POTENTIAL RISKS AND REWARDS | INTELLECTUAL PROPERTY LAW | EPA AND FDA REGULATION

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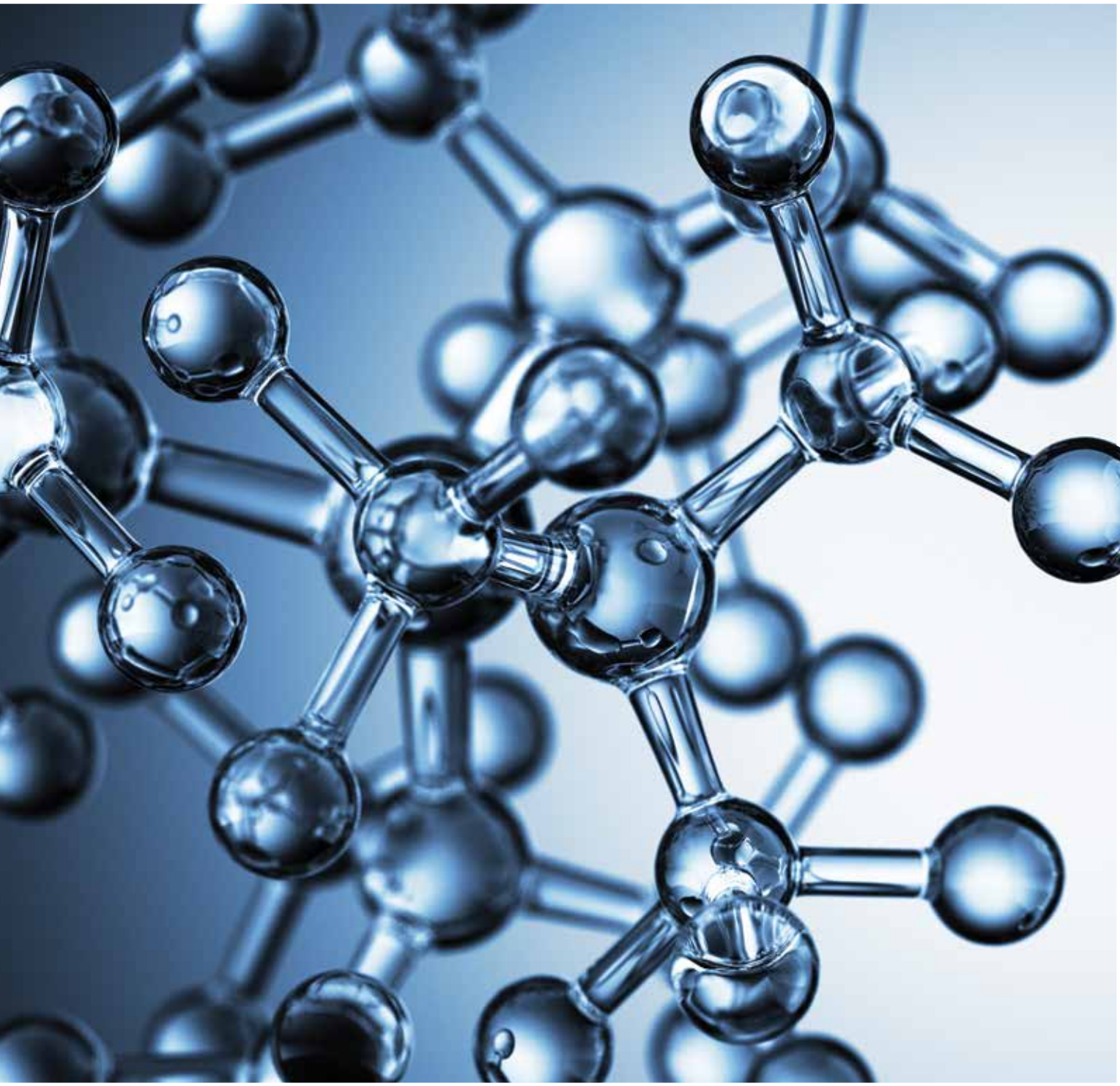

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MESSAGE FROM THE CHAIR

By Julie A. Fleming

NANOTECHNOLOGY: TINY SCALE, MASSIVE PROMISE, UNCERTAIN RISKS

Welcome to the first issue of *The SciTech Lawyer* for the 2019–2020 bar year! The theme for this issue is Nanotechnology. The interdisciplinary field of nanotechnology was born some twenty-five years ago and yet remains an "emerging technology," replete with popular references, public misunderstanding, unrealized revolutionary potential, increasing evolutionary innovation, and risk that cannot yet be fully appreciated. The lineup of articles will guide you through a variety of issues that will help to share the future of nanotechnology.

First, long-time Section member Dr. Diana Bowman's *Lawyers, Take Note: Why the Invisible Matters* provides a background on the development and as-yet unrealized promises of nanotechnology while arguing that the legal issues raised at the birth of nanotech persist today. Raj Bawa, Chair of SciTech's Nanotechnology Committee and Vice Chair of our Precision Medicine Committee, continues the discussion of "nanopotential" in the context of nanomedicine, particularly the drug-delivery sector. Next, the Section's own Dr. Brian Reese and Michael Schmitt explore intellectual property protection for nanotech-related inventions. Don't miss Edward Glady's vivid description of the liability landscape for nanotechnology, which offers the sobering argument that clarity concerning liability can exist only on the basis of future experience and understanding of the harm that nanotech innovation could cause. Finally, Lynn Bergeson and Carla Hutton investigate the ways in which EPA and FDA have designed a regulatory framework that protect both human health and the environment from the potential dangers of nanomaterials. Enjoy this stellar collection of articles.

HIGHLIGHTS OF THE ABA ANNUAL MEETING

The last bar year closed out at the ABA Annual Meeting in San Francisco, where SciTech sponsored a program titled "Shaping our Future: Top Tech Company Lawyers on Innovation and Social Responsibility," featuring general counsels from four top companies: Microsoft, Oracle, Lyft and 23andme. The GCs addressed technologies that are outpacing regulation and social dialogue, such as facial recognition, artificial intelligence, and genetic testing, and the need to have counsel work with developers to anticipate and address legal issues.

SciTech also sponsored a resolution that was adopted by the House of Delegates, urging "courts and lawyers to address the emerging ethical and legal issues related to the usage of artificial intelligence (AI) in the practice of law, including: (1) bias, explainability, and transparency of automated decisions made by AI; (2) ethical and beneficial usage of AI; and (3) controls and oversight of AI and the vendors that provide AI." A cross-ABA working group is now being established to study a possible model standard for legal and ethical usage of AI by courts and lawyers. Among other AI-related initiatives, the Section is also presenting the National Institute on Artificial Intelligence and Robotics on January 9–10, 2020 at Santa Clara University School of Law. Panels will address AI and robotics in transportation, healthcare, financial services as well as the data privacy and data security implications and much more.

Find more highlights of the bar year on the SciTech website, including Immediate Past Chair William Baker's presentation summarizing all of the activity in the past bar year. Cheers to all of the SciTech members and leadership who contributed to such a successful year! We invite your participation as we continue to shape emerging issues at the intersection of law, science, and technology. TSL

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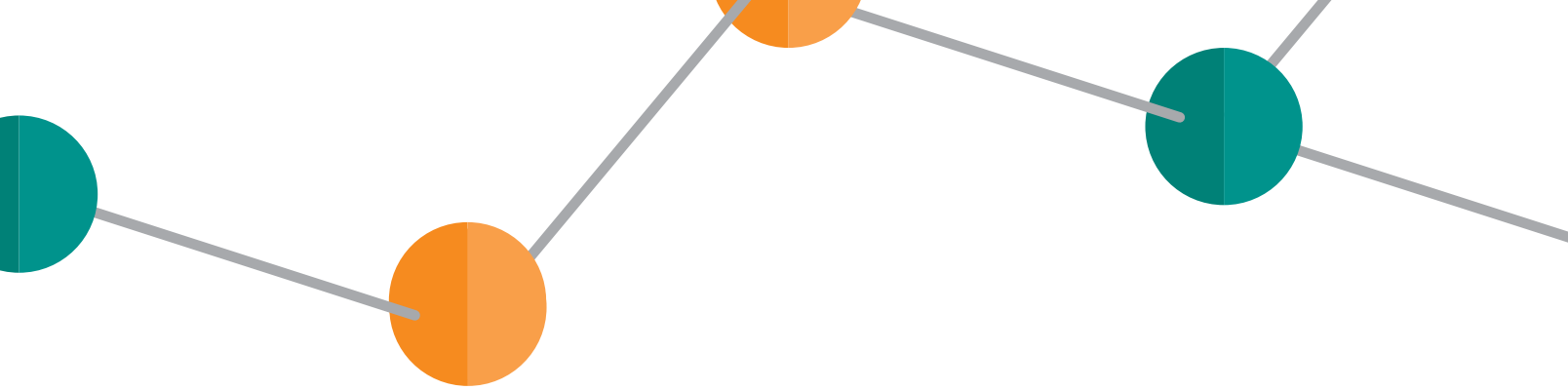
LAWYERS, TAKE NOTE: WHY THE INVISIBLE MATTERS

By Diana M. Bowman, LLB, PhD

Transparent sunscreens. Stain- and wrinkle-resistant clothing. Age-defying lotions. Stronger and lighter golf clubs. Faster-charging batteries that hold their charge for longer. Cheaper and more efficient photovoltaics. Everyday products—unique properties.

Over the last two decades, hundreds, if not thousands, of conventional products have been reengineered to improve their performance and/or enhance their consumer appeal. Chalky sunscreens, for example, renowned for the white cast that they left on skin, have been superseded by sheer sunscreens that promise greater reflection of UVA and UVB light. Interior paints, traditionally difficult to clean, now sit alongside stain-resistant and self-cleaning options. And conventional drugs, including cancer drugs, have been reengineered to be effective on a greater number of cancers and at lower doses. Invisible to the human eye, these advances can be directly attributed to advances in nanotechnologies and the greater use of nanomaterials in conventional products.

The increasing use of nanomaterials across all sectors—from agriculture to the auto industry, food to personal care, medicine and biotech and energy to consumer appliances—has, for the most part, occurred with only limited public awareness. That is not to say that terms such as "nano," "nanotech," or "nanotechnologies" are absent from the everyday vernacular. Such terms have featured in Hollywood movies and television shows such as *Minority Report*, *Red Dwarf*, *Transcendence*, and the *Terminator* and *Avengers* movies. The use of the "nano" term in science fiction and popular culture hasn't, for the most part, informed the public about the ways in which nanotechnologies and nanoscale materials are being incorporated into products across all sectors—or why. Moreover, there is little



understanding about potential future applications and how they could transform the ways in which we, for example, treat cancer, deliver potable water, and generate sustainable energy. And with nanotechnologies likely to be ubiquitous across all sectors, there are just a very few examples of where the public will encounter the technology platform.

The aim of this article is to introduce readers to nanotechnologies by providing an overview of the technology's history, key drivers, and areas of application. In doing so, the article draws upon the early work of two U.S. law professors, Professor Frederick A. Fiedler and Glenn H. Reynolds, who, in 1994, penned the first law review focused on the legal problems posed by what was then a nascent technology—nanotechnologies.[1] As they predicted, research and commercialization of nanotechnologies has not been without controversy. This article provides an overview of some of these scientific debates and subsequent action by governmental bodies such as the European Parliament and multiple U.S. entities. Acknowledging that the technology hasn't lived up to the early hype that surrounded it—at least not to date—the article then considers current and future research areas and application. Returning to the groundbreaking work of Fielder and Reynolds, the article concludes by highlighting the many legal questions and issues raised by the technology.

THE EARLY DAYS OF NANOTECH DEVELOPMENT

It is now more than fifteen years since nanotechnologies made headlines as an "emerging technology," a ubiquitous technology platform that was simultaneously framed as the "next big thing"[2] and also an object of significant scientific concern.[3] Yet, as scholars such as Toumey are quick to remind us, the history of this technology is much older than that,[4] with one of the foundational events associated with the development of nanotechnologies being Richard Feynman's 1959 talk, *There's Plenty of Room at the Bottom*.[5] While Toumey has also sought to remind us that this history is somewhat contested, there are a number of key events that can be said to have advanced the development of the technology and include, for example, the coining of the term "nanotechnology" by Norio Taniguchi in 1974,[6] the development of the scanning tunneling microscope (STM) in 1981 by IBM researchers Binnig and Rohrer,[7] and the futuristic writings on nanotechnology and molecular nanotechnology by Eric Drexler (1986).[8] Collectively, these initiatives have framed the fundamental research and development (R&D) activities that define nanotechnologies of today.

But what are nanotechnologies? And what makes the nanoscale so interesting from a scientific and commercialization perspective? The term "nano" is derived from the Greek word for "dwarf," and conceptually refers to the scale of one-billionth (or 10^{-9}). A nanometer (nm) is a unit of length, equal to one-billionth of a meter. And while there is no universally accepted definition of what "nanotechnologies" are, Hodge et al.[9] suggest five crucial characteristics that define the technology: scale (1–100 nm), heterogenous family of technologies, multidisciplinary approach, the notion of novelty, and the purposeful manipulation of materials at the nanoscale in order to exploit novel properties and functions.[10]

With leading scientific commentators and policymakers heralding nanotechnologies as a key driver for the next industrial revolution and promising everything from sustainable energy solutions to revolutionary cancer treatments,[11] high levels of public-sector interest should be no surprise. The formal establishment of the National Nanotechnology Initiative (NNI) by the Clinton administration in 2001, which sought to coordinate R&D efforts across U.S. federal agencies, was the first of now more than thirty national government nano-focused initiatives around the world.[12] Significant investment in these initiatives has helped to catalyze fundamental R&D efforts, provide infrastructure, and accelerate innovation. The U.S. government, in 2019 alone, allocated $1.4 billion to the NNI. With global consulting firm BCC Investments suggesting that the value of the global nanotech market is likely to exceed $90 billion by 2021,[13] such levels of investment in bringing nano-enabled products and applications into the market appears likely to continue.

CATALYST FOR CONCERNS?

