



## **Focus Report**

### **Nanotechnology and therapeutic delivery**

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**Authors:**

Richard Moore, Institute of Nanotechnology (IoN), Jörn Glökler, Nano & Micro Technology Consulting (NMTC), Matthias Werner, Nano & Micro Technology Consulting (NMTC);

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**Contact:** [richard.moore@nano.org.uk](mailto:richard.moore@nano.org.uk)

[www.observatorynano.eu](http://www.observatorynano.eu)

# Nanotechnology and therapeutic delivery

## Executive Summary

The administration of certain types of modern drugs by conventional means often suffers from a number of drawbacks such as the limited solubility of the drug, poor distribution within the body, lack of selectivity, unfavourable pharmacokinetics and damage unintentionally inflicted on healthy tissues.

To try to overcome these problems, research on drug delivery forms a significant part of overall pharmaceutical research and the market for drug delivery has an estimated size of around 15% of the total pharmaceutical market, around \$109 billion in 2008. The objectives of such research include:

- maintaining drug levels within their therapeutic ranges for longer periods;
- effectively targeting drug delivery to the desired site of action;
- varying the drug dose to achieve the optimum outcome
- facilitating the administration of active substances with otherwise short *in vivo* half-lives;
- reducing the overall amount of drug needed; and as a consequence,
- decreasing drug toxicity and side effects.

The application of nanotechnology is beginning to play an increasingly important role in therapeutic delivery as the characteristics of materials at the nanoscale, such as high surface area, solubility, and size can contribute towards achieving some of these objectives. Particular opportunities for nanotechnology in therapeutic delivery include:

- developing systems that improve the solubility and bioavailability of hydrophobic drugs;
- improving the delivery of protein-based drugs;
- improving the delivery and efficacy of drugs for common conditions such as asthma and osteoarthritis, and for diseases increasingly prevalent in a demographically-ageing population
- designing delivery vehicles that can improve the circulatory presence of drugs;
- delivering drugs across the blood-brain barrier;
- increasing specificity and decreasing toxicity;
- designing mechanisms to target drugs to specific cells or tissues resulting in lower overall systemic drug concentrations whilst maintaining the effective dose at the site of delivery;
- developing delivery systems for the slow or continual release of drugs, sometimes in conjunction with an implant or other medical device;
- improving vaccine adjuvants and delivery
- delivery of cells and cell products
- delivery of other agents, e.g. diagnostics, plastids

- developing novel nanostructures that can be used in specific applications, e.g. ocular, wound management, cancer therapy, neurology, orthopaedics;
- developing delivery systems that can be used in conjunction with medical external devices, e.g. for imaging or to supplying an external source of energy for drug targeting or activation/release.
- stabilizing the structure of the drug
- increasing the shelf life of drugs
- reducing the costs of drugs to healthcare systems

This report examines some of the opportunities that the application of nanotechnology may offer towards meeting these objectives and provides examples of companies known to be developing nanoscale drug delivery systems.

The report also provides an overview of the business opportunities and challenges concerning nanoscale drug delivery. For many pharmaceutical companies, the technology may present opportunities to extend the limited patent life or find new therapeutic indications for existing drug molecules and for others, the opportunity to develop entirely new applications and classes of drugs as well as a more individual patient-centred drug regimen approach.

The report also considers other challenges such as safety aspects and how drug regulatory systems will address nanotechnology as well as the economic challenges faced by healthcare providers due to price constraints and a demographically-ageing European population.

## Introduction

### Definition

For the purposes of this combined report the following definition has been adopted:

***nanoscale drug delivery:*** the discovery and application of innovative methods based on nanoscale science and nanotechnology to enhance the targeting, efficacy and safety of new and existing therapeutic agents for the purposes of improving human health.

