response to it.[38]

A drug's "total action" is measured by its pharmaceutical response at either a single receptor type or at a collection of different receptor types, depending on that drug's target specificity.[39] In either scenario, drug-receptor binding alters cellular function and subsequently produces observable physiological or psychological effects—a result of the drug's total action.[40] Irrespective of whether the total action results from binding at one receptor site or a collection of sites, unavoidable side effects persist.[41] Because nanoparticle-mediated delivery requires a smaller dose to achieve the same therapeutic effect, overall drug consumption is lowered and unavoidable side effects are less likely.[42]

35. *Id.* at 36. Receptors are relatively large (usually protein) molecules that sit on or within a cell. *Id.* at 38. Each receptor contains naturally occurring endogenous compounds, known as transmitters or modulators, that produce their biologic effects. *Id.* It is important to note that not all specialized receptors are located on cell members. *Id.* Some intracellular receptors located in the cytoplasm or nucleus are activated by small, hydrophobic ligand molecules. *See id.* at 38–49.

36. *Id.* at 36.

37. *Id.* at 36–37.

38. *See id.* at 37.

39. *Id.* at 50.

40. JULIEN ET AL., *supra* note 34, at 36–37, 50.

41. *See id.* at 50. Side effects refer to the additional responses of a particle's "total action" and limit a drug's efficacy when intolerable. *Id.* Against common belief, not all side effects are bad. *See id.* But investigating all the beneficial "effects" of side effects is beyond the scope of this Note.

42. Ramya Ranganathan, Shruthilaya Madanmohan, Akila Kesavan, Ganga Baskar, Yoganathan Ramia Krishnamoorthy, Roy Santosham & D. Ponraju et al., *Nanomedicine: Towards Development of Patient-Friendly Drug-Delivery Systems for Oncological Applications*, 7 INT'L J. NANOMEDICINE 1043, 1058 (2012).

B. A "Small" Introduction to Nanopharmaceuticals

Nanopharmaceuticals are colloidal particles ranging in size from ten to one thousand nanometers.[43] The smallest component of nanopharmaceuticals are nanoparticles, which result from combining active molecules or biological substances to enhance targeted drug delivery by the subsequent release of pharmaceutical agents at the targeted site.[44] One of the greatest advantages to nanoparticle-mediated drug delivery is a nanoparticle's ability to quietly bypass a biological system's natural immune response and continue on to its target.[45]

Cell-specific targeting is characterized by attachment of a pharmaceutical compound to specially designed carriers: nanoparticles.[46] Various nanomaterials may be used for nanoparticle construction—including polymers, liposomes, dendrimers, carbon materials, and even gold—and the nanomaterial used for construction consequently influences the nanoparticle's properties.[47] The properties of each particular nanomaterial have a differential effect on the nanoparticle's behavior within the biological system.[48] Differences in

43. Bawa et al., *supra* note 5, at 1–2. Yet it is critically important to note that the size range used to quantify a particle as a nanoparticle is inconsistent. *See id.*

44. *See id.* A typical nanoparticle is produced via chemical synthesis and coated with polymers, drugs, fluorophores, peptides, proteins, or oligonucleotides. Albanese et al., *supra* note 1, at 3.

45. *See* Syed A. A. Rizvi & Ayman M. Saleh, *Applications of Nanoparticle Systems in Drug Delivery Technology*, 26 SAUDI PHARM. J. 64, 65 (2018). A detailed discussion of immune functioning is beyond the scope of this Note, but it is important to mention that once a drug enters the circulation system, it is subject to detection by the lymphatic system. *Id.* If detected, macrophages will "engulf" (essentially kill) the exogenous matter. *See id.* Conventional forms of drug delivery systems generally rely on administering higher doses of a drug to achieve a therapeutic effect, whereas nanoparticle-mediated drug delivery systems rely on a smaller dose and even high therapeutic effect. *Id.*

46. *See* Agnieszka Z. Wilczewska, Katarzyna Niemirowicz, Karolina H. Markiewicz & Halina Car, *Nanoparticles as Drug Delivery Systems*, 64 PHARMACOLOGICAL REPS. 1020, 1020–21 (2012).

47. *Id.* at 1021; KAYE SCHOLER LLP, PHARMACEUTICAL AND BIOTECH PATENT LAW § 2:4.1(A), at 2-9 (David K. Barr & Daniel L. Reisner eds., 2015). Further, nanomaterials may be grouped according to their mechanical properties. *Id.* When classified by mechanical properties, polymers, lipid vesicles, dendrimers, and polymer-protein conjugates are at the "soft" end, while inorganic materials are at the "hard" end. *See* Cassano et al., *supra* note 4.

48. *See generally* Cassano et al., *supra* note 4; JULIEN ET AL., *supra* note 34, at 36. Pharmacodynamics concern the movement of drugs through the body, whereas pharmacodynamics concerns the body's biological response to those drugs. *Id.* at 36. Pharmacokinetics describe a drug's efficacy by characterizing its absorption, distribution, bioavailability, metabolism, or excretion as a function of time. *See id.* at 3–4.

nanomaterials also promote targeted nanoparticle delivery by interacting with cell surface biomolecules to promote cellular uptake.[49]

The "efficacy of most drug delivery systems is directly related to particle size."[50] Particle size is defined by the particle's mean diameter (in nanometers) or specific surface area (SSA).[51] In general, nanoparticles have a mean diameter under 100 nanometers, in comparison to their microparticle counterparts; however, many nanoparticle sizes tend to exceed 100 nanometers.[52] The 100 nanometer ceiling refers to the size at which nanomaterial properties tend to significantly change from their conventional and functional analogs.[53] Nevertheless, changing a compound's particle size—whether micro to nano or nano to micro—often, unpredictably and fundamentally, changes that particle's molecular properties.[54] "As a particle's size decreases, a [higher] proportion of its atoms" relocate to the particle's surface relative to its core.[55] The result is an increase

49. *See* Wilczewska et al., *supra* note 46, at 1021. A particle with a large surface area in the pharmaceutical realm is advantageous for that particle's subsequent affinity for drugs and small molecules, such as ligands or antibodies. *See id.* For example, coating a nanoparticle in a copolymer such as polyethylene glycol (PEG) enhances delivery because of the hydrophilic properties that are responsible for assisting the particle in stealthily passing by the lymphatic system. Rizvi & Saleh, *supra* note 45, at 66. PEG is a hydrophilic and relatively inert polymer that alters the binding ability of blood plasma proteins to bypass detection and remain in circulation longer. *Id.* In fact, PEG remains undetected so long as plasma proteins fail to bind to it. *See id*.

50. *Id.* at 65.

51. *See* KAYE SCHOLER LLP, *supra* note 47. Notably, one (1) micron is equivalent to 10^{-6} or 0.000001 meters. *What is the Nanoscale–Size and Scale*, UNIV. WIS.-MADISON, MRSEC EDUC. GRP. https://education.mrsec.wisc.edu/what-is-the-nanoscale-size-and-scale/ [https://perma.cc/4ZHV-WC7J].

52. *See* THOMAS R. GILBERT, REIN V. KIRSS, NATALIE FOSTER, STACEY LOWERY BRETZ & GEOFFREY DAVIES, CHEMISTRY: THE SCIENCE IN CONTEXT 590–91 (W. W. Norton & Co., Inc., 5th ed. 2018). One hundred nanometers is equivalent to 1×10^{-7} meters. *Id.* at 591.

53. Luigi Battaglia & Elena Ugazio, *Lipid Nano- and Microparticles: An Overview of Patent-Related Research*, 2019 J. NANOMATERIALS 1, 10 (2019). But cutting off nanoparticle classification at 100 nanometers may not tell the full story when the desired or ideal property (i.e., bioavailability, low toxicity, etc.) may be achieved at a larger size range. *See* Raj Bawa, Ph.D., *Will the Nanomedicine "Patent Land Grab" Thwart Commercialization?*, 1 NANOMEDICINE: NANOTECHNOLOGY, BIOLOGY & MED. 346, 346 (2005); *see also* Bawa et al., *supra* note 5, at 2 ("Because there is no universal convention or nomenclature that classifies nanopharmaceuticals, various nanoscale structures of different shapes are sometimes classified as nanopharmaceuticals.").

54. KAYE SCHOLER LLP, *supra* note 47. For example, micronizing the particles of a compound increases a particle's surface area, thereby altering properties such as solubility and processability. *See id.*

55. Bawa et al., *supra* note 5. As a result, the particle is more reactive and more soluble in water. *Id.*

in surface area and solubility.[56] But even more important is the resulting increase in bioavailable drug at the target site—the hallmark of nanoparticle efficacy.[57]

Nanoparticles' newfound efficacy has the potential to alter the current landscape of medicine, and pharmaceutical companies are beginning to reap the benefits of this technology by seeking patent protection.[58] It follows that the future of nanomedicine depends on securing patent protection and intellectual property rights.[59]

C. A Non-Technical Primer on Inherency

To be patentable, an invention must be novel, nonobvious, useful, and comply with the statutory subject-matter requirements.[60] First, the novelty requirement ensures that the claimed invention is truly "novel," or the first.[61] For a single prior art reference to anticipate (or render invalid) a claim under 35 U.S.C. § 102, the reference must disclose every limitation set forth in the claim.[62] Second, the

56. *See id.*; *see also* Rizvi & Saleh, *supra* note 45. Increasing the surface area of a particle increases solubility because surface area increases as particles are broken down and, consequently, more are in contact with the solvent. *See id.* It may be helpful to think about the relationship between surface area and solubility as this: Imagine a sugar cube; it is a solid, singular cube. But if the sugar cube were crushed, the surface area would subsequently increase, and what was once a sugar cube would begin to spread out as a powder. Rather than a mound of sugar, there is a generous blanket of sugar. The surface area of this "sugar blanket" is larger than the cube, and it will surely dissolve quicker than the larger cube because more of its atoms are on the surface. This is the solubility component.

