March/April 2014
Volume 5 ▼ Number 2
http://magazine.embs.org

IEEE PULSE

A MAGAZINE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY

Small and Powerful

Nanomaterials Reshape Biomedical Technology

Plus

- Regulating Nanomedicine: Caution Is Advised
- Talking with Jeffrey Karp About Nano's Future
- Many Uses for Multifaceted Biomaterials
- A Doctor in the Palm of Your Hand
- The Super Aged Society

Indexed in PubMed® and MEDLINE®, products of the United States National Library of Medicine

PubMed MEDLINE U.S. National Library of Medicine

EMB IEEE

IEEE PULSE
A MAGAZINE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY

Regulating Nanomedicine

NEW NANO TOOLS OFFER GREAT PROMISE FOR THE FUTURE - IF REGULATORS CAN SOLVE THE DIFFICULTIES THAT HOLD DEVELOPMENT BACK

Shannon Fischer | March 13, 2014

http://pulse.embs.org/march-2014/regulating-nanomedicine/

In 1979, a Hebrew University biochemist named Yechezkel Barenholz teamed with Alberto Gabizon, a newly minted Ph.D. from the Weizmann Institute of Science, to find a better way to give chemotherapeutic doxorubicin to patients with cancer.

Sixteen years later, the result of that collaboration—Doxil—won approval from the U.S. Food and Drug Administration (FDA). It was a reformulation of doxorubicin into tiny, drug-loaded membrane spheres—liposomes—fewer than 100-nm across. They were so small they could course through the bloodstream until they leaked right through the particularly porous vasculature that marked a cancer site. And though the particles didn't necessarily fight the cancer better, they did fight it with fewer side effects. As it happens, they were also the first formal nanodrug in history.

Since its arrival to market, Doxil has made more than US$600 million in annual sales battling Kaposi's sarcoma, multiple myeloma, and ovarian and breast cancer. It has been joined by dozens of nano bedfellows, most of them also anticancer drugs, many also liposomes, although there are also dextran-coated iron oxide nanoparticles for in vivo organ imaging, hydroxyapatite nanocrystals that act as bone substitutes, and even gold nanoparticles that work outside the body to diagnose infections. But there's a catch: none of these nanomedicines were approved under any specific nano guidelines. Even Doxil passed with a mere expedited review as a reformulation of doxorubicin. But nanomedicines don't always act like their larger counterparts, and when they differ, it's not always predictable. The fact is, despite all the successes and the billions of dollars invested, nanomedicine remains a regulatory minefield rife with exotic toxicology and uncertain policies, badly in need of a few clear answers.

WHAT'S THE PROBLEM?

The problem is that something at the nanoscale is not just the miniaturized equivalent to its larger self. For one thing, its shrunken size results in an enormously increased ratio of surface area to volume ratio. That translates in vivo as exponentially more surfaces that can interact with the biological environment. That may be a good thing—a nanosized drug can be more bioavailable, more stable, or more easily decorated with interactive add-ons that help target organs of interest—but, in some cases, especially with certain nanomaterials, like metal oxides, it also magnifies toxicities that might have been absent or unnoticeable at a larger size.

Then, too, is the fact that when particle sizes drop to under 100 nm or so, all sorts of physicochemical properties can begin to shift in ways that scientists still have not fully mapped. Thermal, optical, and magnetic properties might be different; particles may become more reactive, have faster ion transport or different structural integrity. And, maddeningly, everything from the particle's size and shape to its surface area, solubility, crystallinity, charge, and even aspect ratio affects exactly how those properties manifest.

Because of these variations, the end result of any given nanoscaled particle may be a unique behavior markedly different from one variation to the next. That, again, is part of the technology's desirability—harness these qualities correctly and the result is a potential drug or device that arrives at a given disease site with maximal efficiency and potency. But it can just as easily add unexpected twists. In rats, for example, positively charged nanovesicles caused swelling at the blood–brain barrier, but neutral ones, and small amounts of negatively charged ones, did not. In another study, 10- and 60-nm-sized gold particles resulted in liver damage in mice, but 5- and 30-nm sized particles did not. Unfortunately, that pattern doesn't necessarily apply to other particles, or other sizes, or even the same particles with altered parameters; scientists are still trying to develop the measures they need to predict how such particles will behave because they just don't know yet.

"For bulk size materials, you're basically talking about the chemical composition, dose, and exposure route when studying toxicity—that's a few parameters," says Huan Meng, who studies nanomedicines and nanotoxicology at the Jonsson Comprehensive Cancer Center and the Center for Environmental Implications of Nanotechnology (CEIN) at the University of California, Los Angeles (UCLA). "But with nanomaterials, you have multiple directions that you can play with," Meng says. "You're talking about a really dynamic, complicated system that traditional toxicology cannot fully address."

