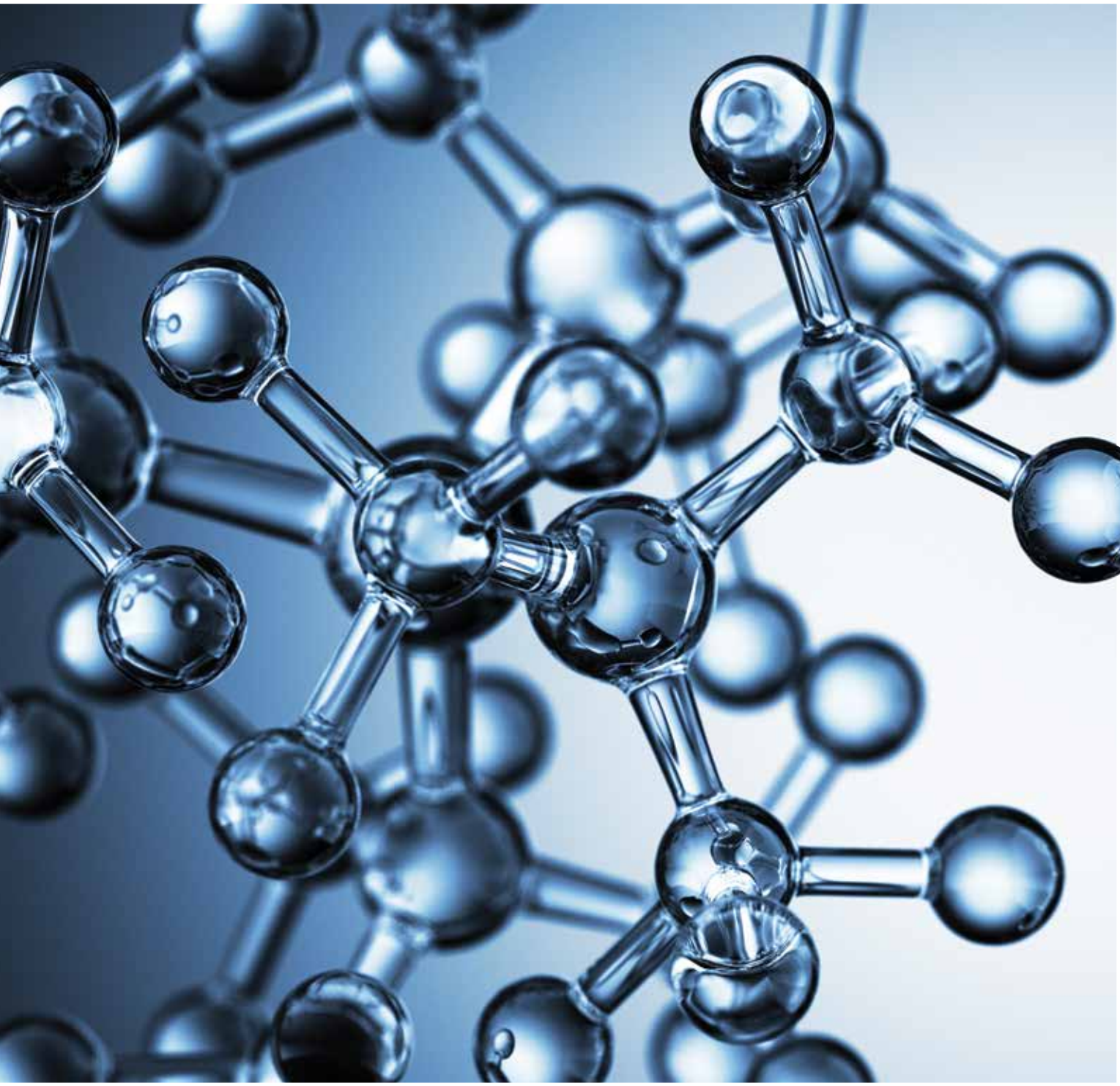
POTENTIAL RISKS AND REWARDS | INTELLECTUAL PROPERTY LAW | EPA AND FDA REGULATION

VOL 16, NO 1
FALL 2019

The SciTech Lawyer

A PUBLICATION OF THE AMERICAN BAR ASSOCIATION | SECTION OF SCIENCE & TECHNOLOGY LAW



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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

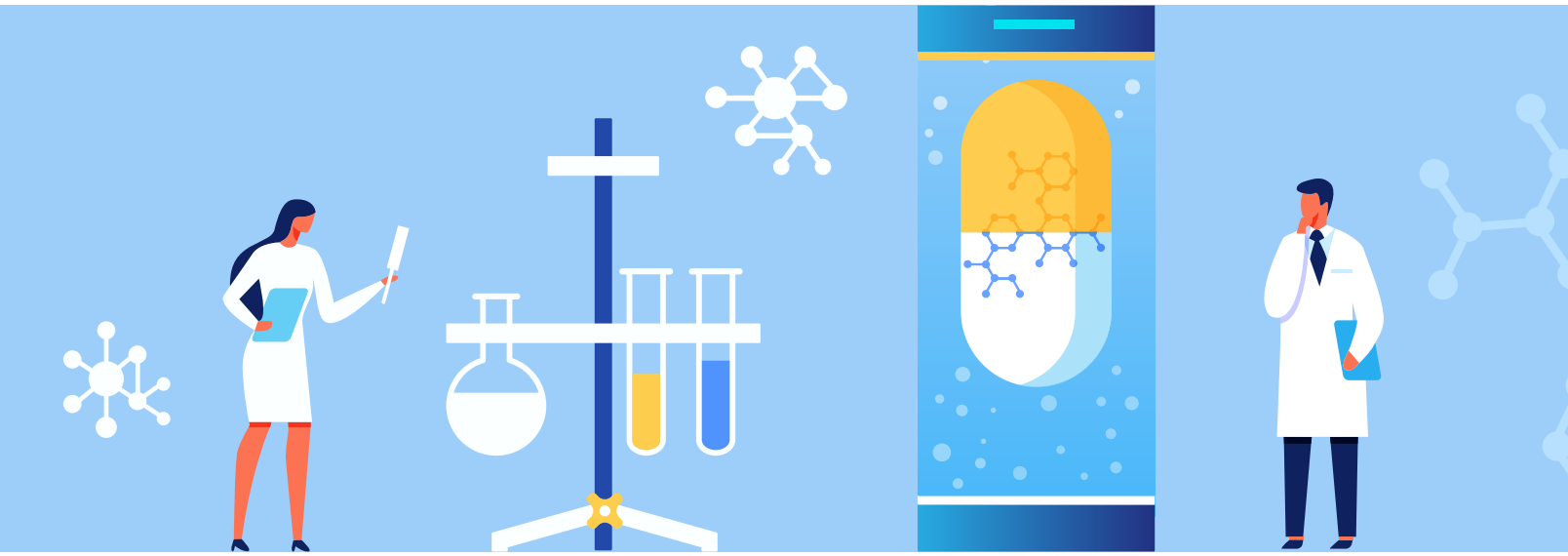
The last bar year closed out at the ABA Annual Meeting in San Francisco, where SciTech sponsored a program titled "Shaping our Future: Top Tech Company Lawyers on Innovation and Social Responsibility," featuring general counsels from four top companies: Microsoft, Oracle, Lyft and 23andme. The GCs addressed 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

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

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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.

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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

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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

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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,

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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).

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