### Keywords

Pharmaceuticals; drugs; drug delivery; drug delivery systems; nanotechnology; nanoscience; nanoscale; nanoparticles; nanomaterials; therapy; human health

### Overview

Drug delivery commands a sizeable proportion of the overall pharmaceutical market (estimated at approximately 15% or around \$109 billion in 2008). It is also expected to grow at a faster rate than the overall pharmaceutical market over the next four years. Reasons include extending the patent life for existing drugs, and offering new alternatives for delivery, in particular for providing solutions for oral

delivery of drugs that are normally broken down in the alimentary canal. In all of this, nanotechnology is a major enabler. Previously insoluble drugs can be re-packaged or formulated both increasing efficacy and decreasing the need for solvents. Greater stability can also be achieved using novel nanostructured materials and processes utilising nanotechnology. Such developments are accompanied by strategic collaborations within the pharmaceutical industry, and mergers and acquisitions are also becoming the norm.

This report provides a brief overview of the emerging nanoscale drug delivery field and a market analysis. It concludes with profiles of some emerging companies in this fast-developing field.

## **Methodology**

Market figures have been quoted on the basis of available market data from press releases, company reports and internet websites including so far unpublished market research studies. However, it should be taken into account that reported market figures are only estimates.

Additionally, experts in the field have been questioned for the critical assessment of the current state of nanotechnology applying nanotechnology to drug delivery. Where appropriate, these assessments are indicated by annotation in the text of the report.

Company profiles have been identified via various reports, conference proceedings and internet searches.

## **Science and technology aspects**

### **Clinical needs in drug delivery**

Administering drugs by conventional means often suffers from a number of drawbacks such as their limited solubility, poor distribution within the body, lack of selectivity, unfavourable pharmacokinetics and damage unintentionally inflicted on healthy tissues. There has been a great deal of research and development devoted to addressing these problems resulting in a broad range of novel delivery systems.

Common aims of drug delivery systems include:

- the continuous regulation of drug levels within the therapeutic range;
- effective targeted delivery;
- reducing the amount of drug needed and; as a consequence,
- decreasing toxicity and side effects.

Modern delivery systems also allow the administration of active substances with otherwise short *in vivo* half-lives. Another approach to meeting these aims has been via drug releasing micro-devices designed to operate from several days to a year.

Two major problems for novel biotechnology-based drugs are their mode of delivery and relative instability in the body. Most current delivery methods for biological drugs involve oral ingestion (frequently the preferred route of delivery and accounting for more than \$15 billion in annual sales globally) or injection, which are not necessarily ideal for many indications.

Oral delivery via tablets or capsules is sometimes inefficient due to exposure of the pharmaceutical agent to the metabolic processes of the body, resulting in both a larger than necessary dose to achieve the necessary therapeutic outcome and reduced effectiveness of the drug through to breakdown before it has reached its active site. Intravenous administration can also be problematic. Specificity for intravenously injectable drugs is often low, necessitating the delivery of large amounts of a drug, thereby creating a high concentration of the drug in the bloodstream that can potentially lead to toxic side effects.

Because biological systems interface with their surroundings via biomolecules and multi-molecular systems operating at the nanoscale (generally defined as 1-100nm but for nanomedical purposes sometimes extending to several hundred nanometres) and because science and technology have now reached the stage where complex manipulation at the nanoscale is possible, considerable interest has recently been focused on the potential to utilize nanotechnology in the medical and lifesciences sectors. As cell systems largely function at the nanoscale, there is considerable focus on manipulating molecules and structures that can interface with such processes.

The use of macromolecules, such as monoclonal antibodies, as therapeutic agents has increased greatly in recent years. The biodistribution and delivery problems and issues for protein-based drugs are shared to a substantial degree with other emerging therapeutic approaches, including pharmacologically active nucleic acids and nanoparticles.

Solving these challenges includes consideration of the multiple biological barriers between the macromolecular drug or nanoparticle at its site of administration and its ultimate biological target. Considerations of size, stability, non-specific versus specific associations, and potency versus toxicity are all important. The creation of delivery approaches that combine high specificity for the target cell or tissue, a high therapeutic payload, and a reduction in toxicity remain a challenge. Recently, new approaches have emerged in relation to drug design and drug targeting based on both combinatorial library methods and bottom-up synthesis. Greater understanding of cell surface receptors, and the ability to synthesise targeting molecules that recognise and bind to these, will facilitate advances in the targeted delivery of highly customised macromolecules and nanostructures.