The emergence of nanotechnologies and the increasing use of nanomaterials in consumer goods such as personal care products and foods, however, have not been without controversy. The commercialization of such products has occurred in parallel to significant scientific debate regarding potential risks, scientific uncertainties, and broad debate over the potential social, ethical, and legal issues raised by the technology.[14] The landmark report by the Royal Society and Royal Academy of Engineering (RS-RAE) in 2004 provided the first comprehensive analysis of the scientific state of the art, potential risks to human and environmental health and safety, and known scientific unknowns.[15] This report also identified numerous regulatory issues relating to the ability of existing legislative regimes to effectively regulate, for example, the production and entry of nanomaterials and nano-based products into the market. It is

therefore not surprising that in response to these uncertainties associated with nanotechnologies, a number of non-governmental organizations, including the ETC Group and Friends of the Earth, called for moratoriums on the use of certain families of nanomaterials in, for example, the agri-food and personal care sectors.[16] However, such calls gained little traction.

Efforts to address the scientific and regulatory uncertainties have shaped national and international research agendas, culminating in a significant number of legislative reviews, regulatory activities, and soft-law initiatives over the past fifteen years. These have included comprehensive regulatory reviews by the European Commission[17] and the Australian Government,[18] voluntary data call-ins by the United Kingdom's government and the U.S. Environmental Protection Agency (EPA),[19] the passage of nano-specific legislative provisions in the European Union (EU) and New Zealand, rulemaking by the EPA, publication of guidance materials by the U.S. Food and Drug Administration (FDA), and the publication of a number of codes of conduct/risk management frameworks by entities such as the European Commission (EC), BASF, and DuPont-Environmental Defense.[20] The proactive approach to technology governance here is arguably unique, with Levi-Faur and Comaneshter noting that "[p]robably for the first time ever, the attempt to develop a regulatory framework for a new technology is emerging on the public agenda hand in hand with the development of the technology itself."[21]

While a myriad of questions still remain over potential risks posted by the technology, an impressive body of scientific research now exists on the potential toxicity, routes of exposure, biological interactions, and environmental impacts of many nanomaterial families. Significant advances have also been made in the applicability of conventional risk assessment protocols, standards, metrology, test methods, reference materials, and nomenclature.[22]

Despite this greater depth and breadth of knowledge, headlines such as "*Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study*"[23] have the potential to fuel public concern over the technology—as did the news that Dunkin' Donuts used nano-scale titanium dioxide (TiO2) as an ingredient in its powdered-sugar donuts—despite TiO2 being approved by the FDA as a color additive.[24] In regards to the former, significant debate over whether carbon nanotubes (CNTs) are the next asbestos has generated worldwide attention, helped shape national and multinational regulatory agendas and scientific studies, and given rise to a "safety-by design" approach to CNT production.[25] In regards to the latter, public outrage against Dunkin' Donuts's use of nanomaterials within its foods led to the subsequent removal of nano-TiO2 in its much-loved donut. While such high-profile incidents have been rare, given the ubiquitous nature of nanotechnologies, similar adverse reports likely will recur.

NANOTECHNOLOGY TODAY AND TOMORROW

There can be little doubt that nanotechnologies have not lived up to the original hype and promises that were sold to policymakers and the public nearly two decades ago. Today's nano-based products and applications are, for the most part, conventional products that have been reengineered to include nanomaterials for the purpose of exploiting specific unique properties. And while a space elevator made out of CNTs remains squarely in the realm of science fiction, innovative nano-based solutions for treating cancer and HIV, generating cheap energy, and creating advanced materials that can be deployed on the battlefield are being tested and deployed in many different forms today. A quick review of scientific journals such as *Nature*, *Nature Nanotechnology*, and *Science* is suggestive of the cutting-edge research being undertaken by the global researcher community using nanotechnologies and the paradigm-changing nature of their discoveries and inventions.

While nanotechnologies alone may not be the panacea for addressing the United Nations Sustainable Development Goals, many of the solutions for addressing climate change, creating sustainable energy networks, promoting economic growth, providing access to potable water, and creating innovative industries and infrastructure will—by design and by necessity—incorporate nanotechnologies in one way or another. As this issue's theme highlights, the law will play a central role in helping to bring the products and applications into the market in a way that balances innovation with protecting human and environmental health and safety.

Fiedler and Reynold's early writings on the governance of nanotechnologies did exactly what they intended it to do: It was more of a "wakeup call than a road map, . . . rais[ing] far more questions than it answer[ed]."[26] While some of these questions have now been answered, many of the questions that they raised some twenty-five years ago relating to legislative fit, legal lag, property rights, and liability remain relevant today—and will continue to be tomorrow—and beyond.

Diana Bowman, LLB, PhD, G.Dip.Leg. Prac., is a professor of law in Arizona State University's Sandra Day O'Connor College of Law, Associate Dean for International Engagement, and a professor in the School for the Future of Innovation and Society. She is a co-director of the Center for Smart Cities and Regions at ASU and an Andrew Carnegie Fellow (2018).

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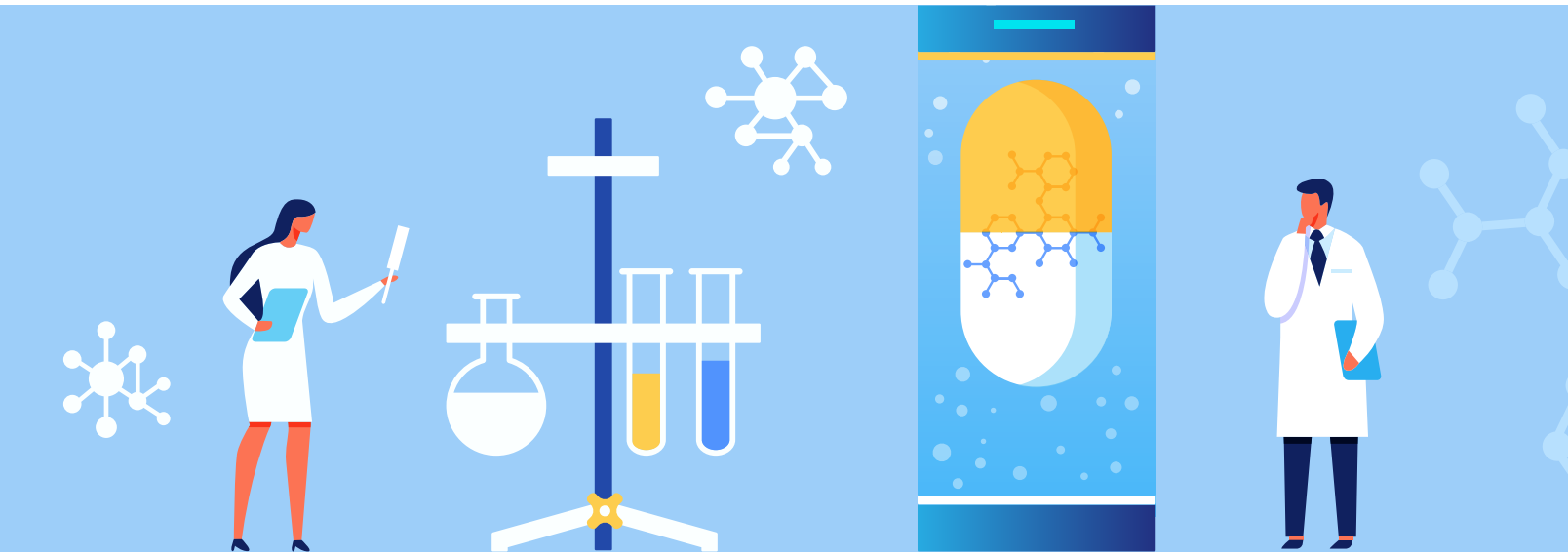
NANO DRUG DELIVERY

Scientific, Patent Law, and FDA Regulatory Perspectives



NANO FRONTIERS: A BRIEF INTRODUCTION

The air is thick with news of nano-breakthroughs. Although "nano" (nanotech or nanotechnology) is a hot topic for discussion in industry, pharma, patent offices, and regulatory agencies, the average citizen knows very little about what constitutes a nanoproduct, a nanomaterial, or a nanodrug. Still, there is no shortage of excitement and confusion when it comes to anything nano. Optimists tout nano as an enabling technology, a sort of next industrial revolution that could enhance the wealth and health of nations. They promise, in particular, that areas within nanomedicine (nanoscale drug delivery systems, theranostics, nanoimaging, etc.) will soon be a healthcare game-changer by offering patients access to personalized or precision medicine. Pessimists, on the other hand, take a cautionary position, preaching instead a go-slow approach, pointing to a lack of scientific information on health risks, general failure on the part of regulatory agencies to formulate clearer guidelines and issuance of patents of dubious scope by patent offices. They highlight that nano is burdened with inflated expectations and hype. As usual, the reality is somewhere between such extremes. Like any emerging technology, the whole picture has yet to emerge, and we are just getting started! Whatever your stance, nano has already permeated virtually every sector of the global economy, with potential applications consistently inching their way into the marketplace. But is nano the driving force behind a new industrial revolution in the making or simply a repacking of old scientific ideas and terms? Dissecting hope from hype is not straightforward.

Nano is the natural continuation of the miniaturization of materials and medical products that have been steadily arriving in the marketplace. It continues to evolve and play a pivotal role in various industry segments, spurring new directions in research, patents, commercialization, translation, and technology transfer. Although not a distinct field or discipline, nano is an interdisciplinary area that draws from the interplay among numerous fields, including materials science, engineering, colloid science, supramolecular and physical chemistry, drug science, biophysics, and more.

Nano's potential benefits are frequently overstated or inferred to be very close to application when clear bottlenecks to commercial translation exist. In this regard, start-ups, academia, and industry exaggerate basic research and developments (R&D) as potentially revolutionary advances and claim their early-stage discoveries as confirmation of downstream novel products and applications to come.[1] This does great disservice to all stakeholders involved. It not only pollutes the medical literature but also quashes public support for translational activities. Another common phenomenon observed is that many players have desperately tagged or thrown around the "nano" prefix to suit their own motives, whether it is for research funding, patent approval, raising of venture capital, or running for office. All of this is happening while hundreds of over-the-counter products containing silver and other metallic nanoparticles, nanoscale titanium dioxide, carbon nanotubes, and carbon nanoparticles continue to stream into the marketplace without adequate safety testing, labeling, or regulatory review.[2] Silver nanoparticles are effective antimicrobial agents, but their potential toxicity remains a major concern. Similarly, nanoscale titanium

By Raj Bawa, MS, PhD

dioxide, previously present in powdered Dunkin' Donuts® and Hostess Donettes®, was classified as a potential carcinogen by the National Institute for Occupational Safety and Health (NIOSH), while the World Health Organization (WHO) linked it in powder form to cancers.

Even so, governments across the globe continue to stake their claims by doling out billions for R&D. In fact, this trend in research funding has stayed relatively consistent, at least in the industrialized world. Stakeholders, especially investors and consumer-patients, get nervous about the "known/unknown" novel applications, uncertain health risks, unclear industry motives, and general lack of governmental transparency. Although venture has mostly shied away in recent years, industry–university alliances have continued to gel, driven primarily by what many refer to as "nanopotential." Wall Street's early interest in nano has been somewhat muted over the years, from cautionary involvement to generally shying away. Despite anemic nanoproduct development, there is no end in sight to publications, press releases, and patent filings.

While the widespread use of nanomaterials and nanoparticles in consumer products over the years has become pervasive and exposure inescapable, the last 25 years have seen limited applications of these rather than the transformative applications envisioned. Instead, the current decade has witnessed relatively more advances and product development in nanomedicine. Its influence on the pharmaceutical, device, and biotechnology industries is starting to show. One can now unequivocally state that R&D is in full swing and novel nanomedical products, especially in the drug-delivery sector, are starting to arrive in the marketplace.

SIZE MATTERS IN DRUG DELIVERY: ADVENT OF NANODRUGS

The global nanomedicine market was reported to be worth $72.8 billion in 2011 and $138 billion in 2016, and it is predicted to be worth $350 billion by 2025.[3] The major impact of nanomedicine today is in the context of drug delivery. But there is no formal or internationally accepted definition for anything "nano." A harmonized definition and nomenclature is urgently needed. There is no standard definition for a nanodrug either. The following is my definition for a nanodrug: "A nanodrug is a formulation, often colloidal, containing (1) therapeutic particles (nanoparticles) ranging in size from 1–1,000 nm; and (2) carrier(s) that is/are themselves the therapeutic (i.e., a conventional therapeutic agent is absent), or the therapeutic is directly coupled (functionalized, solubilized, entrapped, coated, etc.) to the carrier(s)."[4]

Nanodrugs are diverse in size, shape, structural design, and composition. Nanodrugs *may* have unique properties ("nanocharacter") that can *often* provide an advantage over their "bulk" or larger counterparts, primarily due to their reduced size as discussed ahead. It is important to note that properties other than size, such as shape/geometry, zeta potential, composition, delivery route, crystallinity, or aspect ratio, can also have a dramatic effect on the nanocharacter of nanodrugs.

Novel nanodrugs and nanocarriers are being designed that address some fundamental problems of traditional drug formulations—ranging from poor water solubility and unacceptable toxicity profiles, to poor bioavailability, solubility issues, physical/chemical instability, and a lack of target specificity.

Additionally, via tagging with targeting ligands, nanodrugs can serve as innovative drug delivery systems for enhanced cellular uptake of therapeutic's "active agents" into tissues of interest. As a result, nanodrugs are being developed that allow delivery of active agents more efficaciously to the patient while minimizing side effects, improving drug stability *in vivo*, and increasing blood circulation time. Apart from these pharmacological benefits, nanodrugs can also offer economic value to a drug company—the opportunity to reduce time-to-market, extension of the economic life of proprietary drugs, and creation of additional revenue streams. Therefore, nanodrugs are starting to influence the drug and device commercialization landscapes and will likely continue to impact medical practice and healthcare delivery into the next century. In the meantime, a steady stream of first-generation nanodrugs approved by various regulatory agencies, including the U.S. Food and Drug Administration (FDA), has arrived in the marketplace. Few are completely novel, while most are redesigned or reformulated versions of earlier drug formulations. Revolutionary second- and third-generation nanodrugs are in preclinical or clinical stages at this time. Advanced future nanodrugs will be those that can (1) deliver active agents to specific tissue, cells, or even organelles ("site-specific, precision, or targeted drug delivery") and/or (2) offer simultaneous controlled delivery of active agents with concurrent real-time imaging ("theranostic drug delivery"). As nanodrugs move out of the laboratory and into the clinic, various global regulatory agencies and patent offices continue to struggle to encourage their development while imposing some sort of order in light of regulatory, safety, and patent concerns.

