

SELF SIMILAR

Nanomedicines can vary in shape and size.



COVERING THE SPREAD

Variability within—and across—**NANOMEDICINES** is complicating their generics pipeline

MATT DAVENPORT, C&EN WASHINGTON

IN OCTOBER 2011, drug shortages were such a pressing issue in the U.S. that President Barack Obama issued an executive order urging the Food & Drug Administration to streamline the approval process for new therapeutics that could fill the voids. One of the more noticeable voids was in the supply of Doxil, a nanoparticle chemotherapy drug.

To curb this shortage, FDA authorized the temporary importation of an Indian Doxil copycat called Lipodox in February 2012. In keeping with the executive order, the agency evaluated and approved the drug formulation within a year, roughly one-third of the time it takes for an average generic medicine to receive approval. Doxorubicin hydrochloride liposome injection—still widely, but unofficially, referred to as Lipodox—became what many consider to be the first generic nanodrug approved in the U.S.

“You wouldn’t expect the first one to happen like that,” says Dorothy F. Farrell, a program manager at the National Cancer Institute’s Office of Cancer Nanotechnology Research. “I would hope that it’s not going to be representative.”

Many experts believe Lipodox’s story will be unusual in the developing story of generic nanodrugs. But a lack of formal regulatory guidelines is still shrouding further generics development in uncertainty. The absence of regulations, however, does not reflect an absence of effort on the part of regulators.

Nanodrugs tend to be far more complex

than conventional small-molecule therapeutics, where the active pharmaceutical ingredient is the primary concern. In nanodrugs, that ingredient is just one of many critical parameters. Typically, nanodrugs also employ engineered delivery systems made from things such as lipids, polymers, dendrimers, and carbohydrates.

The more thoroughly that drug developers can characterize the shape, size, and chemical composition of their generic formulation, the more certain they can be that the drug will be a safe and effective substitute for the parent product. Even subtle differences in the generic could have serious biological consequences.

But more characterization means higher costs for manufacturers and diminished savings for patients. And how to best characterize any given nanomedicine is a question that looms large. With the diversity of the dozens of approved nanodrugs, there is no one-size-fits-all approach. To complicate matters, FDA approved many of the first brand-name nanomedicines before publishing its modern guidelines on

nanomaterials, meaning generic versions could be subject to more or different tests than their parent products. As the first nanodrugs come off patent protection in the U.S., their complexity is casting ripples of uncertainty through the policies and economics surrounding their would-be generics. If those ripples aren’t quelled, the patients who rely on these expensive medicines could be left without alternatives.

GIVE IT A NAME

As silly as it sounds, nomenclature could play a huge role in the approval of generic nanomedicines. Officially speaking, nanomedicines aren’t exactly a thing.

“You can’t call FDA and ask how many nanodrugs are approved because it doesn’t have a class called nanodrugs,” Farrell says. FDA officials confirmed the latter part of this statement with C&EN, saying, “FDA does not have a regulatory definition of nanomedicine.”

“It does sound like semantics, but I think



that in a lot of ways it's not," Farrell says. Without a regulatory definition, FDA has the flexibility to evaluate potential nanodrugs as individual entities. This is important, given the diversity of nanodrugs on the market, according to FDA.

"Each drug product application is unique, and as such, each is reviewed by FDA on a case-by-case basis," FDA officials tell C&EN. This allows regulators to determine which assays are most appropriate for a certain drug. The analyses needed for liposomal chemotherapeutic nanoparticles will be inherently different from the tests run on carbohydrate-coated iron hydroxide nanoparticles used to combat iron deficiencies.

Still, this regulatory flexibility remains a source of frustration for some drug developers. Without formal guidelines in place, researchers and companies don't always know which criteria a given nanodrug must satisfy.

"It's a very haphazard and disjointed landscape. The uncertainty and lack of firm guidelines could discourage and stifle development in this area," says Raj Bawa, a patent agent at the consulting firm Bawa Biotech and an adjunct professor of biological sciences at Rensselaer Polytechnic Institute. "Nomenclature may impact the generics development because, in the end, you have to deal with a regulatory body like FDA. You can't just come out with a drug and say, 'Here it is. I'm going to market tomorrow.'"

