Nanopharmaceuticals for Drug Delivery – A Review

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Abstract

In today's global economy, pharmaceutical companies are under enormous pressure to maintain profitability in light of numerous challenges, ranging from revenue losses due to patent expirations on blockbusters to enhanced regulatory oversight and ever-increasing challenges from generic manufacturers. These market forces and drivers are dictating change in pharma's quest to discover, develop and deliver novel therapeutics. Clearly, new ground rules and competitive business strategies will be needed in the post-blockbuster world. As a result, pharmaceutical companies are turning to miniaturisation and nanotechnology to enhance drug target discovery and drug development. In fact, nanomedicine – the application of nanotechnology to healthcare – is already influencing the pharmaceutical industry, especially in the design, formulation and delivery of 'nanopharmaceuticals'. Nanopharmaceuticals are a relatively new class of 'therapeutic-containing nanomaterials' that often have unique 'nanoproperties' (physiochemical properties) due to their small size (compared with their bulk-phase counterparts), a high surface-to-volume ratio and the possibility of modulating their properties. They are, in essence, nanoparticles intended for a broad spectrum of clinical therapeutic applications. They have the potential to target a particular organ or tissue site, either passively or actively. Nanopharmaceuticals present novel reformulation opportunities for active agents (e.g. small-molecule drugs, proteins, nucleic acids, etc.) that were previously insoluble or could not be targeted to the specific site of the body where they were needed. In other words, those therapeutic agents that were previously unsuitable for traditional oral or injectable drug formulations can now be 'nanoformulated' for site-specific delivery due to superior pharmacokinetics/pharmacodynamics and/or active intracellular delivery. This approach has the ability to reduce toxicity and enhance bioavailability, thereby improving efficacy and patient compliance. Nanopharmaceuticals can also increase drug half-life by reducing immunogenicity and diminishing drug metabolism. With these advantages, nanopharmaceuticals have the ability to extend the economic life of proprietary drugs, thereby creating additional revenue streams. As a result, they have the potential to affect drug commercialisation and the healthcare landscape. In the process, inevitably, they will become an integral part of mainstream medicine. In fact, a large number of US Food and Drug Administration (FDA)-approved nanopharmaceuticals are already on the market, with many more poised to receive regulatory approval.

Keywords

Nanopharmaceuticals, nanotechnology, drug delivery, US Food and Drug Administration, US Patent and Trademark Office, nanomedicine, commercialisation, patents, nanoparticles, US National Nanotechnology Initiative

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The Nanotechnology Phenomenon

The high-risk, high-pay-off global nanotechnology phenomenon is in full swing. Innovations at the intersection of engineering, biotechnology, medicine, physical sciences and information technology are spurring new directions in research, education, patenting, commercialisation and technology transfer.[1-5] In fact, the future of nanotechnology is likely to continue along this interdisciplinary path, with significant technological advances cutting across multiple scientific disciplines and accelerating under the 'nanotech' banner. Commercial nanotechnology is at a nascent stage of development and its full potential is years away. However, there are a few bright spots where development is progressing more rapidly. One such sector is the application of nanotechnology to drug delivery ('nanomedicine drug delivery' or 'nano-drug delivery'). In fact, the recent advances in nano-drug delivery[6] are beginning to alter the landscape of medicine. Although many sought-after innovations are decades away, there are hundreds of nanotech-based consumer products in the marketplace today.[7] Many more applications will be proposed, validated, patented and commercialised in the next decade.

What Is Nanotechnology?

Nanotechnology is an umbrella term used to define the products, processes and properties at the nano/micro scale that have resulted from the convergence of the physical, chemical and life sciences. Miniaturisation of materials often imparts novel mechanical, electrical and/or optical properties. Specifically, as a particle's size decreases, a greater proportion of its atoms are located on its surface relative to its core, often rendering the particle more reactive (over their conventional 'bulk' counterparts). In addition, as the particle size decreases, its total surface area increases exponentially. This reduction in particle size increases its dissolution rate and saturation

solubility and, if the particle is a drug, it frequently correlates to improved *in vivo* drug performance.