Scientifically speaking, as a particle's size decreases to nanoscale dimensions, a greater proportion of its atoms is located on the surface relative to its core, *often* rendering the particle more chemically reactive. An example of this is nanosilver ("colloidal silver"), a highly reactive and antimicrobial form of silver as compared to its docile bulk counterpart. However, depending on the intended use, such enhanced activities could either be advantageous (antioxidation, carrier capacity for drugs, and enhanced uptake and interaction with tissues) or disadvantageous (toxicity issues, instability, and induction of oxidative stress).

It is also a scientific fact that as we granulate a particle into smaller particles, the total surface area of the smaller particles becomes much greater relative to its volume ("increased surface area–to–volume ratio"). From a drug-delivery perspective, these nanoparticles have a higher dissolution rate, water solubility, and saturation solubility compared to their larger counterparts, properties that *may* result in superior bioavailability due to a greater percentage of active agents being available at the site of action (i.e., at a tissue or disease site). This *could* translate into a reduced drug dosage scheduled for the patient, which in turn *may* reduce potential side effects and offer superior drug compliance. Also, active agents in formulations that have side effects due to triggering an immune response can be entrapped, encapsulated, or embedded within a nanoparticle coat or matrix, potentially evading the immune system. In a clinical setting, all of this can potentially enhance *in vivo* bioperformance.

Finally, nanoparticle therapeutics have a greater potential for interaction with biological tissues, i.e., an increase in adhesiveness onto biosurfaces. This can be a tricky, double-edged issue. On one side, the multiple binding sites of nanodrugs ("multivalence") allow for superior binding to tissue receptors, but on the other side, intrinsic toxicity of any given mass of nanoparticles is often greater than that of the same mass of larger particles. Also, nanodrugs such as liposomes can further contribute to "signal enhancement" over that of a single drug molecule because of the enormous payload of encapsulated active agent molecules.

TERMINOLOGY AND NOMENCLATURE: LOST IN TRANSLATION

In the heady days of any emerging technology, definitions tend to abound and are only gradually documented in reports, journals, handbooks, and dictionaries. Ultimately, standard-setting organizations like the International Organization for Standardization (ISO) produce technical specifications. This evolution is essential as the development of terminology is a prerequisite for creating a common, valid language needed for effective communication in any field. Clearly, an internationally agreed nomenclature, technical specifications, standards, guidelines, and best practices are required to advance nano in a safe and transparent manner. Terminology matters because it prevents misinterpretation and confusion. It is also necessary for R&D, harmonized regulatory governance, accurate patent searching and application drafting, standardization of procedures, manufacturing and quality controls, assay protocols, research grant reviews, policy decisions, ethical analysis, public discourse, safety assessment, translation, and commercialization.

Although various "nano" terms, including "nanotechnology," "nanoscience," "nanopharmaceutical," "nanodrug," "nanotherapeutic," "nanomaterial," "nanopharmacy," and "nanomedicine," are widely used, there is ambiguity regarding their definitions. In fact, there is no precise definition of nano terms as applied to pharmaceuticals or in reference to drug delivery. This definitional issue, or lack thereof, continues to be one of the most significant challenges for regulators, policymakers, researchers, and legal professionals to grapple with.

But what does "nano" mean? A nanometer refers to one-billionth of a meter in size/length and "nano" is a prefix denoting 10^{-9}. Nano does not represent a single technology or field of research but is an umbrella term encompassing several scientific fields/processes at the nano/micro scale. Partly due to this confusion over the definition of these terms and partly because of a lack of any standard nomenclature available, various definitions have sprung up over the years. Even the FDA, which has not adopted any "official" regulatory definition, now uses a loose definition for products that involve or employ nanotechnology that either (1) have at least one dimension in the 1–100

nm range or (2) are up to 1,000 nm, provided the novel/unique properties or phenomena exhibited are attributable to these dimensions above 100 nm. This definition, revised by the FDA in 2014, correctly increased the upper limit of nanodrugs from 100 nm to 1,000 nm. However, various other U.S. governmental agencies continue to use an inaccurate definition proposed in the early 1990s by the National Nanotechnology Initiative (NNI) based on an arbitrary sub-100 nm size that is more relevant to materials engineering than drug delivery.[5] Clearly, in relation to nanodrugs, such definitions based on size or dimensions alone fall short on both scientific and legal grounds.[6]

Apart from creating confusion in the nanomedicine community and among relevant stakeholders, there are concerns that this definitional issue could continue to pose a major bottleneck to translational efforts. Certainly, this has contributed to the evolving "patent thicket" in certain areas of nano along with a lack of specific protocols for preclinical development, slower nanomaterial characterization, and pollution in the scientific literature. It is important that some order, central coordination, and uniformity must be provided to address the rise of diverse nano terms. This is also critical to prevent a significant scientific, legal, and regulatory void from developing.

PATENT LAW ISSUES

Patents can have an impact at all stages in the translational pipeline: at the preclinical research stage, during clinical trials, at the point of commercialization, and when the product is in the clinic. They are the lifeblood of any nano-enterprise, both as an enabler of translation and as a barrier to competition or litigation. The protection of inventions via patents provides an opportunity for companies to recoup the high cost of discovery by preventing competitors from entering the marketplace while the patent is in force. Simply put, securing valid and defensible patent protection from patent offices is critical to any commercialization effort. Understanding the patent process, the patent landscape, and white-space opportunities is essential to translational research and the development of innovations for clinical use. But patent offices continue to be under enormous strain and scrutiny. Issues ranging from poor patent quality, questionable examination practices, inadequate search capabilities, rising attrition, poor examiner morale, and enormous patent backlogs are just a few issues that need reform.

Nanopatent filings and patent grants have continued unabated since the early 1980s. In fact, since then, "patent prospectors" have been on a global quest for "nanopatent land grabs." Universities and industry have jumped into the fray as well with a clear indication of patenting as much nano as they can grab. Often in this rush to patent anything and everything nano, nanopatents of dubious scope and validity are issued by patent offices around the world.

Since the early 1990s, in light of inadequate search tools/commercial databases available to patent examiners at the U.S. Patent & Trademark Office (USPTO) along with and exploding "prior art," overlapping nanotech patents or patents of questionable validity and/or scope have dribbled out.[7] Global patent offices continue to issue multiple nanopatents on overlapping inventions, thereby generating potential "patent thickets."[8]

Another major problem is that the USPTO continues to classify U.S. nanopatents based on the ill-conceived NNI definition of nano that limits all nanodrugs and nanoproducts to a sub-100 nm range. As highlighted above, the shortfall with this definition is well documented. As a result, the numbers for granted U.S. nanopatents is an underestimate (currently, according to USPTO estimates, nanomedicine patents number a few thousand out of a total 10+ million granted U.S. patents). Also, related to this issue is the lack of a universal nano-nomenclature. As a result, distinct terms frequently refer to identical or similar nanostructures, nanomaterials, or nanodrugs, creating confusion and legal misinterpretation during patent prosecution at the USPTO or later during litigation.

FDA REGULATION: GAPS AND BABY STEPS ON A BUMPY ROAD

Advances in nanomedicine and the FDA system for governing nanodrugs are inevitably intertwined. Internationally, regulatory agencies continue to struggle in their efforts to develop new, meaningful, regulatory definitions and balance them with policies and laws that are already in place. However, guidance is critically needed to provide clarity and legal certainty to manufacturers, policymakers, healthcare providers, and, most importantly, the consumer. Common sense warrants that some sort of guidance, oversight, or regulation by the FDA is in order, at least on a case-by-case basis. But, so far, the FDA has chosen to regulate nanodrugs solely via laws that are already in the books.

Transparent and effective governmental regulatory guidance is critical for nanomedical translation. However, emerging technologies such as nanotech are particularly problematic for governmental regulatory agencies to handle, given their insular nature, slow response rate, significant inertia, and a general mistrust of industry. Major global regulatory systems, bodies, and regimes regarding nanomedicines are not fully mature, hampered in part by a lack of specific protocols for preclinical development and characterization. Additionally, despite numerous harmonization talks and meetings, there is lack of consensus on procedures, assays, and protocols to be employed during preclinical development and characterization of nanomedicines. The baby steps the FDA has undertaken over the past decade have led to regulatory uncertainty.[9] The bumpy ride is expected to continue.

Not all nanoscale materials are created equal. Some nanomaterials or products that incorporate nanotech may be toxic. Their toxicities depend upon factors that are material-specific and/or geometry-specific, but the toxicity of many nanoscale materials is not fully apparent either. Moreover, because premarket testing of nanodrugs will not detect all adverse reactions, it is crucial that long-term safety testing be conducted. Therefore, postmarket

tracking or a surveillance system must be adopted to assist in recalls. Toxicity data specific to nanomaterials and nanodrugs needs to be collected and an effective risk research strategy devised. The FDA should seriously contemplate nano-ingredient labeling, where appropriate.

The FDA is also criticized for producing legally nonbinding "draft" guidance documents, while the European Medicines Agency (EMA) has similarly issued "position papers."

Products submitted to the FDA for market approval, including some that may contain nanomaterials, nanodrugs, or involve nanomedicine, are evaluated according to a category-based system in one of nine FDA centers that focus on a specific area of regulation. However, certain therapeutics are combination products, which consist of two or more regulated components (drug, biologic, or device) that are physically, chemically, or otherwise combined/mixed to produce a single entity. In such cases, the FDA determines the "primary mode of action (PMOA)" of the product, which is defined as "the single mode of action of a combination product that provides the most important therapeutic action." This process is frequently imprecise because it is not always possible to elucidate a combination product's PMOA. Especially with the demise of pharma's blockbuster model, future, novel "multifunctional/multicomponent" nanodrugs will be designed that incorporate a drug plus diagnostic (theranostic) in the same engineered nanoparticle. As these combination products seek regulatory approval, they are sure to present additional challenges for the FDA because the agency's current PMOA regulatory paradigm may prove ineffective.

There are potentially serious and inhibitory consequences if nanodrugs are overregulated, and so a balanced approach is required, at least on a case-by-case basis, that addresses the needs of commercialization against mitigation of inadvertent harm to patients or the environment. Obviously, not every nanomedical product needs to be regulated; however, more is clearly needed from regulatory agencies like the FDA and EMA than a stream of draft guidance documents and policy papers that are often short on specifics and fail to address key regulatory issues. There is a very real need for regulatory guidelines that follow a science-based approach and are responsive to the associated shifts in knowledge and risks.

DISTINCT TERMS FREQUENTLY REFER TO IDENTICAL OR SIMILAR NANOSTRUCTURES, NANOMATERIALS, OR NANODRUGS, CREATING CONFUSION AND LEGAL MISINTERPRETATION DURING PATENT PROSECUTION AT THE USPTO OR LATER DURING LITIGATION.

GENERIC NANODRUGS: THE ISSUE OF NANOSIMILARS

Globally, the landscape for approval of generic nanodrugs is a murky one. On the one hand, the FDA has published several draft documents pertaining to specific nanodrugs. On the other hand, some countries have already approved multiple generic nanodrugs (nanosimilars) of dubious efficacy, safety, purity, and composition that are being provided to patients without rigorous physicochemical characterization, without adequate clinical trials, and with little to no manufacturing oversight.

In 2010, the Biosimilars Act was enacted into law in the U.S. that established an approval route for generic biologics analogous to small molecule drugs, expanding patient access to some of the most expensive drugs on the market.[10] Currently, there is no codified generics approval pathway for nanodrugs. Moreover, in the absence of universal nomenclature for nanodrugs, the biosimilar definition does not fit these drugs. The rules in place for small molecule drugs are being tailored for generic nanodrugs; this is an imperfect approach. Furthermore, some of these complex nanodrugs can also be classified as nonbiologic complex drugs (NBCDs),[11] which could present additional issues for the FDA as it reviews generic versions of these NBCDs. NBCD generics will usually lack bioequivalence to their referenced NBCD, thereby prompting submission of clinical data from the generic drug developer.[12]

CONCLUSIONS AND FUTURE PROSPECTS

Nanomedicine continues to evolve and play a pivotal role in various industries, spurring new directions in research,

patents, translation, commercialization, and technology transfer. Effective translation of nanodrug candidates requires a "technological push" coupled to a "clinical pull," which is bridged by logical intermediary data that mechanistically demonstrate the efficacy and safety in biological systems.

Many view nanomedicine and nanodrugs as the next industrial revolution, but widespread business and public support is still lacking. Although the increased media attention and hype has generally led to confusion, caution, and even suspicion, there is also ample interest and excitement in anything "nano," especially pertaining to nanomedicine and nanodrugs. The accuracy of information disseminated and the transparency of the disseminating entity will be crucial to the future course of nanomedicine.

It is imperative that flexible and science-based regulation of nanodrugs must balance innovation and R&D with the principle of ensuring maximum public health protection. Regulatory oversight and legal guidelines must evolve in concert with newer generations of nanodrugs and not lag, as is the case at present.

It is also important that the public's desire for novel nanomedical products, the venture community's modest investment, governmental infusion of funds, and big pharma's lingering interest continue to catalyze nanomedicine. In the end, the long-term prognosis and development of nanomedicine will hinge on effective regulatory policies, issuance of valid patents, clearer safety guidelines, transparency, addressing of social and ethical challenges, and full commitment of all stakeholders involved—big pharma, academia, governmental regulatory agencies, policymakers, the venture community, disease advocacy groups, and the consumer-patient. Everyone must be on board so that nanomedicine translation becomes more widespread and innovative products can move from the lab bench to the patient's bedside. We must endure and continue to traverse the long, complex, and difficult commercial "valley-of-death" for the overall benefit of society.

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ENDNOTES

1. *See* S. Tinkle et al., *Nanomedicines: Addressing the Scientific and Regulatory Gap*, 1313 Ann. New York Acad. Sci. 35 (2014); R. Bawa, *Small Is Beautiful*, *in* Handbook of Clinical Nanomedicine: Nanoparticles, Imaging, Therapy and Clinical Applications, at xxxvii (R. Bawa, G. Audette & I. Rubinstein eds., 2016).

2. A large number of nanomaterials and nanoparticles have been synthesized over the last two decades, yet the EPA or FDA does not seem to know how to regulate most of them. Obviously, consumers should be cautious about potential exposure, but industry workers should be even more concerned. *See* R. Bradley, *The Great Big Question About Nanomaterials*, 171 Fortune, no. 4, 2015, at 192.