57. *See id.*

58. Berger, *supra* note 27. For example, improvements in target specificity potentially address unmet medical needs, like effective chemotherapy agents, and these improvements in target specificity are only made possible by utilizing unique nanoparticle-mediated drug-delivery systems. *Id.*

59. *See id.* Many pharmaceutical companies utilize business models that rely on patent protection for blockbuster drugs. *Id.* Accordingly, securing a patent on each research breakthrough is critical to eventually commercializing and marketing a new product. *Id.*

60. *See* 35 U.S.C. §§ 102(a), 103.

61. *Anticipation*, CORNELL L. SCH., LEGAL INFO. INST., https://www.law.cornell.edu/wex/anticipation#:~:text=Anticipation%20is%20a%20grounds%20for,was%20invented%20by%20the%20patentee [https://perma.cc/G2N2-L2T3].

62. § 102(a). A prior art reference is evidence that the claimed invention is already known. *What Is Prior Art?*, *supra* note 10. *See, e.g.*, §§ 102(a), 103; JANICE M. MUELLER, PATENT LAW 229–30 (5th ed. 2016). In other words, the invention was known or used by others before the patent applicant filed an application for the claimed invention. *See, e.g.*, §§ 102(a), 103; MUELLER, *supra*. When every claimed limitation is known, used, or at least reasonably accessible to the public, then that prior disclosure is said to anticipate the claim. *See, e.g.*, §§ 102(a), 103; MUELLER, *supra*. Claim elements and claim limitations work together. *See, e.g.*, WORLD INTELL. PROP. ORG. (WIPO), PATENT CLAIM FORMAT AND TYPES OF

nonobvious requirement turns on whether a person with ordinary skill or knowledge in the subject area would know to combine the features disclosed in the prior art references to make the claimed invention.[63] For a reference to obviate a claimed invention under 35 U.S.C. § 103, it must have been readily apparent to "a person having ordinary skill in the art," at the time of invention, to combine the features disclosed by the prior art references to make the claimed invention.[64] The nonobvious requirement considers what a person having ordinary skill in the art knew at the time of invention.[65] Thus, retrospect is impermissible.[66] In essence, an invention that is obvious or not new cannot be patented.

CLAIMS 13, 16 https://www.wipo.int/edocs/mdocs/aspac/en/wipo_ip_phl_16/wipo_ip_phl_16_t5.pdf [https://perma.cc/XA4A-AKGB]. Claim elements are the named parts of the invention and can be thought of as nouns that describe the physical structure of the invention. *See* Dennis Crouch, *Query on Elements and Limitations*, PATENTLY-O (Mar. 17, 2009), https://patentlyo.com/patent/2009/03/query-on-elements-and-limitations.html [https://perma.cc/KCC4-66SN]. On the other hand, claim limitations are words or phrases that describe the elements, and can be thought of as adjectives, adverbs, or other modifying phrases. *Id.* For example, an issued patent or patent application may claim:

A [] device, comprising:

a handle;

a head portion connected to the handle; and

a protrusion being secured to the handle.

WORLD INTELL. PROP. ORG. (WIPO), *supra*, at 16. In this example, the handle, head portion, and protrusion are claim elements that describe structural features of the claimed invention, while "connected to the handle" and "secured to the handle" are claim limitations that describe the element to which they are attached. *Id.*

63. *Nonobviousness*, CORNELL L. SCH., LEGAL INFO. INST. https://www.law.cornell.edu/wex/nonobviousness [https://perma.cc/LC8T-W5UA]. A claimed invention is obvious if it is "readily apparent." *Id.* It is worth noting, however, that in some rare circumstances, no prior art reference is needed to obviate a claimed invention if the invention would have been readily apparent to anyone with ordinary knowledge in the subject area at the time of invention. *See id.*

64. *See, e.g.*, §§ 102(a), 103; *see also, e.g.*, MUELLER, *supra* note 62, at 30. The term "person having ordinary skill in the art," or PHOSITA, is patent law jargon. *See* § 103. This hypothetical person refers to an individual who has the same or similar skill level in a particular subject matter area that a standard person in that subject matter area would have. *See, e.g.*, §§ 102(a), 103; *see also, e.g.*, MUELLER, *supra* note 62, at 30. For example, if the invention refers to a chemical compound, a person having ordinary skill in the art would most likely be a chemist having a Ph.D. in the area of chemical sciences most closely related to the chemical compound (i.e., synthetic, organic, etc.). A claimed invention is usually obvious if a person having ordinary skill in the art could make the claimed invention based on the relevant prior art. *Nonobviousness*, *supra* note 63.

65. *Id.*

66. *See* U.S. PAT. & TRADEMARK OFF., *supra* note 10, § 2141.01, at 2100-262–2100-263 ("The pre-AIA 35 U.S.C. 103(a) requirement 'at the time the invention was made' is to avoid impermissible hindsight." (quoting U.S. PAT. & TRADEMARK OFF., § 2145, at 2100-321)); *see also* U.S. PAT. & TRADEMARK OFF., *supra* note 10, § 2145, at 2100-327.

Where a prior art reference discloses a feature of the claimed invention, the disclosure is usually express.[67] But the disclosure need not *always* be express.[68] This is where inherency comes in. An inherent feature may anticipate or obviate a claimed limitation even where that feature's existence was unknown in the prior art at the time it was disclosed.[69] A patent examiner or patent challenger relies on inherency to supply a claim element absent in the prior art by showing the claim element is "necessarily present" in the express subject matter of a prior art reference.[70] But because "inevitability is at the heart of inherency[,]" the "fact that a certain thing *may* result from a given set of circumstances" is insufficient to establish that it was inherent.[71] It follows that mere "probabilities or possibilities" cannot establish inherency.[72] Rather, a prior art reference or a combination of references that teaches the "natural result flowing" from performing the claimed limitation establishes inherency.[73]

Inherency is often invoked in cases involving patents related to pharmaceuticals, biotechnology, life sciences, and now, nanotechnology.[74] These invocations typically arise in cases where an inventor discovers "some previously unappreciated property" of a product or process that is itself anticipated or obvious, but the inventor nonetheless seeks to use this new discovery to patent the otherwise

67. Christopher Holman, *Inherency in the Patenting of Biotechnology and Pharmaceutical Innovation*, 39. BIOTECHNOLOGY L. REP. 79, 79 (2020).

68. *Id.* (emphasis added).

69. *Id.*

70. Ryan Pool, *The Inherency Doctrine: A Performance Review*, 101 J. PAT. & TRADEMARK OFF. SOC'Y 1000, 1000 (2019); Scaltech, Inc. v. Retec/Tetra, L.L.C., 178 F.3d 1378, 1384 (Fed. Cir. 1999). *See* Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003); Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1348–49 (Fed. Cir. 1999). Parties use inherency arguments when the prior art cited contains an incomplete description of the subject matter central to the dispute. *See Scaltech, Inc.*, 178 F.3d at 1382–84. For example, a prior art reference may disclose the claimed invention but may be simply missing an element. *See id.* at 1383–84. The party objecting to the patent makes an inherency argument to supply the element missing from the disclosure. *See id.*; *see also Schering Corp.*, 339 F.3d at 1377; *Atlas Powder Co.*, 190 F.3d at 1348–49.

71. Howmedica Osteonics Corp. v. Zimmer, Inc., 640 F. App'x 951, 957 (Fed. Cir. 2016); *Scaltech, Inc.*, 178 F.3d at 1384. It is insufficient that a certain thing may result from a given set of circumstances. *Howmedica Osteonics Corp.*, 640 F. App'x at 957.

72. *Scaltech, Inc.*, 178 F.3d at 1384.

73. Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991) (quoting *In re* Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

74. *See* Holman, *supra* note 67.

anticipated or obvious subject matter.[75] For example, a metabolite produced by a patented compound cannot itself be subsequently patented because that metabolite existed at the time the compound was patented, whether or not anybody realized it.[76]

Another common inherency issue relevant to pharmaceuticals arises when a composition of matter, product, or apparatus is claimed in terms of a property, characteristic, or function.[77] For example, if a prior art reference teaches a chemical structure identical to one presently claimed, it may be reasonable to assume (and argue) that the characteristics or functions flowing from the claimed structure are necessarily (or inherently) disclosed by the prior art because identical structure indicates identical properties.[78] Similarly, product and apparatus patents that claim features that are substantially identical to prior art products, or that are produced by substantially identical processes, could inherently disclose properties or functions disclosed in the prior art reference.[79] A prior art reference is more likely to inherently disclose a feature claimed in terms of its function, property, or characteristic—despite not expressly disclosing that feature's function, property, or characteristic—when compared to a feature claimed in terms of its structure.[80]

The lines blur even more when inherency is used to obviate (rather than anticipate) a claimed nanopharmaceutical invention. A person having ordinary skill in the art need not recognize an inherent feature at the time of invention irrespective of whether the inherent feature

75. *Id.*

76. *See* Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1375 (Fed. Cir. 2003). A metabolite is a small molecule produced as an intermediate or end product of metabolism. *Id.*

77. Goldman et al., *supra* note 10, at 3.

78. This example presumes no differences between the two chemical structures concerning size, function, and the like. *See In re* Spada, 911 F.2d 705, 708 (Fed. Cir. 1990) ("Products of identical chemical composition can not have mutually exclusive properties."); *see also* U.S. PAT. & TRADEMARK OFF., *supra* note 10, § 2112.01, at 2100-139. Prior art that teaches a chemical structure, identical to the structure in a present invention, also discloses properties that are necessarily present in that structure. U.S. PAT. & TRADEMARK OFF., *supra* note 10, § 2112.01, at 2100-139.