The overall goal for any optimal drug therapy strategy is to meet the needs of the patient while improving the efficiency and safety of the administered drugs. Innovative drug delivery approaches play a crucial role in ensuring and predicting the delivery of promising and successful drugs to the target site of delivery in the human body.

Historically, the pharmaceutical industry has generally maintained and enjoyed strong financial earnings and business growth. Such growth is not only made possible by launching new products but also by the increasingly significant "life-cycle management" of older, existing products. This aspect becomes even more important once the revenue from a therapeutic molecule drops significantly due to the expiry of its patent protection. Furthermore, the length of time required for regulatory approval of a newly discovered drug (an average of around nine years) and the relatively low number of new drugs approved onto the market (only 34 new drugs and biologics in the US in 2009) has increased pressure on pharmaceutical companies.

In the light of these challenges, the introduction of new delivery systems for existing drugs, many of which are still therapeutically effective, such as controlled rate, slow delivery and targeted delivery are being pursued very vigorously by many pharmaceutical companies, both to better meet patients' needs

and also to maintain market share in an increasingly global and competitive marketplace. One example is the development of transdermal systems for the delivery of drugs in chronic illness. Preparation is relatively simple and the product can last for an extended period. The delivery method also overcomes some of the drawbacks of other methods such as immune scar formation. In addition, life-cycle management, patient compliance, improved drug stability and optimization of the drug absorption process are some of the key drivers for developing alternative delivery systems for drugs.

### **The blood-brain barrier and related delivery challenges**

Many neurological disorders are difficult to treat because of natural barriers within the body. The blood-brain barrier, in particular, is a specialized system of endothelial cells that line the capillaries in the brain and act as a protective mechanism for the brain, blocking by “tight junctions” the entry of harmful substances while allowing in necessary nutrients. The barrier is necessary to keep the brain and the central nervous system healthy.

Due to these characteristics, the blood-brain barrier causes problems in drug delivery because it treats many medications as potentially toxic compounds and excludes or denatures them, preventing the drugs from doing their job. Hence many promising drugs cannot cross the barrier by passive diffusion in large enough amounts to be effective or require active transport mechanisms.

In addition to the blood-brain barrier at the level of brain microvessels there are other specialized neural barriers, for example in the eye, the ear and in the CNS and peripheral nervous system that function in equivalent ways.

### **Some key target areas for the application of nanotechnology to drug delivery**

Key areas in which there is major potential for nanotechnology to be applied in drug delivery include:

- developing systems that improve the solubility and bioavailability of hydrophobic drugs
- developing stabilizing agents that keep drugs in their correct form without breakdown in an unrefrigerated environment
- developing proformulations
- improving the delivery of protein-based drugs
- designing delivery vehicles that can improve the circulatory presence of drugs
- delivering drugs across the blood-brain barrier
- reducing toxicity
- increasing specificity
- designing mechanisms to target drugs to specific cells or tissues, including nanoparticulate systems that incorporate layers for binding to cells, intake and release in a specific compartment
- developing delivery systems for slow release
- improving vaccine adjuvants and delivery
- developing novel nanostructures that can be used in specific applications, e.g. ocular, wound management, cancer therapy, neurology, orthopaedics
- new delivery or formulation approaches aimed at reducing costs

## The state of R&D in nanoscale drug delivery

### Nanostructures under development for drug delivery applications

A wide variety of nanostructures can be used as drug delivery vehicles and may at the same time offer significant advantages over traditional delivery mechanisms.

Some of the advantages of nanoscale drug delivery include high stability, high carrying capacities, the ability to transport both hydrophilic and hydrophobic molecules, and the possibility of utilising novel routes of administration including oral application and inhalation. Nanoparticulate systems can also be designed that permit controlled release of the drug from a supporting matrix. Together, these properties can improve drug bioavailability, reduce dosing frequency, and alleviate the problem of non-adherence to therapy.

Nanoparticles may be monolithic (nanospheres) where the drug is adsorbed, dissolved, or dispersed throughout the matrix, or vesicular where the drug is carried in an aqueous or lipid core surrounded by an enclosing wall. Alternatively, the drug molecules can be covalently attached to the surface or within the matrix.