However, one of the major problems regulators and lawyers face regarding nanotechnology is the confusion and disagreement about its definition.[8,9] A popular yet inaccurate definition of nanotechnology is that proposed by the US National Nanotechnology Initiative (NNI), which limits nanotechnology to "dimensions of roughly 1–100 nanometres".[10] Various government agencies, including the US Food and Drug Administration (FDA) and the US Patent and Trademark Office (PTO), continue to use this vague definition based on a sub-100nm size. The NNI definition of nanotechnology presents numerous difficulties. For example, although the sub-100nm size range may be important to a nanophotonic company (e.g. a quantum dot's size dictates the colour of light emitted), this size limitation is not critical to a drug company from a formulation, delivery or efficacy perspective because the desired property (e.g. improved bioavailability, reduced toxicity, lower dose, enhanced solubility, etc.) may be achieved in a size range greater than 100nm. Moreover, this NNI definition excludes numerous devices and materials of micrometre dimensions (or of dimensions less than one nanometre), a scale that is included within the definition of nanotechnology by many nano-scientists. Therefore, experts have cautioned against an overly rigid definition based on a sub-100nm size, emphasising instead the continuum of scale from the 'nano' to 'micro'.

Add to this the fact that nanotechnology is nothing new. For example, nanoscale carbon particles ('high-tech soot nanoparticles') have been used as a reinforcing additive in tyres for over a century. Another example is protein vaccines, which fall squarely within the definition of nanotechnology. In fact, the dimensions of many biomolecules is in the nanoscale rang. Peptides are similar in size to quantum dots and some viruses are in the size range of nanoparticles. Hence, most molecular medicine and biotechnology can be classified as nanotechnology. Technically speaking, biologists have been studying all these nanoscale biomolecules long before the term 'nanotechnology' became fashionable. However, the US National Institutes of Health (NIH) emphasises that, while much of biology is grounded in nanoscale phenomena, the agency has not re-classified most of its basic research portfolio as nanotechnology.

In view of this ongoing confusion, the following definition of nanotechnology, unconstrained by an arbitrary size limitation, has been developed:[8,9] "The design, characterisation, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometre scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property."

Naturally, disagreements over the definition of nanotechnology carry over to the definition of nanomedicine. At present, there is no uniform, internationally accepted definition for nanomedicine. One definition, not constrained by size, yet correctly emphasising that controlled manipulation at the nanoscale results in medical improvements and/or significant medical changes, comes from the European Science Foundation:[11] "...the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain and of preserving and improving human health, using molecular tools and molecular knowledge of the human body." Hence, the size limitation imposed in the NNI's definition must be abandoned, especially when discussing nanopharmaceuticals or nanomedicine. An internationally acceptable definition and nomenclature of nanotechnology should be promptly adapted.

Nanotechnology and Drug Companies

Pharmaceutical companies face enormous challenges, ranging from revenue losses due to patent expirations on blockbusters to greater regulatory oversight and ever-increasing challenges from generic manufacturers. Drug revenues worth US$70–80 billion will potentially be lost by 2011 as various drugs go 'off-patent'.[12] The cost (often US$800 million+) and time involved (frequently spanning more than 10–15 years) in developing and launching a new drug to the market are daunting. Annual research and development (R&D) investment by drug companies has risen from US$1 billion in 1975 to US$40 billion today, while annual new drug approvals in the past few years have remained flat at between 20 and 30 drugs.[12]

Some argue that pharmaceutical companies are more focused on shareholder profits than innovative therapies. All agree that in today's global economy, big pharma faces enormous pressure to deliver high-quality products to patients while maintaining profitability. Therefore, it is not surprising that pharmaceutical companies are turning to miniaturisation and nanotechnology to enhance or supplement drug target discovery and drug formulation. In theory, nanotechnology should reduce the cost of drug discovery, design and development. It should enhance the drug discovery process itself through miniaturisation, automation, speed, massive parallelism and reliability of assays. The resulting improved R&D success rate should enable faster introduction of new, cost-effective products to the marketplace. For example, nanotechnology can be applied to current micro-array technologies, exponentially increasing the hit-rate for promising candidates/targets that can be screened. Inexpensive and higher-throughput DNA sequencers based on nanotechnology can reduce the time for both drug discovery and diagnostics.