79. *See id.*; *see also In re* Schreiber, 128 F.3d 1473, 1478 (Fed. Cir. 1997) (claimed conical-shaped top for dispensing popcorn was the "same general shape" as the conical-shaped spout for dispensing oil from a can in the prior art).

80. Goldman et al., *supra* note 10, at 3. Importantly, method of use claims may also utilize an inherency argument where the use is directed to a result or to a property of known composition or character. *Id.*

was disclosed in the prior art.[81] That said, an unrecognized feature in the prior art can hardly be obvious. To the contrary, surprising results, or results achieved by experimental accident, albeit inherent, are not anticipated or obviated by a prior art reference.[82] Because the hallmark of nanoparticle-mediated drug delivery is improved target specificity, characterized by subsequent increases in bioavailability at the target site, these new, improved drug-delivery systems and their pharmacokinetic advancements often fall victim to inherency challenges.[83]

81. U.S. PAT. & TRADEMARK OFF., *supra* note 10, § 2112, at 2100-136, 2100-137. Yet this contention is seemingly contrary to the § 103 nonobviousness requirement, which is viewed from the perspective of what a person of ordinary skill in the art *knew at the time of invention*. *See id.* (emphasis added) ("Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103."). Older Federal Circuit cases generally state that a prior art reference discloses the claimed invention if the missing element is necessarily present in what is expressly described or taught by the reference *and* the inherent feature would have been recognized by a person having ordinary skill in the art. Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991) (emphasis added). But whether a person having ordinary skill in the art would have recognized the inherent feature in the prior art was specifically addressed in *Schering Corporation v. Geneva Pharmaceuticals*, where the Federal Circuit clarified that *Continental Can* does not require past recognition of an inherent feature. *See Schering Corp.*, 339 F.3d at 1378; Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991). Artisans of ordinary skill may not recognize inherent characteristics or functions in the prior art. Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999). Yet essentially rediscovering a previously unappreciated property or function of an old prior art composition "does not render the old composition patentably new. . . ." *See id.*; *see also* Titanium Metals Corp. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985) ("Congress has not seen fit to permit the patenting of an old [composition], known to others . . . by one who has discovered its . . . useful properties, or has found out to what extent one can modify the composition . . . without losing such properties."). *But see* Honeywell Int'l Inc. v. Mexichem Amanco Holding S. A. de C.V., 865 F.3d 1348, 1354 (Fed. Cir. 2017) (acknowledging that using inherency in an obviousness determination is more complicated because "'[t]hat which may be inherent is not necessarily known' and that which is unknown cannot be obvious." (first alteration in original) (quoting *In re* Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993)).

82. *See, e.g.*, Tilghman v. Proctor, 102 U.S. 707, 711–12 (1880). But the result must not have been appreciated or predicted by a person with ordinary skill or knowledge in the subject area in light of the prior art. *Id.* at 723–24. Accidental results produced under unusual conditions or while in pursuit of "other and different results, without . . . even being known what was done or how it had been done," likewise do not constitute inherent disclosures. *Id.* at 711–12 (noting that it would be "absurd" to consider this anticipation (citation omitted)). Similarly, results that are occasionally obtained are not inherent. *See* MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *see also In re Rijckaert*, 9 F.3d at 1534 (no inherent disclosure where optimal conditions not disclosed implicitly or explicitly). The distinction between accidental disclosure and failure to recognize an inherent limitation is one of necessity, and the question becomes whether it is *necessary* that those who made or used the invention disclosed in the prior art reference "actually recognized" at that time that the inherent feature existed. *See* MUELLER, *supra* note 62, at 234–35 (emphasis added); *see also* 35 U.S.C. § 103.

83. *See generally* Holman, *supra* note 67.

D. The Current Nanopharmaceutical Landscape

To date, the nanopharmaceutical patent landscape is "almost impossible to navigate."[84] First, pharmaceutical companies and research institutions continue to carve out "far-reaching" patent claims in hopes of receiving a broad scope of patent protection.[85] As more companies begin to enter commercialization stages, uncertainty lingers around the scope of nanopharmaceutical patent protection and whether the "far-reaching" claims from these early patents overlap with one another.[86]

Second, only a limited number of judicial opinions exist concerning nanotechnology patents and similarly ambiguous terminology in the field.[87] A targeted search for case law focusing primarily on nanoparticle size or pharmaceuticals at the nanoscale reveals very few patent-related disputes.[88] But, because decreasing particle size—thereby altering the structural characteristics—often impacts the biological properties of a particle, the question of whether changes in a particle's properties (like biological effect) resulting from altering its structural characteristics (like particle size) are inherently present in prior art compositions remains unanswered. Although particles at the microscale exhibit properties that are different from their chemical equivalents at the nanoscale, prior case law concerning microparticles hints at how courts may view patents claiming these conventional pharmaceuticals at the nanoscale.[89] The next section discusses some of the current case law addressing the question of whether new or

84. Bawa et al., *supra* note 5, at 4.

85. *See id.* (noting that the USPTO granted nanopatents of "questionable validity and scope").

86. *See id.*

87. *See id.*

88. As of September 2020, a very general search ("nanoparticle" OR "nanoscale") on LexisNexis' state and federal cases retrieved eighty-one cases thatmention "nanoparticle" or "nanoscale" somewhere in the text.

89. Battaglia & Ugazio, *supra* note 53, at 10 ("[One hundred] nm is the demarcating upper limit as it refers to the size around which the properties of materials can change significantly from conventional equivalents."); *See generally* Apotex Inc. v. Cephalon, Inc., No. 2:06-cv-2768, 2011 U.S. Dist. LEXIS 125859 (E.D. Pa. Oct. 31, 2011); Cephalon, Inc. v. Abraxis Bioscience, LLC, 618 F. App'x 663 (Fed. Cir. 2015).

improved properties observed at the nanoscale (or microscale) are inherent in the prior art.[90]

II. ANALYSIS

Central to the inherency debate is whether modifications in particle size are necessarily present in prior art. Although *Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc.*, sheds light on the appropriate inherency analysis in the nanopharmaceutical context, the Federal Circuit did not answer the question of when functional differences resulting from reducing particle size from microscale to nanoscale might be substantial enough to save the particle from an inherency analysis.[91] Additionally, the Federal Circuit Court only considered the inherency question as it relates to nanoparticle properties in the context of a method patent and not a composition-of-matter patent.[92] This section investigates whether modifications in particle size render a previously valid patent invalid for inherent anticipation or inherent obviousness.[93]

A. A Hint at Inherent Microparticles in the Context of a Composition Claim

In *Apotex Inc. v. Cephalon, Inc.* (*Apotex*), the Court of Appeals for the Federal Circuit held Cephalon's claimed pharmaceutical composition invalid because the pharmacokinetic properties at a 200 micron (μm) threshold were obvious in light of a previously discovered compound.[94] In this case, Apotex, a generic drug manufacturer, challenged the validity of U.S.-based Cephalon's U.S.

90. *See generally Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859; Par Pharm., Inc., v. TWi Pharms., Inc., 773 F.3d 1186, 1189 (Fed. Cir. 2014).

91. *TWi Pharms., Inc.*, 773 F.3d at 1196.

92. *See id.* at 1200.

93. *See infra* Part II.

94. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *5–9, 64. For the purposes of this Note, only the court's invalidity holding under 35 U.S.C. § 103(a) will be discussed. Again, pharmacokinetics refers to what the body does to a drug once administered. Jennifer Le, *Overview of Pharmacokinetics*, MERCK MANUAL, https://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics [https://perma.cc/9VN8-8RDD] (Oct. 2020). In particular, pharmacokinetics concerns the bioavailability of a drug within the body. *Id.*

Reissue Patent No. 37,516 (RE'516 patent).[95] The invalidity dispute revolved around a claimed invention for smaller particles of modafinil, a chemical compound with improved bioavailability and dissolution at its target site.[96] Apotex primarily argued that the RE'516 patent was invalid because French company Laboratoire L. Lafon (Lafon) had already invented the claimed subject matter.[97]

U.S. Patent No. 4,177,290 ('290 patent) was issued to Lafon on December 4, 1979, which covered the chemical composition for benzhydrylsulfinylacetamide, otherwise known as modafinil.[98] Later,

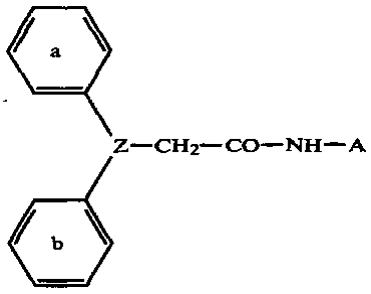
95. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *6. An applicant who already has a patent seeks a reissue patent where the claims in the previously granted patent are either too narrow or too broad. *Id. at* *11 n.4. Filing a reissue patent puts the entire patent, including the original claims, at risk. *Id.*

96. *Id.* at *6–7; U.S. Patent No. RE37,516 (filed Apr. 1, 1999). Modafinil is a drug used to treat sleepiness due to narcolepsy and other sleep–wake disorders. TEVA PHARMS. USA, INC., HIGHLIGHTS OF PRESCRIBING INFORMATION: PROVIGIL® (2015).

97. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *5. Cephalon purchased French company Laboratoire L. Lafon (Lafon) on December 28, 2001, acquiring Lafon's patent assets with that purchase. *Id.* at *9.