Nanoparticles may be made from natural materials such as gelatin, albumin or gold, from synthetic biocompatible and biodegradable polymers (e.g. polylactides, polyalkylcyanoacrylates), or from solid lipids. Once at the target site in the body, the drug payload may be released from the nanoparticle by diffusion, swelling, erosion or degradation. Active systems are also in development, e.g. drug release or enhancement of action in response to the input of external energy such as targeted ultrasound or light, as well as the active targeting of delivery systems based on magnetic nanoparticles to their intended site of action.

The following non-exhaustive list illustrates the wide variety of types of nanoparticles and nanomaterials under study and development as vehicles for nanoscale drug delivery:

- polymeric nanoparticles
- polyketal nanoparticles
- solid lipid nanoparticles
- nanoparticle-aptamer and other conjugates
- colloidal gold nanoparticles
- dendrimers
- hyperbranched polymers
- dendritic polymer-drug conjugates
- nanoshells
- nanocrystals
- niosomes
- micelles
- fullerenes
- carbon nanotubes and nanohorns
- chitosan and lecithin nanoparticles
- nanosponges
- nanodiamonds
- implantable drug-carrying nanofilms

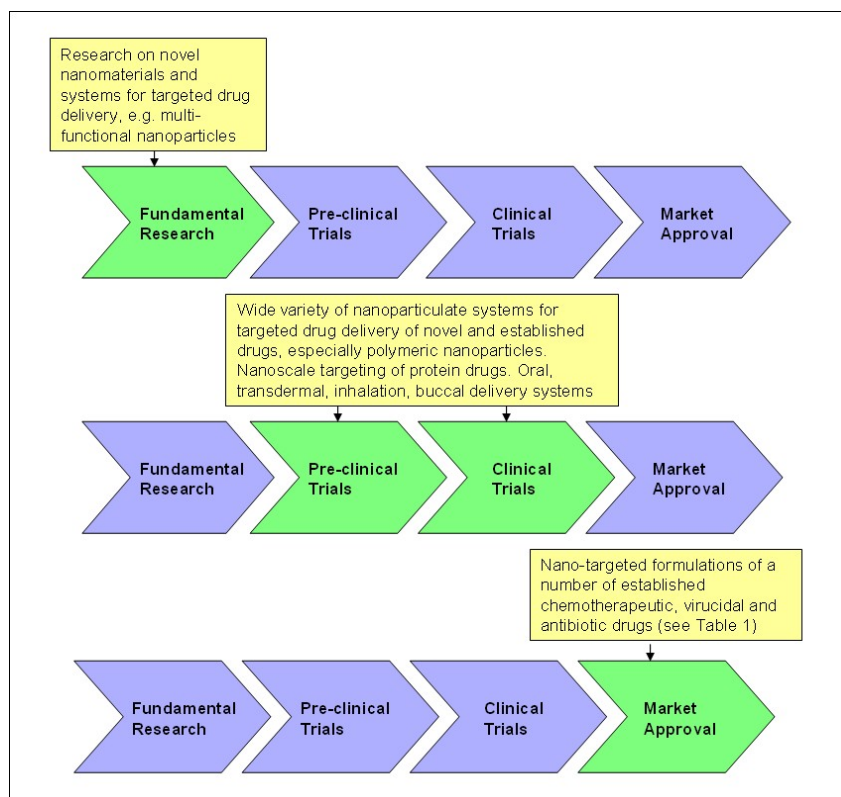


Figure 1. Stages in development of some nanoscale drug delivery systems

## Economic aspects

### General market description

#### Overview

The availability of visualisation, measurement, fabrication and simulation tools has enabled scientists to better understand biological systems and their behaviours. As described in the first part of this report, this has created opportunities for developing new structures with novel properties like nanocrystals, nanotubes, nanoshells which are starting to find applications in drug delivery systems. Advanced knowledge in DNA manipulation and developments in array technology, combined with increased simulation capabilities, are also creating opportunities for new alternative methods to the use of animal testing in drug development.

While soaring drug development costs, complex patent management programmes and competition from generic manufacturers are currently redefining the shape of the pharmaceutical industry, the availability of new tools and techniques enabled by nanotechnology are helping researchers to better understand cellular activities and provide appropriate solutions. Some of these include better solubility, targeted and controlled delivery, and prolonged availability in the target location.