The Rise of Nanopharmaceuticals

A long-standing issue in the drug industry is the difficulty of delivering the correct dose of a particular active agent to a specific disease site. Since this is generally unachievable, active agents have to be administered in excessively high doses, thereby increasing the odds of toxic side effects. The concept of site-specific delivery of a therapeutic arises from this classic drawback of traditional therapeutics. Nanopharmaceuticals have enormous potential in addressing this failure of traditional therapeutics – they offer site-specific targeting of active agents.[13] Such precision targeting via nanopharmaceuticals will reduce toxic systemic side effects, resulting in better patient compliance. Because of this, nanopharmaceuticals present novel opportunities for the reformulation of active agents whose previous versions were unsuitable for traditional oral or injectable delivery.

In this article, nanopharmaceuticals will be defined as colloidal particles of 10–1 000 nanometres (1 micron). Furthermore, in the absence of any standard convention or nomenclature for nanopharmaceuticals, various nanoscale structures of different sizes, shapes and chemical compositions have been included within this broad definition. Some of the common shapes include spheres (hollow or solid), tubules, particles (solid or porous) and tree-like branched macro-molecules.

Nanopharmaceuticals often offer an advantage compared with their 'bulk' counterparts primarily because of their reduced size (i.e. an

enormously increased surface area relative to volume). As a particle's size decreases, a greater proportion of its atoms are located on the surface relative to its core, often rendering the particle more reactive and more water-soluble. Nanopharmaceuticals are selected for characteristics such as biodegradability, biocompatibility, conjugation, complexation or encapsulation and their ability to be functionalised. For simplicity, they can be divided into two groups:[13]

- those where the active agent acts as its own polymeric carrier and possesses intrinsic therapeutic properties (examples include multivalent dendrimers, cerium oxide and platinum nano-particles); and
- those where the active agent is directly coupled (functionalised, entrapped or coated) to a distinct polymeric carrier. In the ideal futuristic situation, these polymeric (or lipid) carriers will be able to transport the active agent to a specific desired target site (ligand, receptor, active site, etc.) to impart maximum therapeutic activity with maximum safety (i.e. protecting body tissues from adverse reactions while preventing the degradation/denaturation/inactivation of the active agent during delivery/transit).

Nanopharmaceuticals are synthesised by various methods (self-assembly, vapour or electrostatic deposition, aggregation, nano-manipulation, imprinting, etc.) where the protocol is dictated by factors such as the specific therapeutic used and the desired delivery route. The functional complexity of nanopharmaceuticals is the result of:

- the large variety of polymeric nanomaterials they are composed of (e.g., liposomes, carbon nanotubes, dendrimers, colloidal gold, nanocrystals, fullerenes, etc.);
- the therapeutics that are packaged with these nanomaterials (e.g. small-molecule drugs, proteins, nucleic acids, etc.);
- the targeting moieties that can be surface-functionalised thereto (e.g. antibodies, ligands, etc.);
- the route of delivery (oral, topical, intravenous, etc.);
- their shape/geometry;
- chemical composition;
- their nano-scale dimensions (large surface-area-to-volume ratio);
- their surface charge; and
- unique release properties.

Nanopharmaceuticals typically accumulate non-uniformly within the body and their ultimate location is determined by their size, distribution, surface charge and surface properties. In fact, these properties can be tuned to provide long or short circulation times. Furthermore, their release kinetics can be adjusted to match the mechanism of action of the active agent making up the nanopharmaceuticals. For example, if a prolonged exposure to the active agent is desired, slow release is the preferred approach.[14] Targeting to specific tissue sites (e.g. hepatocytes versus Kupffer cells in the liver[15]) can be achieved by linking specific ligands or molecules (e.g. antibodies, glycoproteins, etc.) to the polymeric carrier or altering the surface characteristics of the polymeric carrier so that it evades the reticulo-endothelial (RES) system.

Although there are quite a few FDA-approved nanopharmaceuticals (see *Table 1*), several others are under development or nearing commercialisation. The elongated timeline is a consequence of the extremely complex and demanding requirements of clinical trials by the FDA. In future, nanopharmaceuticals will greatly influence medical practice and healthcare because of their ability, in many cases, to shorten the time-market for active agents, extend the economic life of proprietary drugs and create additional revenue streams. However, if this is to occur effectively, there are a few key biological requirements for nanopharmaceuticals to fulfill. They must:

- exhibit 'stealth' qualities to evade macrophage attack and the immune response;
- be non-toxic and traceable;
- display effective pharmacokinetic properties;
- be biodegradable following systemic administration through any route (but the polymer must protect the embedded active agent); and
- be selective to be effective in targeting tissue sites.