98. *Id.*; U.S. Patent No. 4,177,290. The Lafon '290 patent titled, "Acetamide Derivatives" claims:

1. An acetamide derivative selected from the compounds of formula I



wherein ring a and ring b are each substituted zero, one or more times by substituents selected from the group consisting of fluoro, chloro, bromo, trifluoromethyl, nitro, amino, alkyl of 1 to 4 carbon atoms, inclusive, alkoxy of 1 to 4 carbon atoms, inclusive, and methylenedioxy; wherein Z is the radical >CHSO—; and wherein A is selected from the group consisting of hydrogen, alkyl of 1 to 4 carbon atoms, inclusive, hydroxyalkyl of l to 4 carbon atoms, inclusive, and a group of formula R_1R_2N—Y—wherein Y is a divalent linear or branched chain hydrocarbon radical having 1 to 4 carbon atoms, inclusive, in the chain, and R_1 and R_2, being the same or different, are selected from the group consisting of hydrogen and alkyl of 1 to 4 carbon atoms, inclusive; and addition salts of the compounds wherein A is a basic group.

2. A compound of claim 1 wherein A is R_1R_2N—Y—wherein Y is a divalent linear or branched chain hydrocarbon radical having 1 to 4 carbon atoms, inclusive, in the

on May 22, 1990, U.S. Patent 4,927,855 ('855 patent) was issued to Lafon covering a method for the treatment of hypersomnia by administering a therapeutic composition of benzhydrylsulfinylacetamide.[99] The '855 patent claims:

> 1. (—)-Benzhydrylsulfinylacetamide.[100]
> 2. A method for the treatment of hypersomnia, which comprises administering, to a patient in need of such a treatment, an effective amount of a pharmaceutical composition consisting essentially of (-)-benzhydrylsulfinylacetamide as an arousing agent.[101]

On April 8, 1997, U.S. Patent No. 5,618,845 ('845 patent) was issued to Cephalon covering modafinil in the form of acetamide derivative having a defined particle size and was reissued to Cephalon in 2002 as RE'516, which claims:

> A pharmaceutical composition comprising a substantially homogenous mixture of modafinil particles, wherein at least 95% of the cumulative total of *modafinil particles in said composition have a diameter of less than about 200 microns (μm)*.[102]

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chain, and R_1 and R_2, together with the N atom to which they are attached, form a group selected from the group consisting of dimethylamine and diethylamine.
3. A compound of claim 1 wherein rings a and b are both unsubstituted and A is hydrogen, and pharmacologically acceptable acid addition salts thereof.
4. A compound of claim 1 which is benzhydrylsulphinylacetamide.
5. A pharamaceutical [sic] composition having activity on the central nervous system and consisting of, as an essential active ingredient, an active amount of a compound of claim 1.
6. The compound of claim 1, wherein Z is—CHSO—and A is hydrogen, alkyl of 1 to 4 carbon atoms or hydroxyalkyl of 1 to 4 carbon atoms.
'290 Patent.

99. U.S. Patent No. 4,927,855, at [45], [75] (filed Jan. 28, 1987). The '855 patent term expired on April 22, 2010. *Id.*

100. *Id.* at col. 7, l. 19.

101. *Id.* at col. 7, ll. 20–24.

102. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *7 (emphasis added); U.S. Patent No. 5,618,845

In reconciling the '290 and '855 patents with the RE'516 patent, the Federal Circuit grappled with whether the biological effect resulting from a reduced particle size was inherently disclosed in prior art.[103]

Cephalon nearly rests its entire case on the argument that "it discovered the significance of improved bioavailability and dissolution . . . [at a] smaller particle size, which is a [feature] Lafon never appreciated."[104] Although the '290 and '855 patents failed to include any reference to particle size, both parties stipulated to the fact that Lafon "evaluated the effect of small[-]particle modafinil on narcoleptic patients" from 1989 to 1991.[105] Notably, one of the modafinil batches from these clinical studies had 99.8% of particles less than 206.36 microns, which is within the range of the RE'516 patent.[106] The court noted that Cephalon's argument "ignores the fact" that Lafon "previously tested, manufactured[,] and used [modafinil] . . . for the treatment of narcolepsy" and that "Lafon . . . was aware of the compound's chemical structure and particle size . . . ."[107] Ultimately, the court held that there are "no differences" between Cephalon's claimed invention and the information communicated to Cephalon by Lafon because Cephalon's "'discovery' of the 220 micron [therapeutic] threshold" describes an inherent property of modafinil.[108]

Importantly, the court noted in dicta that "[h]ad Lafon not measured particle size, Cephalon's argument may carry more weight."[109] In

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c. 10, ll. 49–53 (filed Oct. 6, 1994) (emphasis added); U.S. Patent No. RE37,516 E col. 10, ll. 49–53 (filed Apr. 1, 1999).

103. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *17–18.

104. *Id.* at *8 (emphasis omitted).

105. *Id.* at *17–18. From October 1989 to June 1991, Lafon conducted a clinical study that "evaluated the effect of small[-]particle modafinil on narcoleptic patients." *Id.* at *17. Lafon then conveyed its particle size analysis to Cephalon in a memo dated November 10, 1993. *Id.* at *18.

106. *Id.* at *18.

107. *Id.* at *57–58.

108. *Id.* at *58, *67–69. Because modafinil was a widely known chemical compound for the treatment of narcolepsy, combined with Cephalon's possession of the compound and all the subsequent communications with Lafon concerning that compound, "a person skilled in the art would have been motivated to measure the particle size of modafinil as part of the FDA process, which requires such information for the approval of new drug substances." *Id.* at *67. As a result, the court found that the "scope of the prior art [as] . . . a pharmaceutical composition of modafinil API having 95% of its particles with a diameter less than 220 microns." *Id.* at *67–69.

109. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *57.

holding that improved dissolution and bioavailability were inherent properties of a reduction in particle size, the court relied almost exclusively on Cephalon's claim that a composition of modafinil had the same particle size that Lafon previously disclosed and tested.[110] Notably, the court concluded that improved pharmacokinetics, which resulted from a smaller particle size, fail to overcome an inherent obviousness analysis where the pharmacokinetic properties were previously known in the art (as the Lafon '290 and '855 patents) but not necessarily related to a particular particle size.[111]

This case implies that biological or pharmacokinetic properties resulting from a reduced particle size ultimately fail an inherency analysis unless the resulting biological or pharmacokinetic properties were previously unknown or unseen in the prior art.[112] The court placed importance on the fact that Lafon previously measured particle size *and* recorded the different sizes that clinical trials were conducted at.[113] Even though Cephalon claimed a composition of smaller-sized modafinil particles, modafinil was nevertheless previously tested and recorded, which suggests that Lafon was at least aware of differences in pharmacokinetic or biological properties associated with different particle sizes.[114] Further, Cephalon used the same composition of modafinil as a basis to patent a specific particle size, despite the fact that the claimed particle size was previously tested and disclosed by Lafon.[115] Accordingly, because the composition of modafinil is physically the same, it follows that its properties must also be the same.[116]

110. *Id.* at *65–69. Cephalon claimed particles less than 200 microns while Lafon disclosed particles less than 206.36 microns, which was "within" the claimed range of the RE'516 patent. *Id.* at *18, *28. Notably, Lafon disclosed the particle size(s) it tested, but the facts fail to indicate Lafon communicated any improved dissolution or bioavailability at the smaller size. *See id.* at *18–20. The improved pharmacokinetics comprised the inherency component at issue. *See id.* at *31.

111. *See id.* at *65–69.

112. *See id.*

113. *Id.* at *57–58, *63–64.

114. *See id.* at *57–58.

115. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *58

116. *See id.* at *62; *see also In re* Spada, 911 F.2d 705, 708 (Fed. Cir. 1990) ("Products of identical chemical composition can not have mutually exclusive properties.").

Nevertheless, the court only evaluated Cephalon's microparticles in the context of a composition patent.[117] So whether Cephalon's microparticles may overcome an inherent obviousness test in the context of a method patent covering the treatment of narcolepsy is a claim-drafting exercise that remains untouched by the courts.

B. Par Pharmaceutical, Inc. v. Twi Pharmaceuticals, Inc.*: The Test for Inherent Properties of Nanopharmaceuticals but Not the Answer*

In *Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc.*, the Federal Circuit established a heightened standard for inherent prior art disclosures in the context of an obviousness analysis.[118] Although the Federal Circuit laid out the proper test for establishing inherency in the context of obviousness, the court implies that something more than reduced particle size, even on the nanoscale, is needed for a finding of nonobviousness.[119]

Whether modifications in nanoparticle size render a claimed invention inherent was touched upon in *Par Pharmaceutical*.[120] In this case, Par Pharmaceutical (Par) received approval to market a generic micronized megestrol formulation of Megace OS, a synthetic progestin medication used as an appetite stimulant to treat wasting syndromes associated with cancer, HIV/AIDS, and anorexia.[121] Megace OS exerts its appetite-stimulating effects when taken with food, a problematic limitation for patients who take the drug for an

117. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *67–68.

118. Par Pharm., Inc., v. TWi Pharms., Inc., 773 F.3d 1186, 1195–96 (Fed. Cir. 2014).

119. *Id.* at 1196.

120. *Id.*

121. *Id.* at 1188–89; *see* Lee Schacter, Marcel Rozencweig, Renzo Canetta, Susan Kelley, Claude Nicaise & Laurie Smaldone, *Megestrol Acetate: Clinical Experience*, 16 CANCER TREATMENT REVS. 49, 57–58, 60 (1989) (discussing Megestrol acetate's effect on anorexia, cachexia, and weight loss associated with AIDS). Megestrol was traditionally used to treat wasting (body weakening) in cancer patients. *TWi Pharms., Inc.*, 773 F.3d at 1188. But in 1993, micronized megestrol was introduced to the market as Megace OS for the treatment of anorexia and cachexia in AIDS patients. *Id.* at 1189. Specifically, Micronized Megace OS helped to improve appetite, treat unexplained weight loss, and encourage weight gain. *Id.* at 1190.

illness that makes food difficult to consume, like an eating disorder.[122] Par experimented with micronized megestrol and subsequently "reformulat[ed] the drug by reducing the particle size from the micrometer range to the nanometer range."[123] The megestrol nanoparticles exhibited "a greatly reduced food effect" relative to micronized Megace OS, prompting Par to file a patent application for its nanosized megestrol formulation.[124] The USPTO granted Par U.S. Patent No. 7,101,576 ('576 patent) covering methods for use of nanosized megestrol formulations to "increas[e] the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass."[125] Par subsequently began marketing its megestrol nanoparticle

122. *See* Sandra F. Simmons, Ph.D., Kathleen A. Walker & Dan Osterweil, M.D., *The Effect of Megestrol Acetate on Oral Food and Fluid Intake in Nursing Home Residents: A Pilot Study*, 6 J. AM. MED. DIRS. ASS'N S5, S10 (2005), https://www.sciencedirect.com/science/article/abs/pii/S1525861005002033 [https://perma.cc/XQP6-DKSG]. Results from one comparative study indicate that Megace OS significantly impacts food and fluid intake "*only* under the optimal mealtime feeding assistance condition," indicating that Megace OS is "not an effective nutritional intervention" to increase food during a fasting state. *Id.* at S5 (emphasis added).