3. *See* Press Release, Grand View Research, Nanomedicine Market Size Worth $350.8 Billion by 2025 (Apr. 2017), https://www.grandviewresearch.com/press-release/global-nanomedicine-market.

4. *See* R. Bawa, *Current Immune Aspects of Biologics and Nanodrugs: An Overview*, *in* Immune Aspects of Biopharmaceuticals and Nanomedicines, ch. 1, at 1 (R. Bawa, J. Szebeni, T.J. Webster & G.F. Audette eds., 2018).

5. The arbitrary upper size limit of 100 nm proposed by the NNI may be relevant to a physical scientist because this is *sometimes* the size range at which there is a transition between bulk and nonbulk properties of metals and metal compounds. On the other hand, the drug scientist is more interested in the *extrinsic* novel properties of nanoparticles that arise because of their interaction with biological systems and/or nanodrug formulation/efficacy properties that improve bioavailability, reduce toxicity, lower required dose, or enhance solubility.

6. *See* R. Bawa, (2016). *What's in a Name? Defining "Nano" in the Context of Drug Delivery*, *in* Handbook of Clinical Nanomedicine, *supra* note 1, ch. 6, at 127.

7. *See* R. Bawa, *Nanotechnology Patent Proliferation and the Crisis at the US Patent Office*, 17 Alb. L.J. Sci. Technol. 699 (2007); R. Bawa, *Patents and Nanomedicine*, 2 Nanomedicine (Lond.) 351 (2007); S. O'Neill et al., *Broad Claiming in Nanotechnology Patents: Is Litigation Inevitable?*, 4 Nanotechnology L. & Bus. 595 (2007).

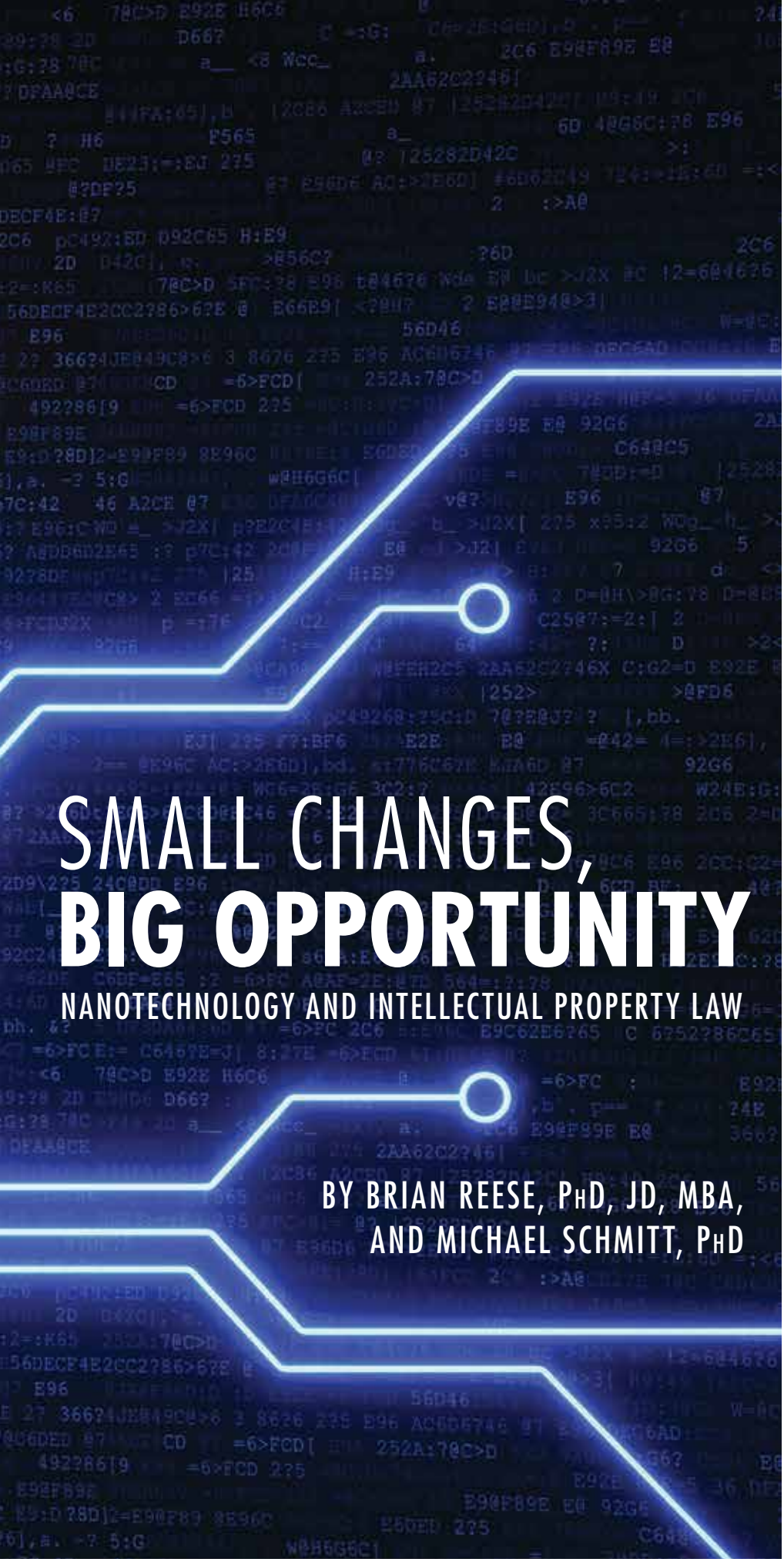
8. *See* R. Bawa, Editorial Commentary, *Will the Nanomedicine "Patent Land Grab" Thwart Commercialization?*, 1 Nanomedicine: NBM 346 (2005); R. Bawa, S. R. Bawa & S. Maebius, *The Nanotechnology Patent "Gold Rush,"* 10 J. Intell. Prop. Rts. 426 (2005).

9. R. Bawa, S. Melethil, W.J. Simmons & D. Harris, *Nanopharmaceuticals: Patenting Issues and FDA Regulatory Challenges*, 5 SciTech Law., no. 2, 2008, at 10; M.A. Hamburg, Science and Regulation: *FDA's Approach to Regulation of Products of Nanotechnology*, 336 Science no. 6079, Apr. 20, 2012, at 299; R. Bawa, *A Practical Guide to Translating Nanomedical Products*, *in* Pharmaceutical Nanotechnology: Innovation and Production, ch. 28 at 663 (J. Cornier et al. eds., 1st ed. 2017); R. Bawa, Y. Barenholz & A. Owen, *The Challenge of Regulating Nanomedicine: Key Issues*, *in* Nanomedicines: Design, Delivery and Detection, ch. 12, at 290 (Royal Soc'y of Chemistry, RSC Drug Discovery Series No. 51) (M. Braddock ed., 2016).

10. *See* J.A. Johnson, Biologics and Biosimilars: Background and Key Issues, Cong. Res. Serv. Rep. R44620 (2017).

11. Therapeutics can be broadly divided into three classes: (1) small-molecule drugs, (2) biologic drugs and (3) non-biological complex drugs (NBCDs). NBCDs have been defined as engineered medicinal products, where the active agent or therapeutic moiety is not a homo-molecular structure but consists instead of different yet closely related and often nanoparticulate structures that cannot be isolated, fully quantitated, and/or characterized via standard analytical or physicochemical techniques.

12. *See* H. Schellekens et al., *How to Regulate Nonbiological Complex Drugs (NBCD) and Their Follow-on Versions: Points to Consider*, 16 AAPS J. 15 (2013).



SMALL CHANGES, BIG OPPORTUNITY

NANOTECHNOLOGY AND INTELLECTUAL PROPERTY LAW

BY BRIAN REESE, PHD, JD, MBA, AND MICHAEL SCHMITT, PHD

Nanotechnology (NT) research, development, and funding has risen sharply since 2000. In this country alone, there has been more than $27 billion in funding in NT through the National Nanotechnology Initiative (NNI).[1] Unsurprisingly, the significant financial resources devoted to the development of NT have led to a corresponding growth in patent applications intended to protect inventions in the field.

The rapidly expanding use of NT to address longstanding technological problems has great potential commercial implications. Accordingly, protection of NT-related inventions must be a focus for commercial entities wishing to establish and/or maintain an effective exclusivity proposition relative to an increasing number of players in the field. While there are several ways to accomplish this, including through patents and trade secrets, patents are the focus of the discussion here. Nearly 20,000 patents and patent applications were published by the U.S. Patent and Trademark Office (USPTO) and 3,500 publications came from the European Patent Office related to the fields of NT in 2016.[2] It is clear, investment in and development of nanotechnologies will continue to grow in the coming years,[3] likely resulting in continued growth in associated intellectual property.

NANOTECHNOLOGY AND IP

Nanotechnology includes many different areas of research and development and, accordingly, the term "nanotechnology" itself has taken on many different, but related, definitions. A broad, conceptual definition of NT is appropriate in the context of patents. An invention can be considered to be in the field of NT generally when one or more of its purported benefits (e.g., properties and/or performance) are derived from its structure (e.g., size and/or shape). Such a broad and conceptual definition reflects the reality that inventions in the field of NT may result from exploitation of one or more of a wide range of structural characteristics of a material, device, or system.

The possible structural characteristics whose manipulation can lead to a patentable invention are nearly endless: size, shape, crystallographic orientation, porosity, surface passivation, and so on. It is of note that patentable inventions may result from synergy between structure and composition, where structure or composition alone is insufficient to achieve the purported benefit(s). The full National Science and Technology Council (NTSC) definition uses some qualification along these lines within its stated size limitations by stating that NT is, within the ~1–100 nm scale, "exploiting the distinct properties and phenomena at that scale as compared to those associated with single atoms or molecules or bulk behavior."[4] Others, including the International Organization for Standardization (ISO), have proposed or adopted similar conceptual definitions for regulatory and research contexts.[5] The above definition is invoked with reference to NT in the following discussion.

PATENT RIGHTS

At its core, a patent is a time-limited right to exclude others from performing a range of activities encompassed by an issued claim within the jurisdiction.[6] The ability for a patent applicant to secure such rights is based upon a quid pro quo exchange—in order to receive a twenty-year monopoly on a claimed invention, an applicant must disclose his or her invention such that one of skill in the art must be able to make and use the claimed invention based on the teachings in the application. Especially in fields such as NT where technological development is rapid and competitive, applying for and obtaining one or several patents that broadly cover a new technology can provide important advantages over competitors.

In order to obtain a patent, there are several statutory requirements that must be met. First, an invention being claimed must meet the utility requirement.[7] In order to be considered as meeting the utility requirement, a claimed invention must "provide some identifiable benefit and [be] capable of use[.]" This requirement is fairly simple to meet, though biotechnology-related inventions in particular have had some difficulty under recent case law.[8]

Second, a claimed invention must meet the novelty requirement.[9] A key concept when discussing both novelty and nonobviousness is that of "prior art." Generally, information made publicly available in any form (e.g., written or oral) that predates a patent application's priority date can be considered prior art. In order to meet the requirement, the elements of a claimed invention must not be "anticipated," or fully disclosed, by a single prior art reference. If even a single element of a claim is not found in a prior art reference, then the claim invention satisfies the novelty requirement. One important point is that a prior art reference may disclose an element explicitly or implicitly (i.e., inherently).

Third, a claimed invention must not be obvious to one of skill in the art over teachings in the prior art.[10] Whether a claimed invention is obvious to one of ordinary skill in the art can be more difficult to determine than whether it has utility or novelty. To do so, it is necessary to make factual determinations about the scope and content of the prior art, any differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether there are any "objective indicia" (also known as "secondary considerations") that indicate the claimed invention was nonobvious based on economic success or motivational issues.[11] On the basis of these facts, an obviousness analysis can be conducted. Unlike in a novelty analysis, the teachings of more than one prior art reference may be combined when assessing if a particular claimed invention is obvious. Obviousness rejections are easily the most common rejection faced by patent application in the U.S.

The fourth, fifth, and sixth requirements are referred to as the "enablement," "written description," and "definiteness" requirements.[12] An applicant must both give sufficient detail for one of ordinary skill in the art to understand what the claimed invention is (written description) and how to make it (enablement) and "particularly point out and distinctly" claim the subject matter considered the invention by way of one or more concise statements or "claims" (definiteness). Although NT can be quite complex, it is generally straightforward to set forth what the claimed invention is and how to make it. Courts have recognized that some amount of experimentation may be needed after reading a patent in order to practice the disclosed invention, but such experimentation must not be "undue."[13] Certain NT-related inventions may therefore require a higher level of detail to be disclosed. For example, a particularly detailed disclosure may be needed to meet the enablement requirement where a specific combination of process conditions is what yields the material, device, or system that is the claimed invention.[14]

CHALLENGES AND OPPORTUNITIES IN PATENTING NANOTECHNOLOGY-RELATED INVENTIONS

There is no question that the NT revolution has resulted in billions of dollars in value creation, and with this, tens of thousands of patents and patent applications have been published by the USPTO. Some applications proceed quickly to issue, while others struggle for years to achieve issuance of valuable claim scope. There are many reasons for this, and we propose that several facets of NT provide both challenges and opportunities to a patent applicant seeking strong patent protection.

SMALL CHANGES . . . BUT LARGE EFFECTS

Because many NT-related inventions result from small changes in structural characteristic(s), it can initially appear the differences between the claimed invention and the prior art are insubstantial and therefore obvious. Moreover, where differences from the prior art appear slight, it is easy to inadvertently apply knowledge gleaned from a patent application's own disclosure of the invention when performing the obviousness analysis, thereby minimizing the significance of the differences, even though the application of such knowledge is impermissible hindsight.[15] In many cases, the apparently

slight differences between an NT-related invention and the prior art hinge on structural characteristics (e.g., sizes) of the claimed invention, often described using values or as being in certain ranges of values. This can be problematic because prior art need only disclose overlapping or encompassing ranges, or merely a value or range that is close in some cases, to establish a prima facie case for obviousness.[16] Moreover, where the prior art discloses a range of usable values for a structural characteristic, optimization through routine experimentation is generally considered obvious, especially when the prior art recognizes a relationship between that structural characteristic and a desirable property.[17] The implications for NT-related inventions are that, as more NT research is conducted, more investigation into the structural and other causes for the enhanced properties many NT-related inventions exhibit will occur. This, in turn, will almost certainly make it more difficult for patent applicants as the likelihood increases that particular differences between an invention and the prior art may appear increasingly trivial.

