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EXTRACT

NanoBioConvergence – Emerging Diagnostic and Therapeutic Applications

a report by
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Margin copy1. Lynn L. Bergeson is a managing director of Bergeson & Campbell, P.C., a Washington, D.C. law firm focusing on chemical, pesticide, and other specialty chemical product approval and regulation, environmental health and safety law, chemical product litigation, and associated business issues. Ms. Bergeson's practice focuses on chemical product approval, including conventional chemicals and products of emerging technologies, including nanotechnology and biotechnology. Michael F. Cole is Of Counsel to the firm. His practice focuses on food contact regulation, medical device approval, and the review and approval of engineered nanoscale materials subject to FDA review and regulations.

Many people regard nanotechnology as a 'stand-alone' technology. While the technology itself is of great interest, the most intriguing aspect of nanotechnology is that it is increasingly being utilised as an integral part of a more complicated convergence matrix. The intersection of nanotechnology, biotechnology, information technology, and cognitive science, otherwise referred to as 'NBIC convergence', is leading to the development of nanobiotechnology products that promise to change radically the provision of healthcare in the decades ahead.

Nanotechnologies Overview

Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. The width of a nanometre is often compared to that of a human hair. One nanometre is 1/800th of a human hair, or 1/70th the diameter of a red blood cell. According to many, the word nanotechnology connotes less a single technology than a generic term for a large and diverse number of applications and products that contain small particles and demonstrate special properties. According to the National Nanotechnology Initiative (NNI), nanotechnology addresses manufactured or engineered nanoscale materials, and excludes naturally occurring (viruses or volcanic ash) and incidental (diesel exhaust particles) nanomaterials.[1] It is well understood that materials at the nanoscale level often exhibit special physical and chemical properties fundamentally different to their macro counterparts. This is largely because the ratio of surface atoms or molecules to total atoms or molecules increases exponentially with decreasing particle size. Nanoscale materials have correspondingly greater surfaces areas, which increases their surface reactivity. This translates into special physical attributes making nanoscale materials unique for their catalytic, electrical, magnetic, mechanical, optical, sterical and biological properties, among others. Companies and individuals are eagerly exploring the unique properties of nanoscale materials and combining them with advances in biotechnology to improve existing care, address medical conditions previously difficult to treat, and use the technology to fundamentally alter the nature of healthcare, moving towards prophylaxis instead of remedial care.

Increased biological activity cuts both ways. On the positive side, as described below, nanoscale materials are useful for their antioxidant activity and their ability to penetrate cells for drug delivery. On the other hand, certain engineered nanoscale materials under certain circumstances have been associated with enhanced toxicity, the induction of oxidative stress, cellular dysfunction, and other adverse effects. No one knows with precision how long nanoparticles that enter tissues will remain, and how they will be cleared. Similarly, it is uncertain in all cases how nanoscale particles will affect tissue and cellular function, or how the short- and long-term stability of such particles will be determined. These issues will have to be resolved as the technology matures. The attitude that federal and state regulators take towards these issues will also significantly influence the short-term commercialisation of many product concepts.

NanoBio Interface

In that nanotechnology is engineering at the molecular level, its utility in biological contexts is seemingly limitless. There are a number of 'pioneer' medical products at or near the stage of marketing, and many more concepts being considered and entering the developmental stage. Even the most cursory of web searches for new applications of nanotechnologies reveals a broad array of products and tools that have enormous potential to improve human health. For example, microscopic and nanoscale imaging have been significantly improved as a result of nanotechnological developments. Improved microscopy and molecular tracking reflect two of the significant advances enabled by nanobiotechnology. As another example,

1. *http://www.nano.gov/html/about/home_about.html*

quantum dots, an often-cited example of a nanostructure, have significant utility in biological applications. Because they are built on an inorganic platform, quantum dots are stable and thus highly successful in eliminating photo instability. According to one manufacturer, quantum dots find significant utility in measuring quantitative gene expression. One manufacturer uses combinations of quantum dots to bar code beads that can be attached to proteins or nucleic acids.

Another nanotechnology application enables diagnosis at the single cell and molecule levels. Several product manufacturers are working on developing faster diagnostic tests utilising nanoparticles. For example, one product uses a nanotechnology-based genome sequencing system. This technology will enable point-of-care diagnostics and personalised medicine. Other products combine molecular diagnostics with nanotechnology to produce cancer detection kits that are used for the detection of certain types of cancer.

There are three general types of therapeutic applications that product manufacturers have begun to promote: drugs with enhanced bioavailability, drug delivery systems, and products capable of tissue-specific targeting. The availability of nanostructured materials enables drugs to access areas previously unavailable through conventional delivery systems, thus improving drugs' bioavailability and their solubility. Thanks to advances made possible through nanotechnology, drug delivery systems are more tailored and capable of delivering doses at specified time intervals. Similarly, drug dose and delivery are being genetically targeted to arrest cell growth, in turn diminishing toxicity and side effects.

The future use of nanomaterials in providing healthcare is almost limitless. The use of the technology to produce artificial bone and tissue material will further regenerate medicine. Implantable sensors may be able to provide retinal processing and neural interconnects. Medical imaging will be further enhanced by the development of new contrast and shielding agents and products capable of tissue-specific image enhancement. Cell-specific gene therapy will be a step in the medicine of prophylaxis, correcting conditions before they become medical problems by delivering proteomic compounds to cellular components of a cell nucleus to correct pathogenic effects or even destroy the cell intentionally.[2] Nanoscale surgery will develop further, with applications such as tissue-specific light/heat ablation.