But Bawa isn't saying that FDA holds all the cards or that it's stacked the deck against potential generics manufacturers. These companies just don't know which game they're playing.

"Once you define the rules of play, I think that it's easy for everyone to follow those rules," says Warren C. W. Chan, a nanotech and biomedical researcher at the University of Toronto. But after years of speaking with regulators at multiple agencies, Chan has found that numerous questions about the best way to set those rules for nanomedicines persist, including, "How do we define nano?"

Were there a regulatory definition of nanomedicines, it could help legislators write laws to make affordable generics possible. The Hatch-Waxman Act of 1984 paved the pathway to modern generics approvals for small-molecule drugs, says Andrew H. Berks, a patent attorney and chair of the Chemistry & the Law Division of the American Chemical Society. In 2010, President Obama signed the Biologics Price Competition & Innovation Act, or Biosimilars

Act, into law that established an analogous approval route for generic biologics, massively complex biomolecular drugs.

But without their own definition and a codified generics approval pathway, nanodrugs have become like the middle child of pharmaceuticals. Because the biosimilar definition doesn't fit nanodrugs, the rules for small molecules are being tailored for nanomedicines and their generics, according to some drug developers.

FDA has started examining drugs containing nanomaterials more closely in recent years. And since 2011, the agency has published guidance for companies determining whether their formulations might be subject to examination beyond what is typical for small-molecule drugs.

FDA has also published several guidance documents pertaining to specific nanomedicines, but many are drafts and contain nonbinding recommendations.

On the opposite end of the regulatory spectrum, some countries, such as India, Mexico, and Argentina, have already approved multiple generic nanomedicines. Some of these nations don't have robust regulatory agencies like FDA, Bawa says. "What they have is a disaster."

In these markets, generic nanodrugs may make it to patients without rigorous physicochemical characterization or sufficiently powerful clinical trials. There can also be little to no oversight of manufacturing, leading to further questions about the safety and consistency of these products.

"There's very little literature available about the quality of the products. Are they inferior? Are they better? We don't know," says Daan J. A. Crommelin, a veteran researcher of drug delivery systems in academia and industry. "There's a lot of them being used in patients, and we have very little information about their performance," says Crommelin, now a professor emeritus of pharmaceuticals at Utrecht University, in the Netherlands. "That's something I worry about."

Animal tests have shown that nanodrugs whose formulations differ slightly in size or composition can have different toxicities (*Cancer Chemother. Pharmacol.* 2010, DOI: 10.1007/s00280-010-1406-x). But as Crommelin points out, little is known about how approved generic formulations in foreign markets are faring in humans.

Back in the U.S., so-called nanodrugs will remain undefined, at least for now. A statement from FDA officials states that "FDA has concluded that the best course at this

time is to continue to pursue its ongoing scientific research and regulatory approach."

ALL THE SMALL THINGS

Despite the regulatory uncertainty, one word proves that companies can make approvable generic nanomedicines: Lipodox. True, a drug shortage aided Sun Pharmaceutical Industries in getting its generic version of Janssen Biotech's Doxil imported to and approved in the U.S. But FDA subjected Lipodox—or doxorubicin hydrochloride liposome injection, as it were—to a full review, including in vivo studies and in vitro tests, and inspected Sun Pharma's manufacturing processes and controls and deemed them adequate. So how did Sun Pharma pull it off?

"They mimicked the Doxil formulation, size, and everything as closely as humanly possible and did a pretty good job on it," says Theresa M. Allen, cofounder of the Centre for Drug Research & Development, a Canadian nonprofit for drug development and commercialization. Allen has researched nanoscale drug delivery systems for more than three decades and was part of the team that developed Doxil.

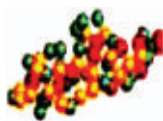
Sun Pharma's straightforward tactic was unorthodox. Generics manufacturers tend to challenge and work around patents rather than wait for the protections to expire and copy the crafts. That trend may not hold for nanodrugs: Given the complexity of these formulations, work-arounds could require extensive and expensive research, characterization, and clinical trials that generics companies prefer to avoid.

Still, copying Doxil—or any nanomedicine—is a nontrivial exercise. Consider Doxil's formulation.