123. *TWi Pharms., Inc.*, 773 F.3d at 1189. Par also contracted with a third party (Alkermes) "to use its 'NanoCrystal' technology to formulate [its] nanosized megestrol." *Id.*

124. *Id.* A drug's food effect describes changes in the drug's rate and extent of absorption when administered orally with food. JULIEN ET AL., *supra* note 34, at 6–7. Patients taking Megace OS with a meal showed a "significantly higher rate and extent of absorption" compared to those who took Megace OS without a meal. *TWi Pharms., Inc.*, 773 F.3d at 1189. Yet, the nanosized megestrol formulation showed a reduced food effect, which means that more of the drug remained in circulation longer. *See id.* In any event, patients taking the nanosized megestrol formulation showed improved efficacy and a "greatly reduced food effect[,]" suggesting that nanosized megestrol does not need to be taken with food. *See id.* Because nanosized megestrol works equally as effective whether taken with or without food, the drug is even more useful for illnesses that make consuming food difficult, like eating disorders. *See id.*

125. Nanoparticulate Megestrol Formulations, U.S. Patent No. 7,101,576 B2 col. 43 ll. 15–17; *TWi Pharms., Inc.*, 773 F.3d at 1188 (first alteration in original). Claim 1 of Par's granted patent is as follows:

> A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:
>
> (a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;
>
> (b) the megestrol acetate formulation comprises megestrol particles having an effective *average particle size of less than about 2000 nm*, and at least one surface stabilizer associated with the surface of the megestrol particles; and
>
> (c) the administration is once daily;
>
> wherein after a single administration in a human subject of the formulation there is no substantial difference in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state[,] . . . wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within

formulation as Megace ES, which "was indicated for use 'without regard to meals . . . .'"[126]

TWi Pharmaceuticals (TWi) filed an abbreviated new drug application (ANDA) with the FDA to market a generic form of nanosized megestrol.[127] Then, Par brought suit against TWi for infringement of its nanosized megestrol formulation.[128] TWi countered the infringement claims by stating that claims toward its nanosized megestrol formulation in the '576 patent were invalid as obvious in light of prior art that disclosed a micronized megestrol formulation.[129] TWi supported its invalidity arguments by citing the label of Megace OS, which disclosed micronized oral suspensions of megestrol used to "treat[] . . . anorexia, cachexia, and unexplained weight loss [in] AIDS patients."[130] In addition, TWi offered U.S. Patent No. 5,399,363 ('363 patent) and U.S. Patent No. 5,145,684 ('684 patent) as prior art against the Par '576 patent and argued that it would be obvious to use nanosized megestrol formulations for the treatment of anorexia.[131]

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approximately 30 minutes of dosing.

U.S. Patent No. 7,101,576 B2 col. 43 ll. 15–31, 37–41 (emphasis added).

126. *TWi Pharms., Inc.*, 773 F.3d at 1189–90.

127. *See id.* at 1190.

128. *Id.* Parties submit an abbreviated new drug application (ANDA) to the FDA to expedite approval of generic drugs. *Abbreviated New Drug Application (ANDA)*, FDA, https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda [https://perma.cc/8DFS-FWRU] (Jan. 14, 2022).

129. *TWi Pharms., Inc.*, 773 F.3d at 1190. The Federal Circuit notes that two general categories of prior art were disputed: (1) pharmacokinetic properties of megestrol and (2) use of nanotechnology in drug formulation. *Id.* TWi cited Megace OS as "demonstrat[ing] that micronized oral suspensions of megestrol were [previously] used . . . [to] treat[] . . . anorexia, cachexia, and unexplained weight loss [in] AIDS patients." *Id.*

130. *Id.*

131. *Id.* at 1191. Both patents teach "the use of the NanoCrystal technology for [making] . . . drug particles less than either 1000 nm or 400 nm in size." *Id.* The '363 patent listed megestrol as one of the anticancer agents to use with the nanotechnology, while the '684 patent teaches that nanoparticle technology could lead to greater bioavailability and a more rapid onset of action. *Id.* Nonetheless, TWi relied on the Megace OS label to disclose micronized megestrol for the treatment of "anorexia, cachexia, and unexplained weight loss for AIDs patients" and a study by Kathleen K. Graham et. al. to disclose dose-dependent weight gain in patients who took micronized megestrol. *Id.* at 1190; Kathleen K. Graham, Dennis J. Mikolich, Alvan E. Fisher, Marshall R. Posner & Michael N. Dudley, *Pharmacologic Evaluation of Megestrol Acetate Oral Suspension in Cachectic AIDS Patients*, 7 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 580, 580–86 (1994). TWi argued that the combination of the '684 patent, the '363 patent, the Megace OS label, and the Graham study disclosed each and every element of Par's claimed invention. *TWi Pharms., Inc.*, 773 F.3d at 1190–91. Because the combination of prior art references "failed to disclose a known food effect in [nanosized] megestrol, both TWi and the [] court rel[ied] on the doctrine of inherency to disclose the food effect limitation." *Id.* at 1194.

Both the District and Federal Circuit courts sought to answer the question of whether "[t]he reduced food effect was thus 'an inherent result' of nanosized megestrol 'even if it was previously not known in the prior art that a food effect existed.'"[132]

The district court found the '576 patent obvious in light of the Megace OS label and disclosures in the prior art, '363 patent, and '684 patent, concluding that the lack of a food effect in nanosized megestrol was an inherent property of micronized megestrol.[133] But the district court ignored the scope of the functional limitation at issue by failing to determine whether a reduction in particle size naturally resulted in "no substantial difference" in food effect as claimed.[134] In fact, TWi's expert testified that improved bioavailability "necessarily results in a decrease in any food effect . . . ."[135] TWi used this expert testimony, coupled with general evidence that smaller particle size improves bioavailability, to support its argument that nanosized megestrol's improved bioavailability is an inherent property of micronized megestrol.[136] "[P]er the district court, the reduced particle size would, ipso facto, lead to a reduced food effect."[137] Such "broad diktats

132. *TWi Pharms., Inc.*, 773 F.3d at 1192 (quoting Par Pharm., Inc. v. TWi Pharms., Inc., No. CCB-11-2466, 2014 U.S. Dist. LEXIS 21704, at *46 (D. Md. Feb. 21, 2014), *vacated sub nom.* Par Pharm., Inc. v. TWi Pharms., Inc. 773 F.3d 1186 (Fed. Cir. 2014)).

133. *Id.*

134. *Id.* at 1196 ("While it may be true that a reduction in particle size naturally results in some improvements in the food effect, the district court failed to conclude that the reduction in particle size naturally results in 'no substantial difference' in the food effect." (emphasis omitted) (quoting *In re* Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981))). *See generally* Megan Leinen Johns, *Federal Circuit Clarifies Inherency Doctrine in Reversing Obviousness Determination*, FINNEGAN (Jan. 2015), https://www.finnegan.com/files/Upload/Newsletters/Last_Month_at_the_Federal_Circuit/2015/January/FCN_Jan15_Print.pdf [https://perma.cc/V4YA-PDE3] (analyzing *TWi Pharms., Inc.* case).

135. *TWi Pharms., Inc.*, 773 F.3d at 1196. Essentially, TWi's expert testified that a person with ordinary skill or knowledge in the subject area would know a decrease in particle size increases bioavailability. *See id.* Moreover, the court in *Apotex* made clear that a person with ordinary skill or knowledge in the subject area knows that decreasing particle size increases bioavailability. Apotex Inc. v. Cephalon, Inc., No. 06-cv-2768, 2011 U.S. Dist. LEXIS 125859, at *30–31 (E.D. Pa. Nov. 7, 2011), *aff'd*, 500 F. App'x 959 (Fed. Cir. 2013).

136. *See TWi Pharms., Inc.*, 773 F.3d at 1196.

137. *Id.* For example, claim one in the '576 patent "requires 'no substantial difference in [the] C_{max}' between the fed and fasted states." *Id.* (quoting U.S. Patent No. 7,101,576 B2 col. 42 l. 67–col. 43 l. 1). The court continues, "[w]hile it *may* be true that a reduction in particle size naturally results in *some* improvement in the food effect, the district court failed to conclude that the reduction in particle size naturally results in 'no substantial difference' in the food effect." *Id.* (quoting *In re* Oelrich, 666 F.2d at

[concerning] the effect of particle size on bioavailability and food effect" fail to even correspond with the actual limitations at issue.[138]

Accordingly, the Federal Circuit vacated the district court's decision and held that the district court applied an incorrect inherency standard in its obviousness analysis.[139] The Federal Circuit cautioned that "the concept of inherency must be limited when applied to obviousness . . . ."[140] Because the record provided insufficient evidence that TWi met the high standard for inherency in the obviousness context, the court clarified that inherency is "present only when the limitation at issue is the '*natural result*' of the combination of prior art elements."[141] Merely reciting a newly discovered function or property inherently present in the prior art does not distinguish a claim drawn to those properties.[142]

The Federal Circuit's holding raises several important considerations. First, the Federal Circuit's inherent obviousness analysis seems to directly contradict the inherent obviousness analysis in *In re Huai-Hung Kao*.[143] That case involved an invention directed

581). The "claimed" food effect is "no substantial difference in C_{max}[.]" *Id.* (emphasis omitted). The C_{max} is the maximum serum concentration a drug achieves at its target site within the body. *See* Tracy, *supra* note 25, at 49. Accordingly, the claimed food effect limitation has no substantial difference in drug concentration at the target site, which is a critical step missing from the district court's analysis. *TWi Pharms., Inc.*, 773 F.3d at 1196.