One of the most likely areas of commercial expansion will be in drug therapy, where the major companies have the resources to develop this expensive technology. Nanotechnology will be used to improve drugs that presently have poor solubility, and to produce drugs capable of transversing membranes and the blood–brain barrier, although the latter must be approached cautiously due to the unknown effects such drugs might have. The literature is full of reports of companies moving quickly to further improve drug delivery using nanotechnology, including delivery via the skin, lungs and gastrointestinal tract.[3]

Regulation of the Technology

An issue that always affects commercialisation is the difficulty and delay that companies may face in complying with applicable regulatory requirements, particularly when the regulator must assess the effect of new technology. The US Food and Drug Administration (FDA) has been carefully and quietly compiling a list of the possible uses of nanotechnology in regulated products, and identifying the issues that may arise in assessing the safety and effectiveness of the materials when used in a medical application. There is no present indication that the use of engineered nanomaterials will significantly delay the approval of products, but there is much that is still unknown about the effect of the materials in use, e.g. materials that pass the blood–brain barrier. Since the FDA must consider each product *de novo*, its decisions on the proof needed for the use of engineered nanoparticles will be made piecemeal, and it will undoubtedly take a number of years before any discernible pattern emerges regarding the proof required for approval of products. The FDA has indicated that nanotechnology is being evaluated in connection with its Critical Path Initiative, designed to speed the provision of new therapies to patients.[4] The FDA has also indicated that it is concerned about the environmental effects of the use of engineered nanoparticles. For example, it is unclear whether these materials can be released into the environment

2. *Ostman C, "Bioconvergence: Progenitor of the Nanotechnology Age", available at http://www.kurzweilai.net/meme/frame.html?main=/articles/art0140.html?*
3. *Several of the medical uses described herein are discussed at "Nanotechnology Biotechnology Convergence", by Dr. Laura Mazzola (July 27, 2005), available at http://www.nanobioconvergence.com/files/lMazzola07-05.pdf.*
4. *Sadrieh N, "FDA Perspective on Nanomaterial-Containing Products", available at http://www.fda.gov/nanotechnology/ILSI-HESI-ann-mtg-pres-1-17-05.ppt.*

after human and animal use or whether any such release can be measured accurately. The FDA has indicated it must consider what the environmental impact of these materials on other species might be over time. The FDA will doubtless look to the US Environmental Protection Agency (EPA) for answers to those questions, and so the position of the EPA may affect the pace of commercialisation of medical products.[5]

The EPA is currently considering the issues the FDA has raised, among others. EPA has publicly recognised the pollution prevention and environmental remediation applications of nanotechnology. As an example, the use of nanoscale zero-valent iron to treat dissolved chlorinated hydrocarbons *in situ* has received much attention in the recent past. Similarly, sensors capable of measuring nanoscale properties, as well as sensors that are themselves nanoscale materials or have nanoscale components, are believed to hold significant promise in the area of detecting biological and chemical contaminants, improving exposure assessments by collecting much data more efficiently and detecting more accurately substances at lower concentrations. The potential to enhance the quality and quantity of air contaminant data has been expressly recognised by the EPA's Office of Air and Radiation. The work on sensors is certain to be relevant to FDA consideration of the use of those materials.

Similarly, nanotechnology's potential 'sustainable' applications potentially make it a powerful pollution prevention tool. Nanotechnology may diminish or replace, for example, the use of chemicals believed to be more toxic, or leave a larger environmental footprint. Nanoengineered fuel cells may offer more diverse, efficient and reliable sources of energy and offer the promise of diminishing our reliance on traditional fossil fuels. While all such 'sustainable' uses are promising, the EPA notes in its External Review Draft Nanotechnology White Paper[6] that there is a "significant gap in our knowledge" regarding the human health and environmental implications arising from exposure to engineered nanoscale materials and that much more needs to be known before we will be able to assess the potential of comprehensively engineered nanoscale materials to pose biological or environmental health risks. The EPA's various programme offices are all assessing the 'implications' and 'applications' of nanotechnologies with a view to using EPA's authorities under the core federal environmental statutes to identify and address the potential risks and benefits offered by nanotechnologies. Of particular interest is the EPA's Office of Pollution Prevention and Toxics (OPPT)'s current consideration of creating under the general auspices of the Toxic Substances Control Act (TSCA) a Voluntary Nanomaterials Stewardship Program to generate much-needed data and information pertinent to new and existing engineered nanoscale materials.[7] The EPA is expected to convene several stakeholder meetings later this year to flesh out the parameters of such a voluntary programme. The FDA is also holding a public meeting on 10 October 2006 to explore the role and effects of nanotechnology.

As is often the case, the regulators are the '500 pound gorillas' that will almost certainly affect the pace at which the endless permutations of products will be commercialised. It is important to stay tuned and stay engaged in this important debate as these regulatory initiatives are as significant to the pace of commercialisation as are the novelty and appeal of the products themselves. ■

5. *Id. See also the proceeding of a workshop hosted by the Center for Science, Technology & Public Policy at the University of Minnesota last September entitled The Nanotechnology-Biology Interface: Exploring Models for Oversight (Sept. 15, 2005), available at http://www.hhh.umn.edu/centers/stpp.*
6. *EPA, External Review Draft Nanotechnology White Paper (Dec. 2, 2005), available at http://www.epa.gov/osa/nanotech.htm.*
7. *NPPTAC Work Group "Overview Document on Nanoscale Materials," available at http://www.epa.gov/oppt/npptac/pubs/nanowgoverviewdocument20051125.pdf.*