A nanoscopic shell the shape of a rugby ball encapsulates a crystalline compound of doxorubicin, a generic cancer therapeutic. The chemical composition of the shell, made from liposomes and polyethylene glycol (PEG), and the doxorubicin precipitate work together to control how quickly the active ingredient leaks out into a patient. Attaining the optimal leakage rate requires specific lipids, a precise length of PEG, and a once-proprietary process for using ammonium sulfate to pack the doxorubicin into liposomal vesicles.

Once the PEGylated liposomes were loaded with the active ingredient, the team filtered out the particles of improper size. Researchers wanted the diameters of their

NANOMEDICINE CABINET FDA has approved a diverse portfolio of nanodrugs, and many are coming off patent soon.



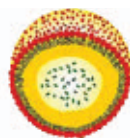
Drug Name: Copaxone
Marketer: Teva
Active Ingredient: Copolymer of amino acids
Nanoscale Formulation: Complex amino acid polymer
Indications: Relapsing-remitting multiple sclerosis
Year Approved: 1996
Patents Expire: No unexpired patents
2013 Global Sales (\$ millions):

4,328



Drug Name: Abraxane
Marketer: Abraxis BioScience
Active Ingredient: Paclitaxel
Nanoscale Formulation: Albumin-bound nanoparticles
Indications: Breast cancer, non-small-cell lung cancer, pancreatic cancer
Year Approved: 2005
Patents Expire: 9/6/2020^a, 12/9/2023, 3/3/2024, 2/21/2026, 8/13/2026
2013 Global Sales (\$ millions):

650



Drug Name: AmBisome
Marketer: Astellas Pharma
Active Ingredient: Amphotericin B
Nanoscale Formulation: Liposomal nanoparticles
Indications: Fungal infections, leishmaniasis
Year Approved: 1997
Patents Expire: 2/23/2016, 10/12/2016
2013 Global Sales (\$ millions):

474



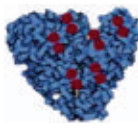
Drug Name: Doxil
Marketer: Janssen
Active Ingredient: Doxorubicin
Nanoscale Formulation: Liposomal nanoparticles
Indications: Kaposi's sarcoma, ovarian cancer, multiple myeloma, breast cancer^b
Year Approved: 1995
Patents Expire: No unexpired patents
2013 Global Sales (\$ millions):

430



Drug Name: Rapamune
Marketer: PF Prism
Active Ingredient: Sirolimus
Nanoscale Formulation: Nanocrystals
Indications: Immunosuppression
Year Approved: 1999
Patents Expire: No unexpired patents
2013 Global Sales (\$ millions):

350

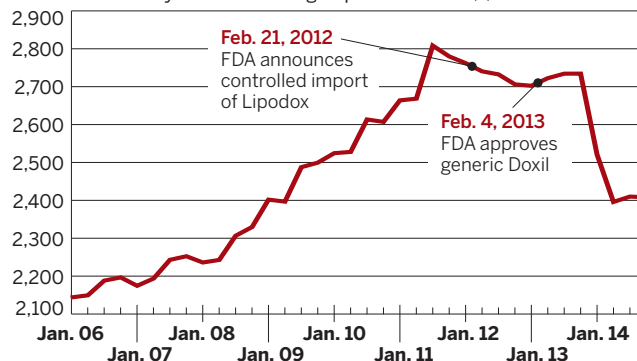


Drug Name: Somavert
Marketer: Pharmacia & Upjohn
Active Ingredient: Pegvisomant
Nanoscale Formulation: Polymer-protein conjugate
Indications: Acromegaly
Year Approved: 2003
Patents Expire: 9/21/2015, 3/25/2017
2013 Global Sales (\$ millions):

217

SMALL DRUG, BIG PRICE A generic drug helped alleviate the Doxil shortage and reduce the cost of care.

Estimated monthly cost for treating Kaposi's sarcoma, \$



SOURCES: FDA, Centers for Medicare & Medicaid Services, Bureau of Labor Statistics, Memorial Sloan Kettering Cancer Center

DOXIL IMAGE COURTESY OF JANSSEN. ALL OTHERS COURTESY OF RAJ BAWA

particles to fall within a narrow distribution around 100 nm so they could easily slip through the openings in immature blood vessels that supply nutrients to tumors.