Despite the challenges, NT-related inventions may also offer unique opportunities to defend and/or illustrate a particular invention's nonobviousness. For example, while optimization of a parameter may be considered likely to enhance a particular associated property of a material, it is not uncommon that small changes in one or more structural characteristic(s) cause "unexpectedly" large changes in a beneficial property. Additionally, the change in a particular parameter may even result in the change of a completely different property than what would be expected by one of ordinary skill. Such unexpected results can be used to rebut a prima facie case for obviousness.[18] After all, if something is truly unexpected, how can it also be considered obvious?

It is also helpful to present evidence that certain results are unexpected, such as through the offering of experimental data. Conclusory argument or speculation is often insufficient.[19] Such evidence is generally easy to provide for NT-related inventions, as they are often developed as a result of extensive experimentation. However, merely changing "form, proportions, or degree" of previous technology does not make a claimed invention nonobvious if the resulting improvement is "in kind" and not therefore unexpected.[20] The unexpected properties of an NT-related invention can sometimes result from the synergistic effects of multiple structural and/or compositional characteristics existing simultaneously. In such cases, nonobviousness can stem from the fact that the claimed invention "as a whole" was not obvious in view of the prior art.[21] For example, showing that each feature of an invention was known individually in the prior art does not make an invention prima facie obvious unless there is a rationale (motivation) underpinning the combination of the different teachings.[22]

Where appropriate, additional arguments can be made to make or bolster the case that apparently small changes were in fact nonobvious. For example, as part of the "as a whole" inquiry, recognition of the source of a problem can entitle an applicant to patent a solution, even if the solution is obvious once the source of the problem is recognized.[23] In some cases, the small change to structural characteristic(s) was made because the change was found to address a known problem associated with current designs with a previously unknown source. Moreover, any disclosed property of the claimed invention that is inherent must also be considered in the "as a whole" inquiry.[24] Evidence of secondary considerations, such as copying by others, long-felt but unsolved need, failure of others, and commercial success, may also further assist arguments for nonobviousness,[25] as, especially in NT, "what may be viewed as a mere incremental step could constitute a great leap in innovation."[26]

DRAWING INSPIRATION FROM ESTABLISHED INDUSTRIES

Ongoing research efforts continue to expand the amount of prior art in NT, which can present challenges for defending the nonobviousness of inventions. Practically, discovery of a beneficial property of a method or material, such as quantum-confinement-based light emission, prompts subsequent testing of a wide range of structural characteristics to determine underlying structure–property relationships, thereby producing a large body of prior art. Such a large body of prior art in a given subfield of NT often results over a relatively short time period after the initial breakthrough. However, having such a large body of prior art may not necessarily be a bad thing.

Analogy may be found in the pharmaceutical industry, where millions of compounds are disclosed in the prior art. There, an applicant for a patent often files an early application directed to certain broad genera of promising compounds and later files another application to its lead clinical candidate, then needing to defend the nonobviousness of the lead compound over the genus from which it is selected. To deal with this obviousness conundrum, the courts and the USPTO have generally adopted a two-prong inquiry referred to as "a lead compound analysis."[27] The analysis involves determining (1) whether one of ordinary skill would have selected one or more lead compounds from the prior art for further development and (2) whether the prior art supplied sufficient motivation to modify the lead compound to arrive at the invention with a reasonable expectation of success.[28] A similar framework can be used to defend the nonobviousness of a claimed NT-related invention.

In analogy to the first prong, even when there is extensive disclosure regarding the effects of varying many structural characteristics on a particular property, it is not necessarily obvious to specifically pick any particular one, or combination, of those structural characteristics for further modification absent a detailed teaching of its, or their, particular importance in the prior art.

In analogy to the second prong, even if one of ordinary skill were to pick the particular structural characteristic(s) to modify, the prior art should need to teach modifying the structural characteristic(s) in a substantially similar way as in the invention, *and* that there is some expectation of a commensurate improvement (e.g., in magnitude) of properties, in order to properly draw a conclusion of obviousness.

Given the range of structural modifications that can be made to a material, device, or system, general teachings in

the prior art about possible or acceptable structural characteristics should not necessarily be sufficient to render an invention obvious to one of ordinary skill in the art. It is not obvious to try any one of a large number of possible choices unless there is a reasonable expectation of success based on the teachings of the prior art.[29] Therefore, a convincing defense of nonobviousness for a claimed NT-related invention may depend on the applicant's ability to effectively communicate why the invention resulted from focused effort that one of ordinary skill in the art would not have instinctively made given the vast sea of possibilities available.

WHAT ARE THE COURTS SAYING?

A recent example from the Federal Circuit, *Par Pharm., Inc. v. TWi Pharms, Inc.*, is an instructive application of some of the aforementioned concepts.[30] Par Pharmaceutical (Par) obtained U.S. Patent No. 7,101,576 for a formulation of megestrol, an appetite stimulant, that used "nano-sized" particles (having "an effective average particle size of less than about 2000 nm"[31]) instead of the previously used micron-sized particles. The nano-sized megestrol unexpectedly had a reduced food effect (associated nutrient absorption rate) compared to the micron-sized formulation, which was beneficial for patient populations affected by wasting. Par later contracted with Alkermes Pharma Ireland to use its NanoCrystal® technology to form the new nano-sized megestrol particles. The NanoCrystal® technology was prior art to Par's patent, as was the micron-sized megestrol formulation. This prior art specifically showed that there was a relatively high level of interpatient variability for micron-sized megestrol and that size reducing (by application of NanoCrystal® technology) could improve bioavailability. Both sides agreed that the prior art did not expressly teach a reduced food effect for smaller sizes of megestrol, but the defendant argued that a reduced food effect was an inherent pharmacokinetic property of a smaller formulation because of its increased bioavailability.

The Federal Circuit's holdings illustrate several concepts discussed herein. The prior art was clear that nano-sizing drug formulations was generally feasible, for example using NanoCrystal® technology, and that nano-sizing was likely to improve bioavailability. Put together, the court found that one of ordinary skill in the art would have been motivated to try nano-sizing megestrol. The observed food effect for nano-sized megestrol may have been unexpected, but, importantly, the unexpectedness of the effect was not substantial when factored against the clear teachings of the prior art. Plaintiffs' other arguments for secondary considerations (including that patients affected by wasting had a long-felt need for treatment) suffered from minimal evidence and were therefore also unpersuasive in face of the prior art. Nonetheless, the Federal Circuit found that the district court had applied the wrong standard for inherency by accepting reduced size having *some* impact on food effect as sufficient proof of inherency without considering whether the extent of the impact would necessarily be to the same extent as in the claimed invention. The Federal Circuit vacated the obviousness determination and remanded for further analysis of inherency using the proper standard.

Overall, the *Par Pharm.* case serves to highlight that the patentability of NT-related inventions is highly fact specific. Referring back to the analogy to the lead compound analysis, the prior art taught a clear reason to choose size as a structural characteristic to manipulate, specifically by reducing it. Further, the prior art taught that a particular benefit, improved bioavailability, was reasonably expected to occur upon modification of the structural property. It is important to note that the claimed invention did not require a particular narrow range of sizes in order for the reduced food effect to be observed; rather, generally nano-sized particles were taught to be sufficient. A specific, narrow required-size range may have caused the Federal Circuit to hold differently. Accordingly, this case serves as a reminder that claim strategies must be carefully considered, and patent applicants should, where possible, include supportive data showing not only positive data, but negative as well, in order to evidence the importance of the particular range to achieving the beneficial effects observed in a claimed invention.

"TIPS AND TRICKS"

In general, patent applicants set out in the hopes of claiming as large of a piece of technological real estate as possible, in order to attract investment and/or keep actual or potential competitors at bay. As discussed herein, convincingly crafting the story of an invention in the field of NT can present particular challenges, in part because the enormous impact on properties and performance realized by an invention can result from only small, seemingly trivial changes to known products, compositions, or methods. The following are some considerations to keep in mind when drafting an application in order to maximize the chance that valuable claims will successfully pass through examination onto issuance, and withstand any post-grant challenges that may arise.

As has been discussed above, it is particularly important for NT-related inventions that the application tell a story. A simple restatement of the technological development may be sufficient to meet the statutory requirements for a patent but prove to be unconvincing during examination or later post-grant challenge. Because NT-related inventions may appear subtle, it is important that the application drafter guide the reader by telling the story of the invention. A good patent story offers some level of insight into how the invention came to be (e.g., some description of problem(s) in the art, and discussion of previous failed attempts to overcome the problem(s)) and how it differs from previous technology, not just a clear simple description of the technical aspects of the invention. In addition, a good story may include acknowledgment that the invention included recognition of the source of a known problem with a previously unidentified source. Of course, care should be taken when drafting an application to not make unnecessary admissions that can be later used against the application.

Additionally, for many NT-related inventions, data are particularly important to include in an application. Data can be used to formulate strong arguments for nonobviousness, especially where particular values, ranges,

compositions, or similar are a critical aspect of the invention. Furthermore, providing data for multiple examples that each has the critical structural characteristic can be useful in supporting a broad scope of protection. In contrast, mere conclusory statements made in an application may be insufficiently convincing when the prior art teaches similar or overlapping ranges or values or even open it up to challenges for failing to meet the statutory disclosure requirements. In this regard, including comparative data for examples falling outside a critical range, composition, or value can be useful in establishing that a claimed critical feature is not simply an arbitrary choice meant to circumvent the prior art. For example, if the thickness of a surface layer should be controlled within a certain range, data should be provided that further establish that the purported beneficial properties or performance is achieved when the thickness is within that range and not when values outside the range are used. As the full scope of the prior art is often not known, even to subject matter experts with extensive experience, failure to include data in the original disclosure can result in significantly prolonged examination and thus delayed issuance or, in the worst case, preclude issuance of a patent altogether.

CONCLUSION

It is clear that our world is in the middle of an NT revolution. Many industries have already enjoyed significant growth as a result of new NT-related inventions including the automotive, consumer good, and pharmaceutical industries. Accordingly, both overall market value for NT and competition are fierce and growing. Appropriately protecting intellectual property for NT-related inventions, thereby excluding others (upon patenting), can be essential to establishing a dominant and sizeable market position.

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ENDNOTES

1. *NNI Budget*, Nat'l Nanotechnology Initiative, https://www.nano.gov/about-nni/what/funding (last visited July 15, 2019).

2. Using the definition of nanotechnology provided by the International Standards Organization (ISO) Technical Specification 18110 (ISO/TS 18110). *See Leading Patenting Countries in Nanotechnology in 2016*, StatNano (Jan. 30, 2017), https://statnano.com/news/57346.

3. Global Industry Analysts, Inc., New and Emerging Applications to Drive the Global Nanotechnology Market, Report No. MCP-1031 (May 2019), https://www.strategyr.com/MarketResearch/market-report-infographic-nanotechnology-forecasts-global-industry-analysts-inc.asp.

4. M.C. Roco, S. Williams & P. Alivisatos, Nat'l Sci. & Tech. Council, Nanotechnology Research Directions: Vision for Nanotechnology R&D in the Next Decade, Springer (previously Kluwer) IWGN Workshop Report (Sept. 1999), *available at* www.wtec.org/loyola/nano/IWGN.Research.Directions.

5. *ISO/TC 229 Nanotechnologies*, Int'l Standards Org. (ISO), https://www.iso.org/iso/iso_technical_committee.html?commid=381983 (last visited July 15, 2019) (nanotechnology definition); R. Bawa, (2016). *What's in a Name? Defining "Nano" in the Context of Drug Delivery*, *in* Handbook of Clinical Nanomedicine: Nanoparticles, Imaging, Therapy, and Clinical Applications, ch. 6 (R. Bawa, G. F. Audette & I. Rubinstein eds. 2016).

6. 35 U.S.C. §§ 271, 154(a)(2).

7. *Id.* § 101.

8. Cleveland Clinic Found. v. True Health Diagnostics LLC, No. 2018-1218, slip op. (Fed. Cir. Apr. 1, 2019).

9. 35 U.S.C. § 102.

10. *Id.* § 103.

11. Graham v. John Deere Co., 383 U.S. 1 (1966); Natalie A. Thomas, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following* KSR v. Teleflex, 86 N.Y.U. L. Rev. 2070 (Dec. 2011).

12. 35 U.S.C. § 112.

13. *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

14. Of course, the specific method may also be separately patentable.

15. *See In re* McLaughlin, 443 F.2d 1392, 1395 (C.C.P.A. 1971).

16. *In re* Wertheim, 541 F.2d 257 (C.C.P.A. 1976); *In re* Geisler, 116 F.3d 1465, 1469–71 (Fed. Cir. 1997); Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 783 (Fed. Cir. 1985).

17. *In re* Aller, 220 F.2d 454, 456 (C.C.P.A. 1955); *In re* Antonie, 559 F.2d 618 (C.C.P.A. 1977).

18. *In re* Dillon, 919 F.2d 688, 692–93 (Fed. Cir. 1990).

19. *In re* Mayne, 104 F.3d 1339, 1343–44 (Fed. Cir. 1997).

20. *In re* Williams, 36 F.2d 436, 438 (C.C.P.A. 1929).

21. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530 (Fed. Cir. 1983).

22. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 415–21 (2007).

23. *In re* Sponnoble, 405 F.2d 578, 585 (C.C.P.A. 1969); Leo Pharm. Prods. v. Rea, 726 F.3d 1346, 1356–57, 1377 (Fed. Cir. 2013).

24. *In re* Antonie, 559 F.2d 618, 620 (C.C.P.A. 1977); *In re* Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993).

25. Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc., 711 F.3d 1348, 1356 (Fed. Cir. 2013).

26. Apple Inc. v. ITC, 725 F.3d 1356, 1375 (Fed. Cir. 2013) (Reyna, J., dissenting in part) (citing *Power Integrations*, 711 F.3d at 1356).

27. Amerigen Pharm. Ltd. v. UCB Pharma GmbH, Case IPR2016-01665 (P.T.A.B. Dec. 7, 2016); Otsuka Pharm. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1291–92 (Fed. Cir. 2012).