138. *Twi Pharms., Inc.*, 773 F.3d at 1196. "[T]he limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Id.* The district court failed to meet this "high" standard because it failed to even require TWi to present evidence on point and sufficient to prove inherency. *Id.* at 1195–96. TWi provided expert testimony that an improvement in bioavailability "necessarily results in a decrease in any food effect," combined with evidence "that a reduction in particle size improves bioavailability." *Id.* at 1196.

139. *Id.* at 1188, 1196 (remanding "for the district court to determine if TWi has presented clear and convincing evidence that demonstrates the food effect *as claimed* is *necessarily present* in the prior art combination").

140. *Id.* at 1195.

141. *Id.* at 1195–96 (emphasis added) (quoting *In re Oelrich*, 666 F.2d at 581); *see* Johns, *supra* note 134. In essence, the record provided evidence that TWi never met its burden in demonstrating that Par's claimed food effect limitations were necessarily present in combination of elements from the prior art. *TWi Pharms., Inc.*, 773 F.3d at 1196; *see* Johns, *supra* note 134.

142. *See TWi Pharms., Inc.*, 773 F.3d at 1196. On remand, the district court held the food effect limitations were "necessarily . . . present, or the natural result of the combination of elements explicitly disclosed by the prior art" and the Federal Circuit subsequently affirmed. Par Pharm., Inc. v. TWi Pharms., Inc., 120 F. Supp. 3d 468, 470–71 (D. Md.), *aff'd per curiam*, 624 F. App'x 756 (Fed. Cir. 2015) (Rule 36 affirmance).

143. *Compare TWi Pharms., Inc.*, 773 F.3d at 1196 (requiring limitation to be present to rely on inherent

to a method of treating pain that recited food effect limitations like *TWi*, but instead claimed a "C_{max} . . . about 50% higher when . . . administered to the subject under fed versus fasted conditions."[144] There, the Federal Circuit held that the claims were inherently obvious, reasoning that the "claimed 'food effect' is an inherent property of oxymorphone itself, present both in controlled release and immediate release formulations of that drug."[145] This apparent inconsistency might reflect the differences in particular quantitative specificity.[146] For example, *In re Huai-Hung Kao* involved a patent which effectively claimed a particular pharmaceutical concentration, while *TWi* involved a patent which claimed a particular pharmaceutical particle size.[147] Pharmaceutical concentration is closely related to improved bioavailability and pharmacokinetic effects, which the disputed patent in *In re Huai-Hung Kao* effectively claimed.[148] Because the Federal Circuit was inclined to reach an opposite result in *TWi*, the court likely viewed new or novel pharmacokinetic properties resulting from a decreased particle size to be more ambiguous in the literature than pharmacokinetic properties resulting from a change concentration alone.[149]

Second, because the Federal Circuit was unable to determine whether a reduction in particle size naturally results in no substantial difference in food effect, the court implies that a claim favors

obviousness), *with In re* Huai-Hung Kao, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (not requiring limitation to be present to find substantial evidence for inherent obviousness).

144. *In re Kao*, 639 F.3d at 1064 (emphasis omitted) (quoting U.S. Patent Application No. 12/167,859 claim 8). The C_{max} refers to the maximum serum concentration a drug achieves at a particular target after administration of the first dose but before administration of a second dose. Tracy, *supra* note 25, at 49. In simpler terms, the C_{max} refers to the maximum amount of a drug found in the blood. *Id.*

145. *In re Kao*, 639 F.3d at 1070.

146. *See id.*; *TWi Pharms., Inc.*, 773 F.3d at 1195–96.

147. *In re Kao*, 639 F.3d at 1061, 1063–64; *TWi Pharms., Inc.*, 773 F.3d at 1189–90.

148. *See In re Kao*, 639 F.3d at 1063. The patent at issue in *In re Kao* was directed to a method of treating pain by administering a controlled release formulation of oxymorphone. *Id.* The claimed method "(1) provides at least 12 hours of sustained pain relief and (2) results in a 'Cmax' (maximum concentration) at least about 50% higher" when given to patient in a fed versus fasting state. *Id.* at 1063–64. Taken together, the sustained effect ("12 hours of sustained pain relief") and the high Cmax (maximum concentration 50% higher in fed versus fasting patients, which indicates that more of the drug reached its final destination point in fed patients) suggests that the disputed patent claimed a particular pharmaceutical concentration and its subsequent biological effects. *Id.*

149. *See TWi Pharms., Inc.*, 773 F.3d at 1196 ("[T]he reduced particle size would, ipso facto, lead to a reduced food effect.").

nonobviousness when the claim's body recites inherent properties with quantitative specificity.[150] But the Federal Circuit's holding appears to directly contradict the outcome in *Apotex Inc.*, where reciting the inherent property with quantitative specificity in the body of the claim failed to save Cephalon's patent from a finding of invalidity.[151] These differences may be reconciled by the weight placed on prior art that disclosed the same particle size that Cephalon attempted to patent, while Par relied on the court's construction of the term "nanoparticle" to differentiate its megestrol from micronized megestrol formulations.[152]

Interestingly, both Par and Cephalon argued for patent validity based on the premise that improved pharmacokinetics were undisclosed in the prior art in either case.[153] Nevertheless, the contrary outcomes in the two cases might be attributable to the differences in statutory subject matter claimed. The disputed patent in *Par Pharmaceutical* claimed a method of treatment while the disputed patent in *Apotex Inc.* claimed a chemical composition.[154] For the

150. *Id.*

151. *See* Apotex Inc. v. Cephalon, Inc., No. 06-cv-2768, 2011 U.S. Dist. LEXIS 125859, at *5, *57–58 (E.D. Pa. Nov. 7, 2011), *aff'd*, 500 F. App'x 959 (Fed. Cir. 2013); U.S. Patent No. 5,618,845; U.S. Reissue Patent No. RE37,516 E col. 10, ll. 51–53 ("[*M*]*odafinil particles in said composition have a diameter less than about 200 microns (μm*)." (emphasis added)). The court held that the improved biological effect was inherent in the prior art and the decreased particle size was obvious where the prior patent owner tested the compound at various particle sizes, including the claimed size. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *57–58, *67–68.

152. *See, e.g.*, *Apotex, Inc.*, 2011 U.S. Dist. LEXIS 125859, at *57–58; *TWi Pharms., Inc.*, 773 F.3d at 1197.

153. *Apotex, Inc.*, 2011 U.S. Dist. LEXIS 125859, at *65–66; *see also TWi Pharms., Inc.*, 773 F.3d at 1196.

154. *TWi Pharms., Inc.*, 773 F.3d at 1188–89; *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *6–7. When claiming a composition, like a chemical compound, patentability depends upon the specific composition materials, not on the method or process of making or mixing those materials. *See* 35 U.S.C. § 101; *see also* KAYE SCHOLER LLP, *supra* note 47 ("Researchers . . . can potentially obtain patents on particular forms of the active compound even if the compound itself is known to the person of ordinary skill."). Chemical compounds "are generally claimed by specifying the compound's molecular formula . . . and . . . structure." *Id.* For example, water would be claimed using its molecular formula (H_2O) and its structure:

O
/ \
H H

Id. Likewise, for a method claim, patentability depends upon the specific steps listed and may be limited by the materials used to carry out the steps recited by the particular method or process. U.S. PAT. &

method of treatment claim, TWi in *Par Pharmaceutical* failed to provide evidence that improved bioavailability was a result of the claimed food effect limitation flowing from nanosized particles, so there was no way for the court to conclude that no food effect necessarily flowed from decreased particle size and improved bioavailability.[155] In contrast, Lafon provided evidence that it previously tested the smaller particle size Cephalon claimed.[156] That, coupled with the fact Cephalon claimed a chemical structure identical to the one Lafon previously patented, rendered the properties of that structure inherent.[157]

Moreover, the opposing outcomes in *Par Pharmaceutical* and *Apotex, Inc.* might be attributable to the differences in general particle size scale. In *Apotex, Inc.*, although Cephalon claimed smaller modafinil particles than the modafinil particles patented by Lafon, both modafinil formulations nevertheless exist at the microscale, just at different sizes on the same scale.[158] In effect, the Federal Circuit provides some hope in *Par Pharmaceutical* that decreasing particle size from microscale to nanoscale at least deserves to be reviewed under a higher standard in the context of an obviousness analysis.[159]

C. The Future of Nanopharmaceutical Patent Litigation After Par Pharmaceutical

Par Pharmaceutical highlights a recent trend in the context of pharmaceutical and nanopharmaceutical patent litigation. Although patent litigation concerning nanotechnology has been relatively limited thus far, "[i]f genetics are a litmus test for emerging medical technologies, then developments and inventions in nanotechnology (and nanopharmaceuticals specifically) will soon be appearing [more frequently] in court dockets."[160] The current "messy" and "fragmented" nanotech-related patent landscape is already blocking

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TRADEMARK OFF., *supra* note 10, § 2106.03, at 2100-20 (A method or process is "a mode of treatment of certain materials to produce a given result.").