Size Does Matter in Drug Delivery

The market for the use of nano-drug delivery in 2005 was US$1.3 billion, with a 35% annual growth-rate projected for the next five years.[14] As explained in the previous section, the size and surface properties of nanopharmaceuticals (including the presence of targeting moieties) largely dictate their *in vivo* behaviour. Specifically, these properties permit systemic circulation and determine their biodistribution within the human body. Therefore, an understanding of these properties can aid in designing nanopharmaceuticals that can be localised to specific tissue/body sites. The small size of nanopharmaceuticals imparts them with unique properties in contrast to larger particles – it is this small size that allows them access to places in the human body where larger particles cannot reach. It is generally accepted that for systemic applications, the diameter of nanopharmaceuticals should be in the range of 10–100 nanometres, with minimum surface charge.[17] As discussed earlier, nanopharmaceuticals have a high surface-to-volume ratio compared with their larger counterparts, and therefore their surface properties are critical to their *in vivo* performance. In fact, their interaction with the local environment (which, again, is the end result of a combination of size and surface properties) determines whether they will be lost to undesired locations within the body. Various approaches focus on both minimising non-specific binding of nanopharmaceuticals to undesired tissue surfaces and reducing interactions with each other. The endothelial surfaces as well as the cell membranes are typically negatively charged, which repels negatively charged nanopharmaceuticals. Also, as the surface charge on the nanopharmaceuticals becomes larger (either positive or negative), a greater clearance by the macrophage-mediated RES is generally observed. In this context, synthesis of sterically stabilised nanopharmaceuticals is the subject of active R&D. For example, incorporation of polyethylene glycol (PEG) polymers on the surface of nanopharmaceuticals (i.e. PEGylation) provides a means of increasing solubility, reducing immunogenicity, prolonging half-life and preventing rapid renal clearance via the RES (due to larger particle size resulting from PEGylation).[18] In addition, it may be necessary to design nanopharmaceuticals that can undergo efficient intracellular uptake and target specific organelles.[19]

Numerous active agents can be delivered in the form of nanopharmaceuticals via a variety of routes (see *Table 1*). Nanopharmaceuticals are better suited than their microparticle counterparts for intravenous (IV) delivery because the tiniest capillaries are in the 5–6 micron range, a size that impedes most microparticles (or aggregations thereof) from distributing into the bloodstream. The blood–brain barrier (BBB) and the blood–retinal barrier (BRB) protect

the brain and eyes, respectively, due to their unique anatomical features, including the presence of tight junctions that seal adjacent cells. The BBB has strict size and surface property limitations for entrance. For gene delivery, both viral and non-viral vectors have been generally unsuccessful – the former are unable to penetrate the BBB or the BRB, while the latter lack sufficient efficiency. On the other hand, nanopharmaceuticals have been shown to cross biological barriers and may be able to cross both the intact BBB[20] and the BRB.[21] Often, nanopharmaceuticals can be delivered directly to the nervous system (NS) without prior need for drug modification or functionalisation (which can affect function). Moreover, both hydrophilic and hydrophobic therapeutics can be delivered without first opening the BBB. However, in this context, systemic delivery for non-NS diseases is of general concern because these agents may cross the BBB and cause brain damage or psychoactive effects.

Nanopharmaceuticals can also permeate the tight epithelial junctions of the skin that normally impede delivery of active agents to the desired target.[22] Topical emulsion systems incorporating nanoparticles are being developed that rapidly permeate tissue to delivery actives or remove lethal toxins from the bloodstream. Nanopharmaceuticals of specific size (generally greater than 10nm) can be designed so that they are able to penetrate tumours due to the 'leaky' nature of the tumour microvasculature. This classic effect, referred to as the enhanced permeability and retention (EPR) effect, results in prolonged particle circulation and accumulation within the tumour.[23] It is generally accepted that nano-particles in the 10–100nm size range and with a slightly positive or slightly negative surface charge should be able to disseminate within tumours when delivered to the circulatory system.