28. *Otsuka Pharm. Co.*, 678 F.3d at 1291–92.

29. *In re* Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

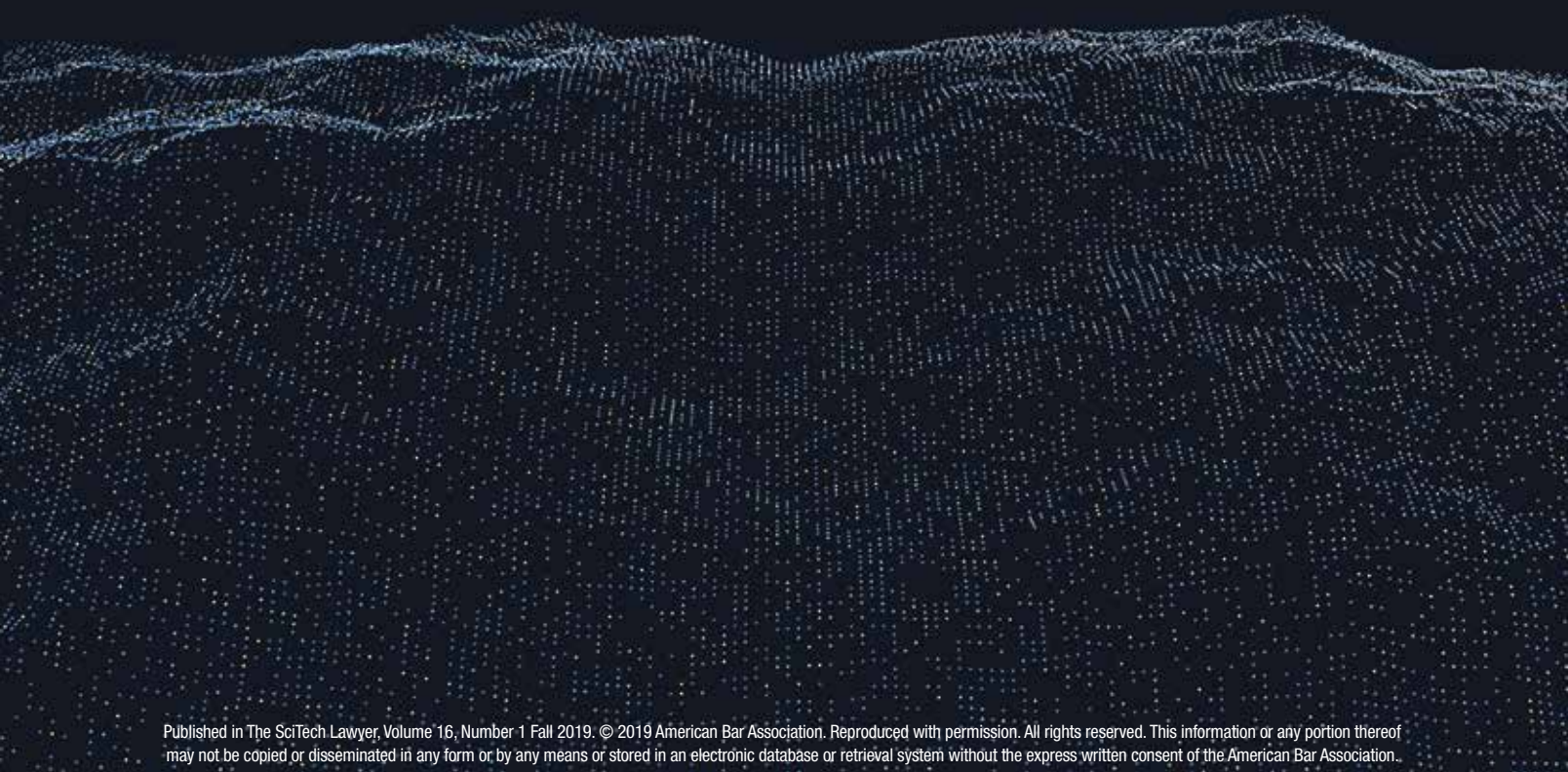
30. 773 F.3d 1186 (Fed. Cir. 2014).

31. That these particles were as large as 2 microns in size and still considered "nano-sized" in this litigation underscores the inadequacies of a strict definition of nanotechnology.

NANOTECHNOLOGY LIABILITY OUTLOOK 2019

STILL IN THE DARK?

BY EDWARD R. GLADY, JR.



Have you ever entered a dark room without a flashlight or other source of illumination and discovered that the light switch was on the other side of the room? Perhaps you were lucky enough to walk through an empty room and thus left whole, or perhaps a box or chair invisible in the dark tripped you up, causing you injury before your path was illuminated.

The liability outlook for nanotechnology in 2019 differs little from this suggested scenario. Predictions of potential dire legal consequences for nanotechnology use made ten or more years ago have yet to come to fruition, but the walk through the dark room is nowhere near complete. Given that we still have no flashlight to show us the way ahead, how does one navigate any liability hazards still before us?

This article will not present a comprehensive overview of the multitude of liability issues and potentials that remain in place for nanotechnology. In an industry involving trillions of dollars and thousands of ideas, innovations, research and development efforts, and ultimately products, such an effort would tax both author and reader beyond endurance. Instead, this article will take a more general approach to examining the liability landscape for a still-emerging technology that promises many wonderous things, but at an unknown cost.

A SHORT HISTORY OF LIABILITY FOR "NEW TECHNOLOGY"

With rare exception, the law lags technological development. Innovators seeking financial gain create new markets, new products, and new uses for scientific and medical discoveries and technological advancements as quickly as possible. Prior to the advent of regulatory efforts, little concern was given to the harm such innovations could or would cause to the workers involved in the manufacturing process, to the consumers who interacted with them during their use, or to the environment that received the waste or other effects produced by the innovations. The law sought to compensate some of those harmed by these innovations, but legal efforts were often slow and not always adequate. In all cases, the remedy was effected after the fact of injury.

The advent of governmental regulation of the marketplace, originating with concerns based on food safety, brought about the first efforts to seek to address potential harm before a product was introduced to consumers.[1] Worker safety concerns also began to be addressed in limited ways.[2] (The environment would not get due attention arising from the effects of innovation for years to come.)

In these early efforts at regulating commerce for the health and safety of workers and consumers, most of the effort was aimed at immediate or acute risks: Food should not immediately poison those who consume it; railroad work should not maim or kill industry workers. No effort was made to examine or regulate long-term effects of innovations put into the stream of commerce. Indeed, science and medicine were ill-equipped at the time to do so. Relying on both for its efforts at redressing wrongs, the legal system also had few tools to suspect or address potential long-term harm.

Into this mix of marketplace reward and primal regulation and legal redress for acute injury entered a "wonder" technology that promised to address numerous needs and situations: asbestos. It is difficult today to imagine the excitement and wonder that greeted a product that promised protection against fire, a ubiquitous source of damage to structures and possessions, as well as injury to persons.[3] Moreover, the ability of asbestos to absorb heat without igniting made it a perfect choice for brake linings, insulation, building materials, and a multitude of other industrial applications and uses involving heat, including fire retardant coatings for military warships. Innovators looked for new opportunities to use asbestos at every turn. Indeed, the future for asbestos seemed to face no limit.

But after a length of time, people who worked around or otherwise were in proximity with asbestos began to exhibit pulmonary issues, often leading to death.[4] Medical studies ensued, building a new understanding of toxicity, epidemiology, and long-term causation not only for asbestos but in the fields themselves. Yet, the legal system was still slow in responding to this newly emerging knowledge, and it took a number of years for civil litigation to process claims and provide compensation for those who claimed to have been injured by asbestos.[5]

The asbestos "circle of life" fairly represents how innovation and new technology thrived under the laissez-faire worldview existing in the mid-twentieth century. Innovation and capitalism were for the most part given a free hand to develop technology and products with little concern or regard for any harm or ill-effects other than those of an immediate or acute nature. It is also fair to say that asbestos dramatically changed this same worldview when its long-term harm came to light, a development that occurred parallel to a general awakening that substances and products might have both short-term and long-term harmful effects and that such harms should be better understood before they are unleashed onto an unsuspecting public. The result of this new worldview is a modern marketplace that still rewards innovation and entrepreneurship, but now holds such efforts liable for any harms they cause, even if such harms are not known for years to come. And part of this marketplace is a more mature legal system that seeks to regulate harm before it happens, as well as compensate those affected by the harm. The key for all these efforts, however, is knowledge. Regulators cannot govern how technological innovation is unleashed into the marketplace without knowledge of possible consequences, nor can the civil litigation system fairly compensate those injured by the new technology without knowledge of the cause and effect involved. Indeed, it is this bedrock need for knowledge that darkens our vision when discussing potential nanotechnology liability. Yet, darkness or not, the marketplace wants, encourages, welcomes, and rewards nanotechnology innovation. But by entering this marketplace with its continuing darkness regarding potential

liability, is the nano industry whistling in the dark?

TREADING IN THE DARKENED ROOM

The nanotech industry is huge and covers a broad landscape of products and services, including medical, consumer goods, and industry applications. Like asbestos in its day, nanotechnology is seen as an answer to a thousand different needs and uses, upgrading life in some instances (thick, white "ugly" suntan lotion becomes clear and "unobtrusive" with nano-sized active ingredients) and hopefully saving lives in other instances (nano-imaging improves treatment and diagnosis of asbestos-caused mesothelioma[6]). Innovators are daily trying to uncover new properties and new uses for nanotechnology, with trillions of dollars at stake. As with asbestos, the future of nanotechnology seems to contain no limits.[7]

But, because of asbestos, we no longer just think of a technology's potential for good; we also now think of its potential cost in terms of harms to worker, user, and the environment. And, unlike asbestos, we now have a strong regulatory framework in place that is designed to frontload safety concerns so that harm is detected and regulated before products are distributed to a consuming public.

Given this new reality, we're now in a better place to measure and calculate potential harm and liabilities of nanotechnology before entrepreneurs, investors, innovators, and business entities risk capital and develop and launch their nano products and services into the marketplace, right? Maybe not.

Even though we have developed a much more sophisticated appreciation of the potential harm new substances and products might cause, and even though we have developed new understanding and procedures to probe for such harm in both animal and human populations, the uncomfortable truth is that we have not advanced much past the days of asbestos when clear knowledge of harm comes only from long-term exposure of a human population and actual harm manifests. Without this real-world experience, we can at best only take an educated guess at what harms might result from exposure to various nano components and uses.

Some of these educated guesses come from animal testing, where a large population of test animals are exposed to a nano element or compound to see what harmful effects arise.[8] In addition, scientific or medical literature might report an individual's physical reaction to a possible nano exposure.[9] Regardless whether from animal testing or isolated human experience, suggested connections between nano exposure and resulting harm from such studies must be replicated many times over in similar situations before a scientifically justifiable connection can be made for a cause-and-effect determination that supports legal causation conclusions. In this setting, a great deal of time and experience must accrue before there is a sufficient body of scientific and medical knowledge to understand how nano components might or do cause harm to humans.

Regulators are charged with the obligation to minimize risk to the public from the multitude of harms potentially confronted in daily life, including something as seemingly innocuous as drinking a glass of water. U.S. regulators in this regard come in two forms: those that govern the things the public consumes or comes in direct contact with, such as food, cosmetics, and consumer goods, and those that govern the environment encompassing the public and the environs in which the public dwells, such as air, soil, or water contamination or work conditions. These regulators use scientific and medical knowledge to set "safe" limits of exposure to identified harms, often using very conservative standards such as an exposure level thought to cause no more than one death related to the exposure out of a population of a million. Regulators often rely heavily on animal studies or on existing human studies regarding suspected harm to determine toxicity and perceived "safe" dosage levels for exposure.

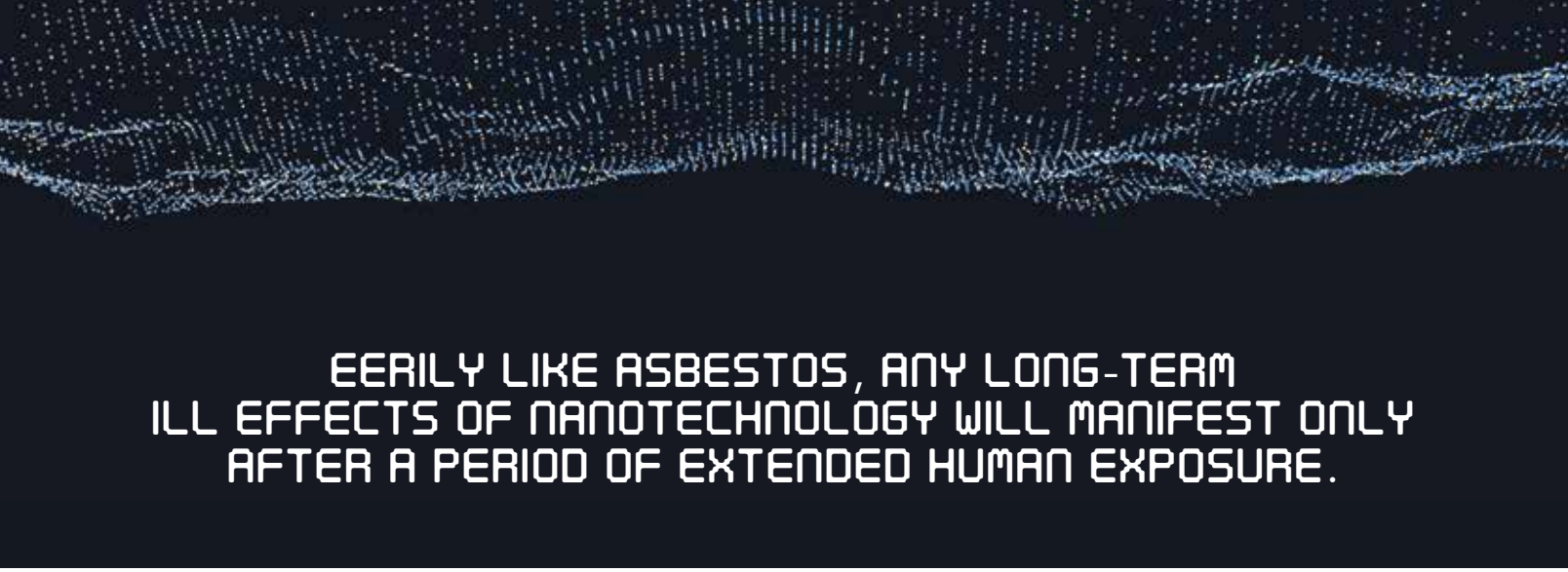
As of 2019, there remains a paucity even of animal studies for regulators to determine if and how to set "safe" standards for those nano products within their regulatory jurisdiction.[10] Without this body of science and medicine, regulators are moving slowly in how they deal with nano products. To the extent nano innovators—and the public—rely on regulators to provide them with a cloak of protection based on scientific and medical knowledge, they must wait for another day. So how does a nano innovator operate without the light of knowledge?