While some of the nanotechnological developments in drug delivery are enhancing the value of already established activities, others are creating new formulations and entities for entirely new applications.

Although there are currently relatively few nano-delivered drugs on the market (estimated at around 50 at the time of publication of this report), many are in the pipeline at different stages of development. In the next 5 -10 years, a rapid increase in the number of nanotechnology-based drugs is expected. Venture and government organizations have facilitated the generation of new spin-offs and start-ups, and have played an important role in the R&D and commercialization activities of new companies. This section briefly analyzes how different forces have shaped the nanotechnology-based drug delivery market, who the key players are, how much the market is worth and how pharmaceutical companies are accommodating new technologies.

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Figure 2. Some key drivers of Change

### Competition

Soaring costs, high failures in R&D programmes and increased competition from generic drug companies are putting immense pressure on pharmaceutical manufacturers. Companies which relied on organic expansion for growth in the past are now increasingly involved in mergers and acquisitions (M&A), horizontal and vertical integrations, as well as divestments, to remain competitive in the market and to maximise profits. There were record-breaking M&A activities during 2006 and 2007. However, due to the lack of cash in the market following the credit turmoil of 2007, acquisition activities were affected during 2008 and 2009. In the nanoscale drug delivery field, the trend is that smaller specialist companies are increasingly licensing their technologies to larger pharmaceutical manufacturers. Companies are increasingly favouring collaboration and co-operation to develop and market their technologies. This new

idea of 'coopetition' is helping smaller companies to use the supply chain and marketing resources of their partners, and to reach expanding global markets.

### Emerging markets

The emerging pharmaceutical market in countries such as Brazil, Russia, India and China along with Mexico, South Korea and Turkey is expected to have an annual growth rate of 12 -14 % over the next few years. Of interest is that the private health insurance market is also growing at a high rate in these countries. It was estimated that these markets would contribute nearly 25% of the total pharmaceutical growth in 2008<sup>1</sup>. These tremendous opportunities have also brought a number of challenges as the companies involved have had to deal with different governmental rules, intellectual property laws, procurement and licensing laws, and regional disparities. Similarly, they have faced immense competition from domestic players and other international competitors. Future revenue growth of major companies will depend to a large extent on how efficiently they adapt their strategies to suit these markets.