155. *TWi Pharms., Inc.*, 773 F.3d at 1196.

156. *Apotex Inc.*, 2011 U.S. Dist. LEXIS 125859, at *54–55.

157. *Id.* at *58.

158. *Id.* at *8.

159. *TWi Pharms., Inc.*, 773 F.3d at 1195–96.

160. Paradise, *supra* note 4, at 182.

novel nanoparticle patents and possesses the ability to cause extended legal battles and potentially stall nanotechnology's development, as seen in the cases discussed above.[161] Patent blocking, and its associated legal battles, alone poses the biggest threat to commercialization.[162]

This patent blocking is characterized by unduly broad patents, making it "almost certain" that nanotech-related patent enforceability will be a "major problem" in the future as companies attempt to sort out who owns what patent right.[163] Accordingly, patent owners are likely to challenge the validity of competing patents to determine who has the best claim to each patent right. And one ever-increasing method to challenge pharmaceutical patent validity is through an inherent obviousness argument.[164] But despite the Federal Circuit cautioning lower courts to limit its application of the inherency doctrine to obviousness inquiries, the court's holding nevertheless reaffirms inherent obviousness as a tool for alleged infringers and the USPTO to challenge patent validity.[165]

D. Inherent Obviousness After Par Pharmaceutical

"Anticipation by inherency is a well-recognized, and generally well-understood, patent law doctrine."[166] On the other hand,

161. Bawa, *supra* note 6, at 728. In the context of inherency, patent blocking is likely the result of overclaiming, which refers to the practice of drafting overly broad patent claims. *See id.* at 728–29 n.144. Patent thickets are another way new patents may be blocked. *Id.* at 728–29, 728 n.144. Patent thickets are characterized as a "dense web of overlapping intellectual property rights" that make it difficult to commercialize new technology. *Id.* at 728 n.144 (quoting Richard Raysman & Peter Brown, *Patent Cross-Licensing in the Computer and Software Industry*, N.Y. L.J., Jan. 11, 2005, at 3, 6). These patent thickets naturally block new patents from the patent landscape and subsequently discourage innovation. *Id.* at 728–29 n.144.

162. Bawa, *supra* note 6, at 729.

163. *Id.* at 729, 731.

164. *See generally* Paul W. Browning, Ph.D., William B. Raich, Ph.D. & Paul Townsend, *Inherency in Obviousness—A Worrying Trend?*, FINNEGAN (Apr. 13, 2018), https://www.finnegan.com/print/content/64398/Inherency-in-ObviousnessA-Worrying-Trend.pdf?q= [https://perma.cc/K4KM-KFVY] (discussing inconsistencies in applying inherent obviousness).

165. *Id.*; *see* Par Pharm., Inc. v. TWi Pharms., Inc., 773 F.3d 1186, 1196 (Fed. Cir. 2014); Apotex Inc. v. Cephalon, Inc., No. 06-cv-2768, 2011 U.S. Dist. LEXIS 125859, at *66–68 (E.D. Pa. Nov. 7, 2011), *aff'd*, 500 F. App'x 959 (Fed. Cir. 2013).

166. Browning et al., *supra* note 164, at 1; *see* Daniel P. O'Brien & W. Murray Spruill, *Does Inherency Have a Place in Determinations of Obviousness?*, 32 BIOTECHNOLOGY L. REP. 3, 3, 6, 13 (2013).

obviousness by inherency is confusing and has led to "improper applications" of the doctrine in lower courts.[167] This confusion arises from the fact that "[a]nticipation focuses on what [was] disclosed in the prior art" while obviousness focuses on what a person with "ordinary skill in the art . . . understood or appreciated based on that disclosure."[168] Obviousness encompasses what was known *at the time* of invention—thus, hindsight is forbidden.[169] Yet this prohibition on hindsight directly conflicts with the principle of inherency, which permits later recognition of unknown properties that existed at the time of the invention.[170] Because confusion lingers over the precise scope of applying inherency in the context of an obviousness analysis, litigants have increasingly attempted to invoke inherent obviousness arguments.[171]

III. PROPOSAL

The Federal Circuit's holding in *Par Pharmaceutical* highlights ambiguities surrounding the inherency doctrine when used as a sword to challenge nanopharmaceutical patents.[172] Although the Federal Circuit laid out the appropriate test for inherency in the context of an

167. Browning et al., *supra* note 164, at 2.

168. *Id.* at 1; *see* O'Brien & Spruill, *supra* note 166, at 3, 13–14, 16. "[A] prior art disclosure may inherently disclose a claim element even where a person [with] ordinary skill [or knowledge] in the art would not have recognized that inherent element at the time of invention." Browning et al., *supra* note 164, at 1–2. Accordingly, this represents the existing nuance present in inherent anticipation, as compared to inherent obviousness. *See id.*

169. Browning et al., *supra* note 164, at 2; O'Brien & Spruill, *supra* note 166, at 6.

170. *See* Brassica Prot. Prods. LLC v. Sunrise Farms (*In re* Cruciferous Sprout Litig.), 301 F.3d 1343, 1349 (Fed. Cir. 2002) ("Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." (first quoting MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999); and then quoting Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999))).

171. *See, e.g.*, Browning et al., *supra* note 164, at 2; Par Pharm., Inc. v. TWi Pharms., Inc. 773 F.3d 1186, 1195–96 (Fed. Cir. 2014); Apotex Inc. v. Cephalon, Inc., No. 06-cv-2768, 2011 U.S. Dist. LEXIS 125859, at *66–68 (E.D. Pa. Nov. 7, 2011), *aff'd*, 500 F. App'x 959 (Fed. Cir. 2013); Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V., 865 F.3d 1348, 1354–55 (Fed. Cir. 2017); Endo Pharms. Sols., Inc. v. Custopharm Inc., 894 F.3d 1374, 1381 (Fed. Cir. 2018) ("Obviousness cannot be predicated on what is unknown." (quoting *In re* Shetty, 566 F.2d 81, 86 (C.C.P.A. 1977))).

172. *See generally TWi Pharms., Inc.*, 773 F.3d 1186 (vacating district court's decision because it did not analyze, in its inherency decision, whether TWi proved that the claimed food effect was necessarily present in the prior art).

obviousness analysis, the court's silence concerning the proper scope of that test foreshadows inevitable delays at the commercialization stage while companies hash out their patent rights in court.[173] Further, litigation might financially compromise future research and development by companies and research institutions in the business of designing cutting-edge nanotechnology products, such as nanoparticles. Accordingly, the courts and the USPTO alike should refrain from relying on inherent obviousness to invalidate or prevent biological or chemical patents.

A. Eliminating the Concept of Inherency in the Context of an Obviousness Analysis in Courts and at the USPTO

When considering the precise nature of chemical and biological patents, courts and the USPTO should avoid applying the inherency doctrine to these "poorly[] understood . . . inventions."[174] The confusing and seemingly contradictory nature of inherency in the context of obviousness has necessarily prompted practitioners and legal scholars to demand its eradication entirely.[175]

The Federal Circuit in *Par Pharmaceutical* established the heightened standard for applying inherency in an obviousness analysis, but this standard ultimately fails to keep up with the scientific advancement of poorly understood inventions, especially those concerning nanotechnology.[176] Combined with the Federal Circuit's holding in *Honeywell International Inc. v. Mexichem Amanco Holding S.A. de C.V.*, the standard for inherent obviousness seems to be: if a

173. *See* Bawa, *supra* note 6, at 728–29.

174. Paul G. Alloway, Note, *Inherently Difficult Analysis for Inherent and Accidental Biotechnology Inventions*, 38 SUFFOLK U. L. REV. 73, 77 & n.33 (2004) ("[G]iven the particular problems associated with . . . inventions for which technological understanding is limited, . . . courts should apply less stringent requirements for holding patent claims . . . inherent[] . . . ."); *see also* Jeffrey Coleman, *"Undetected, Unsuspected, and Unknown": Should We Anticipate Problems for Scientific Innovation Following* Schering Corp. v. Geneva Pharmaceuticals*?*, 82 FORDHAM L. REV. 165, 195 (2013) (discussing commentators who warn that the inherency anticipation doctrine may discourage innovation and undermine the goals of patents).

175. *See* Janice M. Mueller & Donald S. Chisum, *Enabling Patent Law's Inherent Anticipation Doctrine*, 45 HOUS. L. REV. 1101, 1102, 1107 (2008) (proposing a narrower interpretation of inherent anticipation such that it would eliminate analysis of inherent obviousness); *see also* Coleman, *supra* note 174, at 204.

176. *TWi Pharms., Inc.*, 773 F.3d at 1195–96.

combination of prior art elements naturally results in an unknown property, then that property is inherent unless the opposing party shows it was unexpected.[177] Pharmaceutical and nanoparticle patents are notably susceptible to this inherency analysis, presumably because the Federal Circuit's standard effectively crosses off pharmacokinetic effects as an inherent result of new pharmaceutical formulations.[178] Moreover, the current standard discounts the fundamentally different biological effects that a nanopharmaceutical composition might exhibit in response to structural changes, such as particle size.[179]

Science is moving faster today than courts can keep up with. For instance, researchers have already developed a fully autonomous DNA robotic system designed to seek and destroy solid tumors and vascularized metastases.[180] Researchers aim to use this same DNA robotic system as a precise drug-delivery platform for treating additional diseases by modifying the geometry of nanostructures, the targeted grouping, and the loaded cargoes.[181] What if changing a nanostructure's geometry results in remarkable pharmacokinetic improvements and overall patient experience, but nevertheless succumbs to subsequent inherency challenges? Inherent obviousness acts as a weapon to the rapidly expanding base of scientific and nanotechnological knowledge by preventing scientists from putting their ideas into practice and by stalling research institutions from putting those reduced ideas on the market.[182] In light of nanoscale drug-delivery research's critical importance to society and the quickly

177. Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V., 865 F.3d 1348, 1355 (Fed. Cir. 2017) ("What is important regarding properties that may be inherent, but unknown, is whether they are unexpected."). But, resting the inherency standard on whether the resulting properties are unexpected conflicts with obviousness, which is based on what a person having ordinary skill in the art knew at the time of invention. *See TWi Pharms., Inc.*, 773 F.3d at 1196; *see also* Sanjeev Mahanta, Ph.D., J.D., *Inherency in Obviousness – What Is the Correct Standard?*, IPWATCHDOG (Aug. 1, 2017), https://www.ipwatchdog.com/2017/08/01/inherency-obviousness-correct-standard/ [https://perma.cc/D33G-BS85].