LIVING IN DARKNESS

Current scientific and medical knowledge and accompanying regulatory actions shed little light on liabilities nanotechnology innovators, entrepreneurs, and producers potentially face with the interaction of their products on workers, consumers, or the environment. Eerily like asbestos, any long-term ill effects will manifest only after a period of extended human exposure. Given the ultimate price tag arising from the eventually revealed long-term harm caused by asbestos (lives ruined, companies destroyed, insurers decimated), no reasonable person or entity wants to create or be part of another such industry Armageddon. Yet, without sufficient scientific or medical knowledge about the potential short-term or long-term harmful effects of nano products, how do nano producers or their financial backers move ahead in the marketplace with any sense of security? And how does a legal system charged with compensating victims of defective products do its work when precious little medical or scientific knowledge exists to inform its decisions?

Like the problem, potential solutions are neither simple nor surefire. But several areas offer some rays of light.

As a starting point, anyone who is involved in releasing new nano products into the stream of commerce must understand that legal responsibility flows from that action.[11] No product is immune from attack or allegations that it caused harm. This basic premise is crucial as it informs how those involved in the innovation, production, and distribution process must see that



EERILY LIKE ASBESTOS, ANY LONG-TERM ILL EFFECTS OF NANOTECHNOLOGY WILL MANIFEST ONLY AFTER A PERIOD OF EXTENDED HUMAN EXPOSURE.

process as not only one to transform an idea into a product, but also to question from the beginning how that product might cause harm and be modified as a result or reasonable warnings given to users so that they understand the risks of using the product.[12] This suggestion might at first seem counterproductive: Why should we look for trouble? Shouldn't it instead come looking for us? Unfortunately, such a question ignores the reality of our judicial system: If your product is harmful, you will be called to account for it someday. And actual ignorance of the harm will provide you no shield against legal liability for if by reasonable effort you could have known of its harmful potential, but sought to take no steps that might gain that information, you could still face product liability exposure.[13]

Indeed, some in the nanotechnology industry have sought to establish standards for determining a risk management process for nano materials and products. One process, developed jointly by DuPont and the Environmental Defense Fund, establishes a disciplined process for evaluating and addressing nanotechnology risks.[14] Others exist as well. [15] By conducting such efforts, a nano product producer can analyze the nano component materials for a potential risk of harm based on current knowledge. It may not totally shield the nano producer from legal claims but provides a powerful defense that reasonable efforts were made to make the product as safe as possible based on knowledge available at the time of its design and manufacture.

Likewise, participation in industry groups and compliance with any voluntary standards and codes that might exist provide the nano producer with the ability to follow current state-of-the-art practices, another important plank in any legal defense raised in response to legal claims.[16]

Obviously, if a nano producer in doing its due diligence acquires actionable knowledge that its product or nano components are in fact or reasonably could be harmful, it absolutely must take immediate steps to address the potential harm, including warning others of the potential harm.[17] Any notion that such knowledge can be concealed while production and distribution continue unabated should be greeted with an invitation to study the repercussions from similar decisions by the asbestos and tobacco industries.

Of course, part of the risk management process is risk allocation. Specifically, nanotech innovators might look to insurers to share some of the risk inherent in launching nano products into the marketplace. As the nanotech industry began to blossom, a number of insurers entered the nano marketplace to offer coverage to nanotechnology producers. As the nano industry exploded, however, insurers became less enthused as risk calculations became more complicated and less clear.[18] Insurers like liability risk "darkness" even less than those involved in the nanotech industry, so until there is clearer loss experience and more certainty as to liability risks faced by the nano industry, insurance coverage may offer only limited options for risk management efforts.

IS THERE A LIGHT AHEAD?

As noted at the outset, despite predictions starting many years ago that the nano industry soon would be deluged with lawsuits claiming an untold number of injuries and bankruptcy-inducing-sized damages, the nanotech civil litigation battlefront is still very quiet. Is this good news and a sign that we are near the light switch with its promised illumination of our way? Or, like the asbestos life cycle, are we still too early to see the whirlwind headed our way?

As cliché as it may sound, only time will tell. Some nanotech products have seemingly passed the "no acute harm test,"[19] but for many others, the jury may still be out.[20] More importantly, what can we know about long-term harm liability issues with a form of technology barely into its teenage years?

Like it or not, our legal system is informed by experience and is still, for the most part, reactionary to harms caused. It is a system that requires knowledge, experience, and reasoned scientific and medical conclusions to act, to remedy, and to compensate. An inescapable corollary to such a truth is that people must suffer actual harm for knowledge to be gained and remedies provided. If a nanotech material, component, product, or technology results in harm from long-term exposure or use, it will fall on future generations to use that acquired knowledge to adjudge who will bear the brunt of

the now-revealed harm. This is not an entirely satisfactory result or process for all stakeholders involved, including those facing harm—workers, consumers, and those living in an affected environment. But perhaps past experience will educate us to be more effective in how we seek and analyze experiential data, be more responsive and responsible in how we apply new knowledge, and be more attuned to the hard-learned lesson of the past that human lives are inexorably linked—for better or worse—to the technology we devise and employ.

Nanotechnology potential liability exists, and perhaps that risk can be partially managed by the nano industry and regulators, at least based on current knowledge, but in the end, this potential liability will depend on information gained through future experience and the understanding it will bring. Such a reality should not stop nanotech innovation, investment, or implementation but should bring a sober realization that what is done for good purposes or intentions today may bring unforeseen or unwanted consequences tomorrow. As we reach for the light switch, we must be ready to accept what is illuminated when the darkness fades.

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ENDNOTES

1. The first such legislation, the 1906 Food and Drug Act, was enacted in response to claims of unhealthy food, a claim famously illustrated in Upton Sinclair's novel *The Jungle*.

2. *See, e.g.*, the Safety Appliance Act of 1893, requiring basic safety equipment for the protection of railroad workers.

3. A 1942 newsreel shows cheerful workers without safety equipment assembling many useful devices utilizing asbestos: British Pathé, *Newsreel of the Week: The "Wonderful" Uses of Asbestos (1942)*, YouTube (Aug. 27, 2015), https://www.youtube.com/watch?v=HxfZSEboVM4.

4. British medical researcher Dr. Edward Merewether began linking asbestos to pulmonary issues starting in the 1930s. Other studies showing the same links followed.

5. Claimants argue that this delay was caused by intentional efforts on the part of the asbestos industry to keep hidden facts regarding the toxicity of asbestos.

6. Alexander De Ridder, *Mesothelioma Treatment and Diagnosis Improved by Nanotechnology*, Edgy (Dec. 23, 2016), https://edgy.app/mesothelioma-treatment-nanotechnology.

7. "This tiny science [nanotechnology] has limitless potential to revolutionize our daily lives and solve the daunting challenges of our future[.]" Press Release, Senators John Kerry & Olympia Snowe, Kerry-Snowe Bill Strengthens Safety in Nanotech Research (July 17, 2008) (statement by Senator Snowe).

8. *See, e.g.*, C.A. Poland & R. Duffin, *Carbon Nanotubes Introduced into the Abdominal Cavity of Mice Show Asbestos-like Pathogenicity in a Pilot Study*, 3 Nature Nanotechnology 423 (2008).

9.*See, e.g.*, W. Journeay & R. Goldman, *Occupational Handling of Nickel Nanoparticles: A Case Report*, 57 Am. J. Indus. Med. 1073 (2014).

10. Professor Marchant's 2014 observation still rings true today: ". . . we still know relatively little about the hazards of . . . nanomaterials, never mind being able to perform quantitative risk assessments." G.E. Marchant, "*Soft Law*" *Mechanisms for Nanotechnology: Liability and Insurance Drivers*, 17 J. Risk Res. 709 (2014).

11. Restatement (Third) of Torts: Product Liability § 1.

12. This process must be well documented and include efforts to involve outside expertise regarding the safety analysis, if practicable. Juries may someday be asked to judge these actions and decisions, and the more complete the record of the decision process that is kept, the better the chance of convincing a jury of the reasonableness of the product design and warnings.

13. "Dangers that a seller 'should know' include those that are reasonably foreseeable or scientifically discoverable at the time the product is sold." Wood v. Phillips Petroleum Co., 119 S.W.3d 870, 873 (Tex. App. 2003) (citations omitted).

14. For more information, go to http://www.nanoriskframework.com/.

15. For a nice summary of risk management options for nanotech innovators and "soft" incentives for using them, see Professor Marchant's previously cited article, *supra* note 10.

16. Restatement (Third) of Torts: Product Liability § 4(b) affords a defense based on compliance with an applicable safety statute or administrative regulation. In the absence of such statutes or regulations, compliance with voluntary codes—if shown to be reasonable—may also offer the nano product defendant some protection in a product liability lawsuit.

17. Restatement (Third) of Torts: Product Liability § 10.

18. "[I]nsurance industry leaders agree that the industry will n ot be able to quantify potential losses related to nanotechnology risks, and that it is too soon to tailor policy forms to nanotechnology risks." T.F. Segalla & T.S. Flascher, Perspectives: *How to Evaluate Emerging Risks of Nanotechnology*, Bus. Ins. (Feb. 24, 2013), https://www.businessinsurance.com/article/20130224/story/302249974/perspectives-how-to-evaluate-the-emerging-risks-of-nanotechnology.

19. *Nanoparticles in Sunscreens*, Envtl. Working Grp.: 2019 Guide to Sunscreens, https://www.ewg.org/sunscreen/report/nanoparticles-in-sunscreen ("we believe [nano ingredients] zinc oxide and titanium dioxide lotions are among the best choices on the American market").

20. T. Chernova et al., *Long-Fiber Carbon Nanotubes Replicate Asbestos-Induced Mesothelioma with Disruption of the Tumor Suppressor Gene* Cdkn2a *(*Ink4a/Arf*)*, 27 Current Biology 3302 (2017).

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Nanotechnology and Regulatory Certainty

CLOSER NOW THAN EVER

By Lynn L. Bergeson and Carla N. Hutton

Nanoscale technologies and their resultant innovations have long captured the imaginations of scientists and inventors, the scrutiny of regulators, and the apprehension of nongovernmental organizations and consumer watchdogs. Over the past decade or so, however, a compelling case can be made that the scientific and regulatory communities have done a credible job of allaying these initial concerns and thus can claim victory over nay-sayers who portended global calamity occasioned by the commercialization of nano-enabled products.

In the United States, the U.S. Environmental Protection Agency (EPA) is responsible for regulating chemical substances, including nanoscale substances, under the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[1] The U.S. Food and Drug Administration (FDA) is responsible for regulating ingredients, including nanomaterials, in food, drugs, cosmetics, and related products. The core regulatory paradigms that have evolved over decades under these federal laws and calibrated to bulk materials have proved to be durable and effective in their application to nanoscale materials, despite the unique properties derivative of the nanoscale, such as stronger magnetic properties, improved conduction of heat or electricity, or better light reflection.[2]

This article provides an overview of how EPA and FDA are using their existing authorities (prudently and proactively) to ensure that nanomaterials do not pose a risk to human health and the environment.

TSCA

On June 22, 2016, President Obama signed the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg Act), and in so doing significantly revised TSCA for the first time since its enactment in 1976.[3] Although the new TSCA dramatically changes how EPA evaluates and manages industrial chemicals, including nanoscale chemicals, the absence of words or phrases such as "nano" or "nanoscale" materials in the law means that there are no specific or additional requirements that apply explicitly to such materials. This was a significant shift from many of the earlier TSCA

reform bills, which explicitly addressed nanoscale materials by proposing new definitions such as "substance characteristics" and "special substance characteristics" that included concepts such as size or size distribution, shape, surface structure, and reactivity. The new TSCA is noticeably silent on this subject and does not distinguish nanoscale materials or treat such materials differently from the other chemical substances regulated under TSCA. This relatively recent congressional action is a compelling statement that TSCA's fundamental approach to defining and regulating unreasonable risk, honed over four decades, is equally applicable to conventional and nanoscale chemical substances.

Because new chemicals are subject to additional requirements under new TSCA section 5, an important task for chemical manufacturers, importers, and processors, including nanoscale chemical manufacturers, is identifying new chemical substances prior to its commercial activity. This has been an especially tricky area for the nano community, and the Lautenberg Act makes the new chemical review process much more demanding than under old TSCA. EPA's prior development of a comprehensive section 5 new chemical review process for nanoscale chemicals under TSCA pre-Lautenberg had served the nano community well, and noticeably, the new law's implementation has not materially impacted the commercialization of new nanomaterials.

In this regard, in January 2008, EPA published a document outlining its approach to determining whether a nanoscale substance is a new chemical for the purposes of TSCA section 5 Inventory requirements.[4] EPA refers to TSCA section 3(2)(A), which defines a chemical substance as "any organic or inorganic substance of a particular molecular identity." EPA states that for the purposes of the TSCA Inventory, it historically has not used particle size to distinguish chemical substances that have the same molecular identity. Thus, the nanoscale form of an existing chemical substance would also be considered an existing chemical substance. EPA has continued to apply this approach—using molecular identity rather than particle size—to determine whether a nanoscale chemical is an existing or a new chemical.

Since January 2005, EPA has received and reviewed more than 220 new chemical notices for nanoscale materials such as fullerenes, quantum dots, and carbon nanotubes.[5] EPA has taken actions intended to control and limit exposure, including limiting the use of the nanoscale material; requiring the use of personal protective equipment and engineering controls; limiting environmental releases; and requiring testing to generate health and environmental effects data.