By controlling both the particle size and architecture of nanopharmaceuticals, a particular pharmacokinetic release profile of the drug may be generated. Often, a near zero-order kinetic drug release profile is desired since it maintains a steadier therapeutic concentration at the site of delivery. Such a profile is more likely to be achieved by nanopharmaceuticals where a drug has been functionalised onto or encapsulated within a polymeric carrier matrix. Nano Del Technologies (Germany) employs just such an approach where polymeric nanoparticles serving as 'Trojan horses' have been functionalised via a variety of active agents. For oral applications, research has focused on lymphatic uptake of nanopharmaceuticals by the Peyer's patches of the gut-associated lymphoid tissue (GALT). It has been shown that during oral delivery, nanopharmaceuticals are disseminated systemically while their microparticle counterparts remain in the Peyer's patches.[24] Particle size has an impact in another way as well. The efficiency of drug distribution within various body cavities is influenced, in part, by the size of the drug particles. As the particle size of a drug decreases, its total surface area increases exponentially. This reduction in particle size increases its dissolution rate and saturation solubility, which frequently correlates to improved *in vivo* drug performance.[25,26] In some cases, the pharmacokinetic behaviour of nanopharmaceuticals may help minimise peak plasma levels (which may be toxic), as well as prevent a drop below the targeted therapeutic range (which may lower efficacy).

It is known that drugs with poor bioavailability often result in a higher cost to the consumer, not to mention the inefficient treatment and increased risk of toxicity. Ironically, due to the high-throughput technologies available today, there has also been an increase in the number of potential new chemical entities (NCEs) that are poorly water-soluble.[27,28] In recent years, various nanoparticle technologies have been successfully employed to tackle drugs with this low water (or lipid) solubility.[28–30] In fact, numerous pharmaceutical companies are revisiting shelved drugs that are 'difficult' from a formulation point of view and relying more on nanotechnology to address these formulation challenges.

Because consumers prefer oral drugs to implantables or injectables, nanoengineering traditional or shelved compounds could greatly enhance oral bio-availability in some cases. A classic example of improving the bio-availability of poorly soluble drugs is Ireland-based Elan Corporation's NanoCrystal® technology. This is an enabling technology for evaluating NCEs that exhibit poor water solubility. It can also serve as a valuable tool for optimising the performance of current drugs. NanoCrystal® technology can be incorporated into both parenteral and oral dosage forms. The particles are produced by proprietary attrition-based wet-milling techniques that reduce the size of drug particles to less than one micron.[30,31] This reduction in size substantially increases the surface area, and hence increases the solubility. The nanosized drug particles are then stabilised against agglomeration by surface adsorption of selected and generally safe (GRAS) stabilisers.[30] This results in a final product that behaves like a solution (a colloidal dispersion). Studies have shown that reformulating old drugs using this technology can enhance bioavailability compared with commercial products,[32] reduce the time to achieve maximum concentration (C_{max}) and increase the area under the curve (AUC) during the first hour.[32,33] This technology may enable an increase in drug loading, thereby enhancing the maximum tolerated dose compared with commercial products.[34] The solid-dosage tablet formulation of the immunosuppressant sirolimus (Rapamune®) is the first marketed drug developed with NanoCrystal Technology and the first commercial launch of a nano-pharmaceutical (see *Table 1*). Other examples of reformulated FDA-approved drugs that employ this technology are fenofibrate (TriCor®), aprepitant (Emend®) and Megase® ES. It is interesting to note that the variability observed in the fasted and fed patients upon administration of micronised TriCor was not observed upon administration of the reformulated nanopharmaceutical.

It should be pointed out that reformulation of an existing drug into a 'nanoversion' often results in a novel NCE because it generally displays an altered pharmacokinetic profile (altered AUC and C_{max}) compared with its parent (larger) counterpart.[9,12] In other words, nanopharmaceuticals are usually not bioequivalent to their parent (larger) counterparts, and hence cannot apply for FDA approval via an Abbreviated New Drug Application (ANDA) route. Clearly, if the nanopharmaceutical is bioequivalent to its parent (larger) version, an ANDA can be filed to seek regulatory approval. The FDA approval process for NCEs generates two benefits for the innovator: the new drug enjoys a three- to five-year non-patent exclusivity period that prevents generics from entering the marketplace, and under the Hatch Waxman Act, the owner can recover some of the patent term lost due to delay caused by the FDA regulatory review process.