The net result of this nanoengineering is that Doxil particles accumulate within a tumor and deliver most of their payload there, instead of dispersing doxorubicin throughout the body. The doxorubicin in Doxil isn't any more potent than in any other formulation, but the nanoparticle motif is ultimately less toxic to patients. Although FDA originally approved Doxil in 1995 for treating an AIDS-related cancer known as Kaposi's sarcoma, it has also become a staple as a therapy for ovarian cancer.

Lipodox is a carbon copy of Doxil in virtually every way—the lipid choice, the

amount of PEG, even the doxorubicin packaging process—which was likely an advantage when it came to FDA, patients, and physicians accepting Sun Pharma's product for the same indications.

"You start getting into trouble if you start substituting one of the ingredients for something else," Allen says of developing generics for liposomal nanomedicines. For example, swapping out hydrogenated soy phospholipids for egg phosphatidylcholine would be frowned upon. "There's not a lot of tolerance with the regulatory committees with substituting ingredients, including nonactive ingredients."

But this strategy of churning out generic clones of nanomedicines may not work across the board.

IT'S COMPLICATED

Copaxone is a jumble of amino acids and polymers that Teva Pharmaceutical Industries developed as a nanomedicine for relapsing-remitting multiple sclerosis. Copaxone brought in more than \$4 billion last year according to the biopharma analytical firm Decision Resources Group. Although all of its patents have expired, there is no generic version of it.

"Copaxone is not a single molecular entity, but a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides," says Bawa, who, in addition to founding Bawa Biotech, serves as scientific adviser to Teva. Teva has shown that Copaxone is a safe and effective therapeutic, but Bawa says the drug is too complex to characterize completely. "The generics of that are going to be very, very difficult, if not impossible."

& MORE ONLINE

For additional images and a more comprehensive list of nanomedicines, go to <http://cenm.ag/ndrug>.

Some in the business call this exclusivity by difficulty. Copaxone may be the poster child for such exclusivity, but it's not alone.

Every aspect of nanomedicines and their generics seems mired in complexity, which is one reason why researchers at the Nanotechnology Characterization Laboratory (NCL) are looking to develop new ways to quantify these formulations. In collaboration with FDA, the National Cancer Institute, and the National Institute of Standards & Technology, NCL researchers use their characterization expertise to analyze nanodrug candidates.

As nanodrugs become more complex, researchers hope they can learn how to best characterize these drugs in vivo and in vitro. Doing so may enable scientists to identify which parameters are most important for establishing the therapeutic equivalence of two similar products.

What makes this so challenging for nanomedicines is that particles or structures within the same formulation can differ from one another—they're not homogeneous. There's some variability, or polydispersity, even within approved drugs. This adds another layer of complexity for those trying to copy or characterize the drugs.

"Nanomedicines always have some polydispersity. There's an inherent polydispersity in size, charge, surface characteristics, et cetera," says Stephan Stern, a principal scientist at NCL. "It's this lack of a pharmaceutical identity that leads to a lot of complexity in their regulation."

Chan of the University of Toronto has found that concerns about polydispersity plague other scientists and regulators as well. "At what size or chemistry variability can you consider a product good enough?" Chan asks. "I don't know. And it might be different for different materials."

Determining what "good enough" is will take time and effort, but Stern has a rough idea on how to get there. "You basically throw every assay under the sun at a drug to characterize it," he says.

"Overall, we need a clear regulatory path. We need a better understanding of how to characterize products to ensure therapeutic equivalence," says Stern. "Then we can get these drugs to market and we can protect the patient."

Patient protection is a matter of drug safety and accessibility. Following the approval of Lipodox, the average price per milligram of nanoformulated doxorubicin fell to its lowest point in roughly six years, according to inflation-adjusted data from the

Centers for Medicare & Medicaid Services. The price of other nanodrugs will likely erode similarly—markedly, but gently—with the introduction of their generics, suggests Niamh Buckley of Decision Resources.

Given the complexity of the drugs, the generics savings will likely be more in line with biosimilars—up to 30%—than it is with generic small-molecule drugs—up to 85%.

Still, nanomedicines can add thousands of dollars to a patient's monthly medical bills, so generics could save patients hundreds.

"The ability to have two of something should drive the price a little bit," says Farrell of the National Cancer Institute, adding that she is not an economics expert. "But it seems to me that competition is always good." ■



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