178. *See* Browning et al., *supra* note 164, at 2 (discussing several cases regarding pharmaceutical patents where the Federal Circuit discussed inherency in obviousness).

179. *See* KAYE SCHOLER LLP, *supra* note 47.

180. Ariz. State Univ., *Cancer-Fighting Nanorobots Programmed to Seek and Destroy Tumors*, PHYS.ORG (Feb. 12, 2018), https://phys.org/news/2018-02-cancer-fighting-nanorobots-tumors.html [https://perma.cc/EXA4-JLFB].

181. *Id.*

182. *See* MUELLER, *supra* note 62, at 231.

advancing base of scientific knowledge, inherent obviousness should be eradicated entirely when evaluating the validity of pharmaceutical and nanopharmaceutical patents.

The underlying policy furthered by recognizing obviousness is to limit patent protection to subject matter that is truly nonobvious, which turns on whether a person having ordinary skill in the art would know to combine the prior art references to make the invention.[183] But when an inherent property is "secret," or unknown in the prior art, how would an inventor know to combine the prior art references in a way to produce the claimed invention?[184]

For example, consider a hypothetical drug A. Drug A was patented in 1995 and has since been used as a general anticancer medication. Publication B was released in 2010 and discloses the general contention that smaller particles can cross the blood-brain barrier. Drug C was subsequently produced for the first time in 2020. Drug C is similar to drug A, except that drug C was reproduced on the nanoscale using crystallography. But drug C demonstrates a remarkable pharmacokinetic effect at the nanoscale: improved ability to cross the blood-brain barrier and penetrate reproductive cancer cells in the brain because of drug C's increased bioavailability.[185]

Under the current inherent obviousness standard, a patent for drug C will likely be invalidated because the combination of references discloses an increase in bioavailability as an inherent result of a nanoparticle's ability to cross the blood-brain barrier. The possibility

183. *Id.* at 229–30.

184. 3 R. CARL MOY, MOY'S WALKER ON PATENTS § 9.28 (4th ed.), Westlaw (database updated Dec. 2020) (noting that secret events shall be excluded from prior art because inclusion "hold[s] the patentee responsible for knowing things that are in fact unknowable").

185. The blood-brain barrier is a highly selective semipermeable layer of endothelial cells that protects against solutes in circulating blood from nonselectively entering the extracellular fluid of the central nervous system (where neurons reside). *See generally* Richard Daneman & Alexandre Prat, *The Blood-Brain Barrier*, 7 COLD SPRING HARBOR PERSPS. BIOLOGY 1 (2015) (discussing what the blood-brain barrier is and observing how penetrating the blood-brain barrier is common in several diseases and in therapeutics). When a drug crosses the blood-brain barrier, its bioavailability necessarily increases. *See* Rodrigo Marmo da Costa e Souza, Inaê Carolline Silveira da Silva, Anna Beatriz Temoteo Delgado, Pedro Hugo Vieira da Silva & Victor Ribeiro Xavier Costa, *Focused Ultrasound and Alzheimer's Disease: A Systematic Review*, 12 DEMENTIA & NEUROPSYCHOLOGIA 353, 356–57 (2018) ("[S]mall lipid-soluble molecules with less than 400 Daltons (6.64×10^{-19} milligrams) in weight . . . can cross the BBB unassisted . . . .").

of this finding is sufficient to disincentivize pharmaceutical companies from exploring more specified applications of preexisting medications.[186] Accordingly, the valuable nature of nanopharmaceutical research demands that either the Federal Circuit eradicate any consideration of inherent obviousness in the context of biological or chemical patents or Congress eradicate the concept of inherent obviousness.

B. Tools to Use Instead of Inherent Obviousness

Although eliminating inherent obviousness in the context of biological or chemical patents means that patentees will likely prevail against the USPTO or accused infringers at a higher rate, it does not follow that patentees will always prevail.[187] Nor does it follow that the patent landscape will become overly saturated with biological or chemical patents.[188] Rather, accused infringers simply need to rely on other tools to challenge patent validity.[189]

1. Inherent Anticipation

Inherent anticipation is used to supply a claim limitation that is necessarily present in a single prior art reference but may be unknown.[190] The inherency principle seeks to prevent patenting an invention that was already available to the public and thus cannot be truly novel.[191] Inherent obviousness, however, differs from inherent anticipation because no single prior art reference teaches the claimed invention; thus, that claimed invention was not practiced in the prior

186. *See* ROBERT A. WEINBERG, THE BIOLOGY OF CANCER 869–70 (2d ed. 2014) ("[T]ruly successful clinical outcomes and durable clinical responses will depend in the future on the development of multi-drug therapies . . . ."); *see also id.* at 871 sidebar 16.6 ("[E]conomic forces . . . create disincentives for pharmaceutical companies to test their own proprietary drugs in combination with those produced by their competitors. Patent regulations have also discouraged . . . uses of patented compounds by firms that are in direct competition with the patent holders.").

187. *See* Bawa et al., *supra* note 5, at 4; Mueller & Chisum, *supra* note 175, at 1157.

188. *See* Bawa et al., *supra* note 5, at 4.

189. *See id.*

190. *See* O'Brien & Spruill, *supra* note 166, at 13.

191. Mahanta, *supra* note 177.

art.[192] Because anticipation permits retrospect and does not turn on what a person having ordinary skill in the art knew at the time of invention, the doctrine of inherency should be limited to the contours of anticipation.[193]

Moreover, limiting inherency to the context of an anticipation analysis eliminates the issue surrounding what a person with ordinary skill or knowledge in the art recognized at the time of invention.[194] Anticipation permits retroactive recognition of a feature unknown at the time of invention.[195] By contrast, obviousness does not, and should not, permit such retroactive recognition because an unknown or unrecognized feature can hardly be obvious.[196] Accordingly, relying on inherent anticipation to capture those elements not expressly disclosed in prior art avoids the unnecessary determination of whether a seemingly unknown or inherent feature in the prior art might be obvious in light of that disclosure.[197]

2. Plain Old Obviousness

Rather than relying on prior art to supply missing claim limitations, courts and accused infringers should perform the fact-intensive obviousness inquiry.[198] An obviousness inquiry requires courts to consider evidence such as "the level of ordinary skill in the pertinent art[,]" "reasonable expectation of success . . . in combining . . . the prior art" references, whether the prior art "teach[es] away" from the claimed invention, and objective indicia such as commercial success and failure of others, among others.[199] In addition, under the U.S. Supreme Court's interpretation of obviousness in *KSR International Co. v. Teleflex Inc.*, "courts [may] consider whether an invention

192. *Id.*
193. *See* Irah Donner, *Anticipation by Inherency*, WILMERHALE (Nov. 14, 2003), https://www.wilmerhale.com/en/insights/publications/anticipation-by-inherency-november-14-2003 [https://perma.cc/39KC-3FGQ].
194. *See id.* ("[A] prior art source may anticipate even if one of ordinary skill would not have recognized the inherent features in the prior art.").
195. *See* Mueller & Chisum, *supra* note 175, at 1157.
196. *See id.*
197. *See id.*
198. *See id.*
199. *Id.*

would have been obvious from the perspective of a [person having ordinary skill in the art] endowed with 'common sense' . . . ."[200] Accordingly, these obviousness factors "permit a . . . rich[] analysis of patent validity"; thus, the scope of obviousness should not extend beyond the metes and bounds of what was expressly disclosed in the combination of prior art references.[201]

CONCLUSION

Cases like *Par Pharmaceutical* exhibit the rather harsh stance the Federal Circuit has taken when considering whether a patentee's claimed invention should fall under the catch-all invalidation umbrella known as inherent obviousness.[202] As a result of the Federal Circuit's decision in *Par Pharmaceutical*, accused infringers have increasingly attempted to use inherent obviousness as a shield for their own alleged infringing activities.[203] Biological and chemical patents are especially susceptible to inherency challenges where a pharmaceutical composition's novel and "nonobvious" feature is a discovery or improvement in pharmacokinetics.[204] In light of the expanding field of nanotechnology and the promising benefit that nanoparticulate formulations offer in comparison to conventional drugs, the law needs to adapt in a way that will incentivize pharmaceutical companies to continue developing targeted drug-delivery systems by way of nanoparticles. Eliminating the concept of inherent obviousness in the context of biological or chemical patents is a good place to start.

200. *Id.* (quoting KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 421 (2007)); *see also KSR Int'l Co.*, 550 U.S. at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

201. Mueller & Chisum, *supra* note 175, at 1157; *see KSR Int'l Co.*, 550 U.S. at 421.

202. *See generally* Mahanta, *supra* note 177 (discussing confusion with inherent obviousness); Donner, *supra* note 193 (discussing inherent anticipation); MUELLER, *supra* note 62, at 229–30 (discussing inherent anticipation); Mueller & Chisum, *supra* note 175 (arguing for narrower interpretation of inherent anticipation to remove inconsistencies in framework); Coleman, *supra* note 174 (discussing inconsistences in caselaw regarding inherent anticipation).

203. *See* Browning et al., *supra* note 164, at 2.

204. *Id.* at 2, 3.