CAUTION IS ADVISED

So far, the regulation of nanomedicines and devices has erred on the side of caution. The FDA, for example, hasn't adopted any formal guidelines for nanotechnology, although it has released guidelines describing how it defines a nanoscale product—specifically, as having at least one dimension between 1 and 100 nm, or as being fewer than a micron in size and demonstrating size-dependent behaviors. With that, however, the FDA reviews nanomedicines and devices on a case-by-case, component-by-component basis under existing drug and device guidelines, with additional questions and tests as desired—although in a 2012 comment in Science, FDA Commissioner Margaret Hamburg indicated that it may yet fold in product-specific regulation in the future.

Russell Mumper, vice dean of the University of North Carolina's Eshelman School of Pharmacy, calls it a rational, thoughtful approach given how little is known and how stringent the review process is. "It's really no different than a non-nanotechnology approach," he says, "they're going to want to see, on a nanomedicine by nanomedicine basis, a comprehensive data set of not only the physicochemical characterization of the manufactured nanomedicine, but batch-to-batch reproducibility. They want to see this comprehensive data set and manufacturing information, before they'll ever let you dose even the first patient."

Other countries take a similar approach, including Canada, Japan, and some in the European Union (EU), which, like the United States, also rely largely on the scrutiny of their pre-existing processes to evaluate nanomedicines (which they define similarly to the United States, although there is still no formal internationally agreed definition). Indeed, according to a 2013 Organization for Economic Cooperation and Development survey of a dozen different nations, including Australia and Poland, as well as the EU and the United States, folding nanoproducts into existing regulatory and legislative processes is by far the most common strategy to date.

And to an extent, it's worked. After all, nanobased medical products have been on the global markets for nearly 20 years, and no major incidents have occurred. Yet, many are not entirely satisfied with current measures, and the situation remains in flux.

WHAT WE DON'T KNOW CAN HURT US

Critics accuse the measures of being both too risky and too cautious. Cautious because such hesitancy toward definite regulation, along with the absence of established testing protocols or manufacturing guidelines, leaves the powerhouses of the industry reluctant to join the fray. Big pharma has dabbled in nanomedicine, but it has yet to throw its muscle into the field largely because of

the potentially multiplied expense and time that such an amorphous regulatory landscape will likely entail, especially for novel nanomedicines that propose to use new ingredients.

And it's also a risky stance because of how many unknowns remain in the science, says Raj Bawa, adjunct professor at Rensselaer Polytechnic Institute and patent agent at Bawa Biotech LLC. Nanoparticles are so unpredictable in vivo, he explains, in ways that hinge on so many different elements and properties that it is entirely possible current toxicology tests simply cannot ask the right questions. Maybe they do, but it is hard to even know that for sure. "We're dealing with a very dynamic system in the human body, and really, we don't understand fully the interaction of nanoparticles and the biosurface at that nanoscale," he says. "You're having reactions at the molecular and atomic level that aren't fully studied."

But regulators are first to acknowledge their failings, and many are at work to address these shortcomings. The FDA has invested heavily in new in-house nanotechnology regulatory science programs, aimed at ramping up new methods to profile and test nanomaterials in vitro and vivo. The National Cancer Institute's Nanotechnology Characterization Laboratory (NCL) has examined nanomaterials and their complexities since 2004. Every year, it accepts a dozen or so potential nanotherapeutics developed from labs nationwide and runs a battery of tests that serve to both assess those drugs and add to its growing body of assay protocols and troublesome manufacturing pitfalls such as sterility and batch-to-batch variability—all of which it shares with the science community and FDA. In the past ten years, it has characterized nearly 300 different nanomaterials and sent six on to clinical trials. Meanwhile, the information and standards that it has gathered have begun to unofficially reshape not only the FDA's own review practices but strategies internationally.

"As the field is developing very quickly, a benefit is that people are looking to establish protocols and norms—similar to best practices—and the NCL has helped to establish that," Mumper says. His lab, he explains, has submitted investigational new drug applications to the FDA for nanomaterials and was referred to protocols established by the NCL. "The position the FDA takes," he says, "is: 'These are the accepted best practices in terms of standard operations, and this is generally what the community has adopted. You may not have to do all the protocols, but you have to justify why you're not doing them'."

Internationally, the European Commission is collaborating with the NCL to develop a European nanotechnology characterization lab network of its own, which it hopes to launch this year in existing labs. Recently, the European Medicines Agency (EMA)—partially in collaboration with Japan's Pharmaceutials and Medical Devices Agency—has published a series of reflection papers highlighting specific considerations for novel so-called next-generation nanomedicines and known classes of nanomedical products, such as liposomes and copolymer micelles. In addition, in 2009, the EMA, with the United States, Japan, and Canada, launched an international dialogue on the technology through the International Regulators Subgroup on Nanomedicines. This exchange was also aimed at identifying global knowledge gaps and upcoming regulatory needs.