Conclusions and Future Prospects

From a business point of view, nanopharmaceuticals offer the ability to extend the economic life of proprietary drugs and create additional revenue streams, thereby significantly affecting the drug commercialisation landscape. Although early forecasts for commercialisation are encouraging, there are currently several challenges and risks that beset the commercialisation of

Table 1: Selected US Food and Drug Administration-approved Nanopharmaceuticals*

Drug Product/ Brand Name	Nanoparticle Drug Component/ Active Ingredient(s)	Delivery Route	Manufacturer/Alliance	Indication(s)	FDA Approval Date
Doxil, Caelyx (outside the US)	PEGylated doxorubicin (Adriamycin)HCl liposomes (80–90nm)	IV	OrthoBiotech, Schering-Plough	Metastatic ovarian cancer and AIDS-related Kaposi's sarcoma	November 1995
Abraxane	Paclitaxel (taxol)-bound albumin nanoparticles (~120nm)	IV	Abraxis BioScience, AstraZeneca	Various cancers	January 2005
AmBisome	Amphotericin B liposomes (~45–80nm)	IV	Gilead Sciences	Fungal infections	August 1997
Rapamune	Nanocrystalline sirolimus	Oral solution, oral tablet	Wyeth, Elan	Immunosuppressant for kidney transplants	September 1999
TriCor	Nanocrystal fenofibrate	Oral tablet	Abbot, Elan	Primary hypercholesterolaemia, mixed lipidaemia, hypertriglyceridaemia	November 2004
Emend	Nanocrystal aprepitant	Oral capsule, IV	Merck, Elan	Nausea in chemotherapy patients	March 2003
Diprivan	Propofol liposomes	IV	Zeneca Pharmaceuticals	Anaesthetic	October 1989
Renagel	Cross-linked poly(allylamine) resin (sevelamer hydrochloride)	Oral tablet (capsule discontinued)	Genzyme	Control of serum phosphorus in patients with chronic kidney disease on dialysis	October 1998
Triglide	Nanocrystalline fenofibrate	Oral tablets	SkyePharma, First Horizon	Lipid disorders; markedly reduces elevated plasma concentrations of triglycerides, LDL and total cholesterol and raises abnormally low levels of HDL	May 2005
Myocet	Liposome-encapsulated doxorubicin-citrate complex	IV	Zeneus Pharma, Sopherion Therapeutics	cardio-protective formulation of doxorubicin used in late stage metastatic breast cancer	(Approved in Europe and Canada)
DepoCyt	Sustained release cytarabine liposomes	IV	SkyePharma, Enzon	Lymphomatous meningitis	April 1999
DaunoXome	Encapsulated daunorubicin citrate liposomes	IV	Gilead Sciences	Advanced HIV-related Kaposi's sarcoma	April 1996
Estrasorb	Estradiol hemihydrate micellar nanoparticles (emulsion)	Transdermal	Novavax	Reduction of vasomotor symptoms, such as hot flushes and night sweats, in menopausal women	October 2003
Macugen	PEGylated anti-VEGF aptamer	Intravitreal	OSI Pharmaceuticals, Pfizer	Neovascular age-related macular degeneration	December 2004
Abelcet	Amphotericin B phospholipid complex	IV	Enzon	Invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy	November 1995
Adagen	PEGylated adenosine deaminase	IV	Enzon	Enzyme replacement therapy for patients with severe combined immunodeficiency disease	March 1990
Pegasys	PEGinterferon alfa-2a	Subcutaneous	Nektar, Hoffmann-La Roche	Chronic hepatitis C virus infection	October 2002
Somavert	PEGvisomant (PEG-hGH)	Subcutaneous	Nektar, Pfizer	Acromegaly	March 2003
Neulasta	PEG-G-CSF or PEGfilgrastim (covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol)	Subcutaneous	Amgen	Febrile neutropenia	January 2002
Copaxone	Glatiramer acetate (copolymer of L-glutamic acid, L-alanine, L-tyrosine and L-lysine)	Subcutaneous	TEVA	Relapsing–remitting multiple sclerosis	December 1996
Amphotec	Colloidal suspension of lipid-based amphotericin B (~115nm)	Subcutaneous	Sequus	Invasive aspergillosis patients who are refractory to or intolerant of conventional amphotericin B	November 1996
PEGIntron	PEGinterferon alfa-2b	Subcutaneous	Enzon, Schering-Plough	Chronic hepatitis C virus infection in patients with compensated liver disease	January 2001
Oncaspar	PEGasparginase	Subcutaneous	Enzon	Leukaemia	February 1994
Epaxal	Hepatitis A vaccine adjuvanted with immunopotentiating reconstituted influenza virosomes (IRIV)	Intramuscular (in the deltoid muscle)	Berna Biotech	Active immunisation against hepatitis A for adult and children >12 months (age may vary and depend on the country)	(Available in Canada and elsewhere)
Elestrin	Estradiol gel (0.06%) incorporating calcium phosphate nanoparticles	Transdermal	BioSanté	Treatment of moderate to severe hot flushes in menopausal women	December 2006