Under old TSCA, if EPA did not respond to a premanufacture notification (PMN) and take action within ninety days, a company could submit a notice of commencement and begin manufacture, processing, or import. New TSCA section 5(a)(3) requires EPA to review PMNs, make one of three affirmative "determinations," and take the appropriate action depending upon the determination. EPA's review may not consider costs or other nonrisk factors in determining that the new chemical presents an unreasonable risk. New TSCA also requires EPA to consider unreasonable risks to potentially exposed or susceptible subpopulations that are identified as relevant by EPA under the conditions of use in making determinations under section 5(a)(3)(A) and (C).

On January 12, 2017, EPA promulgated a final TSCA section 8(a) rule imposing reporting and recordkeeping requirements for certain chemical substances when they are manufactured or processed at the nanoscale.[6] The rule excludes from the reporting requirement chemical substances manufactured at the nanoscale as part of a film on a surface; certain biological materials such as DNA, RNA, proteins, enzymes, lipids, carbohydrates, peptides, liposomes, antibodies, viruses, and microorganisms; and chemical substances that dissociate completely in water to form ions that are smaller than one nanometer. The final rule also requires manufacturers, importers, and processors to report the specific chemical identity, actual or anticipated production volume, methods of manufacture and processing, use, exposure and release information, and existing data concerning environmental and health effects. The rule imposes a one-time reporting requirement for discrete forms of existing chemical nanoscale materials manufactured or processed any time prior to May 12, 2017, the effective date of the final rule. It also imposes a reporting requirement for new discrete forms of existing chemical nanoscale materials 135 days before they are manufactured or processed. According to EPA, the information will facilitate evaluation of the nanomaterials and a determination of whether further action, including additional information collection, is needed.

FIFRA

Under FIFRA, EPA regulates the distribution, sale, and use of pesticides. This includes reviewing pesticide registrations to ensure that a pesticide product "will not generally cause unreasonable adverse effects on the environment."[7] The use of modern technologies could pose less risk to human health and the environment than conventional pesticides.[8] Emerging technologies, such as nanotechnology, biotechnology, and synthetic biology, can be used in more targeted ways, reducing the use and cumulative impact of more conventional pesticides.

EPA acknowledged the potential benefits of nanoscale materials in its June 2011 proposed policy statement describing two possible approaches to obtain information about nanoscale materials used in registered pesticide products.[9] Under the first approach, EPA would use FIFRA section 6(a)(2) to obtain information regarding nanoscale materials present in registered pesticide products and their potential effects on humans or the environment. Under the second approach, EPA would obtain information using a data call-in (DCI) under FIFRA section 3(c)(2)(B). EPA also proposed how it would determine whether a nanoscale active or inert ingredient is a new active or inert

ingredient for purposes of FIFRA and the Pesticide Registration Improvement Act (PRIA), "even when an identical, non-nanoscale form of the nanoscale ingredient is already registered."[10]

In December 2011, EPA announced its first conditional registration for a pesticide product containing nanosilver as a new active ingredient.[11] As a condition of the conditional registration, EPA required additional data to confirm its assessment "that the product will not cause unreasonable adverse effects on human health or the environment." On May 19, 2015, EPA announced a conditional registration for another nanosilver-containing antimicrobial pesticide product.[12] This second nanosilver registration reflected EPA's growing expertise in addressing, processing, and approving nanopesticide registration applications. EPA based its decision "on its evaluation of the hazard of nanosilver after reviewing exposure data and other information on nanosilver from the applicant, as well as data from the scientific literature." According to EPA, these data show that plastics and textiles treated with nanosilver "release exceedingly small amounts of silver." Based on its evaluation, EPA states that it determined not only that the nanosilver pesticide would not cause unreasonable adverse effects on people, including children, or the environment, but also "that it would be beneficial because it will introduce less silver into the environment than competing products."[13] EPA noted that it was requiring the company "to generate additional data to refine the Agency's exposure estimates."[14]

While EPA did not issue a final policy statement concerning products containing nanoscale materials, in 2015, EPA responded to a 2008 petition for rulemaking filed by the International Center for Technology Assessment (ICTA) requesting that EPA regulate products containing nanosilver as pesticides and assess products containing nanosilver as "new and different" products from products containing macro-silver.[15] EPA granted ICTA's request to use its authorities under FIFRA and the Federal Food, Drug, and Cosmetics Act (FFDCA) to address concerns related to the potential for different toxicity profiles for macro-silver and nanosilver ingredients that may be regulated under FIFRA and FFDCA and that have a pesticidal purpose.[16] EPA stated that it would "use its discretion on how best to address these concerns under each of these authorities," applying it to registration applications for products containing a new nanosilver active ingredient or to its review of existing registrations. EPA also committed to using its enforcement discretion on how best to address the distribution and sale of unregistered pesticides in the U.S.

In October 2018, EPA posted the Final Work Plan (FWP) for the nanosilver registration review process.[17] The FWP explains what EPA's Office of Pesticide Programs "knows about nanosilver generally, highlighting anticipated data and assessment needs for each unique nanosilver chemistry, identifying the types of information that would be especially useful to the Agency in conducting the review, and providing an anticipated timeline for completing review of the nanosilver case."[18] EPA anticipated issuing a DCI in 2018 requiring certain data anticipated as needed for the registration review of nanosilver, but it has not issued one to date.

FDA

In its approach to the regulation of nano-enabled products, FDA has noted that the application of nanotechnology "may result in product attributes that differ from those of conventionally-manufactured products."[19] As a result, when evaluating the safety or effectiveness of FDA-regulated products including nanomaterials or otherwise involving the application of nanotechnology, FDA acknowledges that it should consider the unique properties and behaviors that nanomaterials may exhibit. FDA stated that it "does not categorically judge all products containing nanomaterials or otherwise involving the application of nanotechnology as intrinsically benign or harmful,"[20] however. FDA intends to regulate nanotechnology products under its existing statutory authorities, "in accordance with the specific legal standards applicable to each type of product under its jurisdiction."[21]

FDA has issued many helpful guidance documents concerning the application of nanotechnology or the use of nanomaterials in FDA-regulated products, including cosmetic products, food ingredients, food contact substances, food for animals, and drug products:

- *Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*;[22]
- *Guidance for Industry: Safety of Nanomaterials in Cosmetic Products*;[23]
- *Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients That Are Color Additives*;[24]
- *Guidance for Industry: Use of Nanomaterials in Food for Animals*;[25] and
- *Guidance for Industry: Drug Products, Including Biological Products, That Contain Nanomaterials (Draft Guidance)*.[26]

These guidance documents are just that—guidance, not rules or regulations. They represent FDA's current thinking on the above topics. Industry may use alternative approaches as long as the approach meets the requirements of the applicable statutes and regulations. In all cases, FDA recommends that manufacturers consult it to discuss an alternative approach or early in the development process.

More recently, FDA published a proposed rule on February 26, 2019, that would put into effect a final monograph that would establish standards for nonprescription, over-the-counter (OTC) sunscreen drug products.[27] The proposed rule describes the conditions under which FDA proposes that OTC sunscreen monograph products are generally recognized as safe and effective (GRASE) and not misbranded. While FDA expressed concern

regarding the safety of several sunscreen ingredients, noting that the public record has insufficient data to support their safety, FDA did not do so regarding the nanomaterial forms of zinc oxide and titanium dioxide. FDA states that "having examined the scientific information in the record, including for nanomaterial forms of zinc oxide and titanium dioxide, FDA is not now proposing conditions of use for these two active ingredients under the sunscreen monograph that distinguish nanomaterials from other forms of these ingredients." FDA "also does not propose to categorically classify sunscreen products that are manufactured using nanotechnology or contain nanomaterials as GRASE or not, solely on that basis."[28]

DISCUSSION

While certain nanomaterials may be considered new chemicals under TSCA, or new active ingredients or inerts under FIFRA, or used in food, drugs, or cosmetics, EPA and FDA have demonstrated that the authority to regulate nanomaterials that each agency currently possesses is sufficiently durable and as effective as the authority to regulate more conventional industrial chemicals, pesticidal ingredients, or active ingredients. This level of certainty was absent a decade or so ago when early nano stakeholders were struggling with whether and, if so, how best to apply the then regulatory paradigms and frameworks that had evolved under these and other federal and international authorities to address potential risks from nano-sized materials. Nano advocates argued persuasively that with research, additional data, and suitable scaling methodologies, the core traditional approaches to identifying, classifying, and regulating risks could also apply to nanoscale materials. This was the unanimous view of the federal government, across party lines and over multiple administrations, and global authoritative bodies throughout Europe, Asia, and South America.[29]

When considering the broad arc of scientific developments, and the daunting complexity of evolving technologies, in hindsight the past decade or so seems relatively uncomplicated. Our more recent analysis of legal and regulatory challenges in regulating synthetic biology and products derivative of nano, synbio, and other technologies suggests many of the same issues arise. These issues include regulatory uncertainty regarding jurisdictional boundaries, limited technological literacy among regulators and legislators, and quantifying of potential risks from innovations that find no precedent—all of which lead to costly delays in commercialization.[30] Innovators and manufacturers need to determine as soon as possible in which jurisdictional box their nanoscale innovation belongs and if none exists, help the legislator or regulator build a suitable one derivative of existing authority that will provide a glide path for landing the product on solid commercial footing. Any lesser effort will stall commercialization and deprive the marketplace of a newer, better, and more sustainable product.

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ENDNOTES

1. 15 U.S.C. § 2601(c) ("It is the intent of Congress that the Administrator shall carry out this chapter in a reasonable and prudent manner[.]"); 7 U.S.C. § 136(a) ("To the extent necessary to prevent unreasonable adverse effects on the environment, the Administrator may by regulation limit the distribution, sale, or use in any State of any pesticide that is not registered[.]").

2. *What It Is and How It Works*, Nat'l Nanotechnology Initiative, https://www.nano.gov/nanotech-101/what (last visited July 8, 2019).

3. Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-182, 130 Stat. 448 (June 22, 2016). The text of the Lautenberg Act is available at https://www.congress.gov/114/plaws/publ182/PLAW-114publ182.pdf (last visited July 8, 2019).

4. EPA, TSCA Inventory Status of Nanoscale Substances—General Approach (Jan. 23, 2008), *available at* https://www.epa.gov/sites/production/files/2015-10/documents/nmsp-inventorypaper2008.pdf.

5. Org. for Econ. Cooperation & Dev., Series on the Safety of Manufactured Nanomaterials No. 89, Developments in Delegations on the Safety of Manufactured Nanomaterials—Tour De Table: February 2018–March 2019, at 59 (May 27, 2019), *available at* http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2019)11&doclanguage=en.

6. Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements, 82 Fed. Reg. 3641 (Jan. 12, 2017).

7. 7 U.S.C. § 136a(c)(5)(D).

8. Lynn L. Bergeson, *Enlisting Modern Technologies to Ensure a Safe Food Supply*, 31 Nat. Res. & Envt., no. 3, Winter 2017, *available at* http://www.lawbc.com/uploads/docs/00199887.pdf.

9. Pesticides; Policies Concerning Products Containing Nanoscale Materials; Opportunity for Public Comment, 76 Fed. Reg. 35383, 35388 (June 17, 2011).

10. *Id.* at 35384.

11. Press Release, EPA, Pesticide News Story: EPA Announces Conditional Registration of Nanosilver Pesticide Product (Dec. 1, 2011), *available at* https://archive.epa.gov/pesticides/news/web/html/nanosilver-2.html.

12. Press Release, EPA, EPA Pesticide Program Updates: EPA Announces Registration of Nanosilver Pesticide Product (May 19, 2015).

13. *Id.*

14. One of the conditional registrations was overturned because "EPA failed to support its finding that [the nanosilver product] was in the public interest," not because of a finding that the product posed any adverse effects to human health or the environment. Lynn L. Bergeson & Timothy D. Backstrom, *Appellate Court Vacates Conditional Nanosilver Registration*, 18 ABA Sec. of Envt., Energy & Res. PCRRTK Newsl., no. 5, Aug. 2017, at 9, *available at* http://www.lawbc.com/uploads/docs/Appellate_Court_Vacates_Conditional_Nanosilver_Registration.PDF.

15. Letter from EPA to Int'l Ctr. for Tech. Assessment, EPA Response to "Petition for Rulemaking Requesting EPA Regulate

Nano-Silver Products as Pesticides" (Mar. 19, 2015), *available at* https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0650-1406.

16. *Id.* at 2.

17. EPA, Dkt. No. EPA-HQ-OPP-2011-0370, Nanosilver Final Work Plan (FWP): Registration Review: Initial Docket Case Number 5042 (Oct. 2018), *available at* https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0370-0021.

18. *Id.* at 5.

19. *FDA's Approach to Regulation of Nanotechnology Products*, FDA: Nanotechnology Programs at FDA, https://www.fda.gov/science-research/nanotechnology-programs-fda/fdas-approach-regulation-nanotechnology-products (last visited June 26, 2019).

20. *Id.*

21. *Id.*

22. FDA, Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, Dkt. No. FDA-2010-D-0530 (June 2014), *available at* https://www.fda.gov/media/88423/download.

23. FDA, Guidance for Industry: Safety of Nanomaterials in Cosmetic Products (June 2014), *available at* https://www.fda.gov/media/83957/download.

24. FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients That Are Color Additives (June 2014), *available at* https://www.fda.gov/media/115075/download.

25. FDA, Guidance for Industry: Use of Nanomaterials in Food for Animals (Aug. 2015), *available at* https://www.fda.gov/media/88828/download.

26. FDA, Guidance for Industry: Drug Products, Including Biological Products, That Contain Nanomaterials (Draft Guidance) (Dec. 2017), *available at* https://www.fda.gov/media/109910/download.

27. Sunscreen Drug Products for Over-the-Counter Human Use, 84 Fed. Reg. 6204 (Feb. 26, 2019).

28. *Id.* at 6216.

29. For example, on September 20, 2013, the Organization for Economic Cooperation and Development (OECD) approved a recommendation that its Member Countries apply existing regulatory frameworks to manage risks associated with manufactured nanomaterials. *OECD Countries Address the Safety of Manufactured Nanomaterials*, OECD (Sept. 20, 2013), https://www.oecd.org/chemicalsafety/oecd-countries-address-the-safety-of-manufactured-nanomaterials.htm.

30. Lynn L. Bergeson et al., The DNA of the U.S. Regulatory System: Are We Getting It Right for Synthetic Biology? (Oct. 15, 2015) (Woodrow Wilson Int'l Ctr. for Scholars Synthetic Biology Project Report), *available at* https://www.lawbc.com/uploads/docs/0168960.pdf.

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