Work like this—identifying gaps, building the science—has become a global effort, taking place in government and academic labs alike. At UCLA, Andre Nel, the director of CEIN, and chief of the Nanomedicine Division, are developing a robotic system to perform high-throughput and high-content screenings to assess the safety of and even discover new nanomedicines. "One of the goals is to link the material properties to the biological outcome and establish the predictive biology," says Meng, who works with Nel. Between them, labs like his and the funding agencies "are gaining a lot of new knowledge and expertise," he says. "We are learning. And we are practicing."

FUTURE TENSE

Laying this foundation will be essential to the future. Across the world, hundreds of nanomedicines and devices are wending their way through the clinical testing pipeline. If the pace continues as is, market forecasters predict that the global nanomedicine market will hit US$130.9 billion by 2016.

Many of these compounds will still be relatively known quantities—liposomes, nanocrystals—but as time goes on, more novel creations will emerge and begin to blur the lines between physical devices and chemical drugs, and that may be a problem. The FDA has an Office of Combination Products to determine whether multifunction products should be assessed as the drug, biologic, or device, depending on its primary mode of action. Multipurpose "theranostic" agents that can diagnose, treat, and track diseases may not always be easily categorized and some researchers worry that that could lead to inconsistent evaluations. Critics such as Bawa are concerned that this process is too imprecise—particularly because, he says, at the time of an investigational application, it's not always clear which mode of action provides the most important therapeutic action and some products can even have two different, equally critical modes of action.

Furthermore, not all regulatory bodies have defined combination product offices, either—the EU assesses medical products and devices separately and differently. Currently, advanced and biotechnological drugs like nanomedicines are evaluated under the centralized body of the EMA, but devices are regulated under the various authorities of the individual member states. If a medicine with a device component arrives for review at the EMA, the EMA evaluates it in consultation with medical device authorities, and vice versa.

With respect to the evaluation of the device component, "Logistically, it's more difficult," says Falk Ehmann, the Innovation Task Force coordinator in the EMA's Specialised Scientific Disciplines Department. A worst-case scenario where one state rules one way and its neighbor rules differently can happen, he says. There are robust procedures in place to prevent that occurrence, and collaboration is the norm, "but still the potential is there," he says. "And with the theranostics, it's getting more and more complicated."

Rogério Gaspar, vice rector at the University of Lisbon and head of its Pharmaceutical Technology Department in Portugal, worries that current device regulations in particular are poorly constructed to handle the type of nanobased therapeutic-diagnostic devices that might be delivered by routes traditionally used for drug products. "They will fall into the gap between medical devices and medical products," he says, "and that might bring us a number of products that are not consistently regulated."

In time, yet thornier quandaries will emerge. As Mauro Ferrari, president and chief executive officer of the Houston Methodist Research Institute and the Alliance for NanoHealth in Houston, Texas, points out, nanotechnology's improvements on drug delivery and kinetics could be readily weaponized for mass destruction. "For instance," he argued in a 2012 discussion of nanomedical ethics, "nanoparticles could be used to change the modality of infection of certain viruses, from blood contact-only to nanopathogens that are effective through inhalation or oral ingestion." Regulatory hurdles will not slow that concern, he points out. Terrorists, after all, are hardly beholden to the FDA.

Less alarming but more complicated will be the fact that nanotechnology will almost certainly enable truly personalized medicine. "Microtechnology opened the way to genomics," Ferrari tells me. "Nanotechnology opens proteomics and metabolomics, and all the other 'omics' where you need to be a lot smaller to process a lot more information." When that area hits its stride, he worries, it will open a more potent Pandora's box of privacy and consent issues than even genetics has done. "Genomic information tells who you are and tells you your risk profile. When you unlock the proteomic and metabolomic world, it not only tells you risk, it tells you where you are, where you've been, what you're doing, how you're feeling," he says. On one hand, the benefits to health care are huge. On the other hand, it means a brave new world where the definition of privacy is concerned.

These are more difficult issues that regulations cannot handle on their own. Discussions among researchers and ethicists are underway, but the critical group that needs to participate will be the public, and that has yet to happen at a broad level. But the greatest fear, as far as Ferrari can see, is that regulatory fears and ethical quandaries be allowed to grow so large that nanomedicine's future is stifled. "It's easy to build scary scenarios," he says. "But I live in a world where every patient who comes to me is facing death." Nanomedicine's abilities, in the end, will be key to saving lives like theirs from cancer and other diseases, and not to take advantage of it would be the greatest risk of all.