**Note that therapeutic approval by the US Food and Drug Administration (FDA) does not necessarily indicate that the therapeutic is available to consumers. Myocet and Epaxal have not been approved by the FDA.*

IV = intravenous; PEG-hGH = pegylated human growth hormone; PEG-G-CSF = pegylated granulocyte colony-stimulating factor; PEG = polyethylene glycol; VEGF = vascular endothelial growth factor; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

nanopharmaceuticals. Some formidable challenges include legal, environmental, safety, ethical and regulatory questions as well as emerging thickets of overlapping patent claims.[35,36] The emerging thicket of nanopharmaceutical patent claims has resulted from patent proliferation and also because of continued issuance of surprisingly broad[37] and/or overlapping[38] patents by the PTO. In fact, patent systems in general are under greater scrutiny and strain, with patent offices around the world continuing to struggle with evaluating the swarm of nanotechnology-related patent applications.[8,9] Added to this is the confusion around NNI's definition of nanotechnology, which is inaccurate and irrelevant in relation to nanopharmaceuticals. As nanopharmaceuticals move out of the laboratory and into the clinic, federal agencies such as the FDA and the PTO will continue to struggle to encourage their development while imposing some sort of order. At present, both of these critical agencies are in flux, and their credibility has sunk to an all-time low. It is hoped that desperately needed reforms to overhaul the PTO and the decades-old US patent system,[39-41] along with clearer regulatory/safety guidelines from the FDA regarding nanopharmaceuticals,[12] will be forthcoming.

Investors have been cautious as to what route, if any, the FDA will take in regulating nanopharmaceuticals in the future. Undoubtedly, regulating nanopharmaceuticals will require greater co-operation between drug companies, policy-makers and drug regulators. Although the FDA has previously downplayed the safety issues of nano-scale products,[42] it is starting to recognise that there are knowledge gaps in this area. In light of these challenges, a multidisciplinary team of experienced drug-regulators from the drug, biologic and device areas of the FDA (working with a scientific panel of experts), should: identify the unique safety issues associated with nanopharmaceuticals, develop a new paradigm for evaluating data pertaining to their safety and efficacy and assist in developing unique tools and techniques to characterise nanoscale materials (with an eye on quality, safety and effectiveness). As nanotechnology begins to appear in a wide variety of products, the safety and effectiveness of those products will warrant careful review because size changes within the nanoscale are likely to add additional complexity to the FDA product review process. Generally, nanopharmaceuticals may be viewed by the FDA as technologically overlapping from a review perspective. Therefore, they may be considered as 'combination products', for which established examination guidelines are already in place.

In the future, novel 'multifunctional' nanopharmaceuticals will be designed and delivered to the human body via a variety of routes. It will be imperative that each of these be evaluated and characterised on a case-by-case basis in an effort to correlate nano-pharmaceutical physiochemical property with biological behavior and therapeutic outcome. In this regard, any research strategy must involve adsorption, distribution, metabolism and excretion (ADME) testing, toxicology tests and physiochemical characterisation. Given this backdrop, it is hard to predict the exact course nanomedicine and nanopharmaceuticals will take. This author believes that, eventually, all of these undertakings will expand the burgeoning field of nanopharmaceuticals. It is likely that pharma and biotech will embrace nanopharmaceuticals, especially if they offer novel properties that address unmet medical needs and if their development costs and risks are low. ■

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