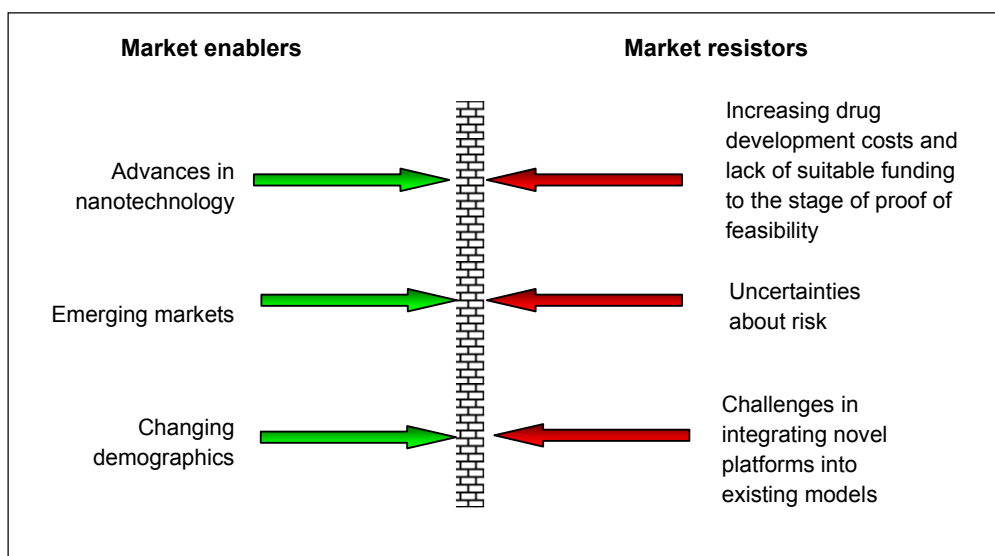


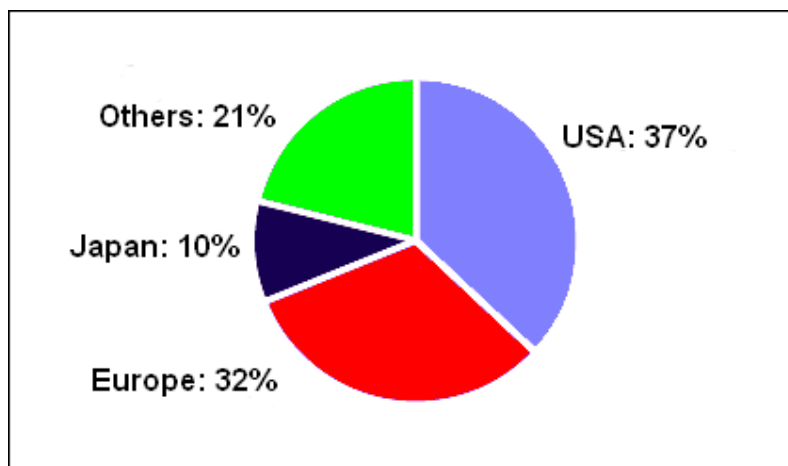
Figure 3. Enablers and resistors in the global drug delivery market

### Key players and the competitive environment

The increasing emphasis on targeted drug delivery and controlled drug release has played an important role in accelerating innovation through nanotechnology. The ability to provide prolonged availability, better control and better solubility of drugs has increased the application of nanotechnology to drug delivery technologies. Such properties are also expected to reduce the number of doses required, make treatment a better experience and reduce treatment expense.

In recent years, the global pharmaceutical market has grown at a rate of 5 - 6% annually. This trend is expected to continue for the next few years with an expected cumulative market growth of 5.9% between 2008 and 2012. The global pharmaceutical market is expected to grow from \$740 billion in 2008 to \$930 billion in 2012.

Over the same period, the global drug delivery market is expected to grow from \$109 billion to \$157 billion with a growth rate between 8.5% - 9.5%, accelerated by growth in the oral drug delivery market and new innovations enabled by nanotechnology. Nanotechnology will help companies to extend the lifecycle of existing products and will also help them to develop better formulations and identify new chemical entities. By 2008, Europe's share of the world market had grown to 32% from 26% in 2003, primarily due to the strength of the Euro against the US dollar (see figure 4).



**Figure 4: Global pharmaceutical market shares in 2008** (Source: IMS Health, vfa ([www.vfa.de/en/statistics/pharmaceuticalmarket/](http://www.vfa.de/en/statistics/pharmaceuticalmarket/)))

The current drug delivery market is led by oral drug delivery systems which account for around 38% of the market followed by pulmonary delivery systems with a market share of around 27%. However, it is estimated that, by 2012, oral drug delivery will increase its market share to 39% along with the combined transmucosal and transdermal sector which will increase its share from 9% to 13%.

The presence of nanotechnology in the drug delivery market is gaining visibility and new nanotechnology-delivered products are in advanced pipeline development. As an example Australian pharmaceutical development company Starpharma reported positive results in March 2010 from a clinical trial of the company's dendrimer-based VivaGel® product intended for use in preventing bacterial vaginosis, genital herpes and HIV transmission, and as a condom coating. Flamel Technologies are also in the process of conducting Phase 2 clinical trials of recombinant interferon alpha-2b using its Medusa® self-assembled poly-aminoacid nanogel delivery system.

The delivery of drugs through oral/nasal routes is increasingly attracting market interest as they are considered to be convenient and painless methods of drug delivery from the patient's perspective. A US-based company, Nanotherapeutics, won a \$20 million contract from the US National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA), to develop an inhaled version of gentamicin for the treatment of respiratory infections. Such market requirements are acting as a driving force behind nanotechnology-based drug delivery innovations. Another factor driving nanotechnology in drug delivery is the requirement for improving the solubility of poorly soluble drugs. It is estimated that 1 in 10 marketed drugs have solubility problems and that two-thirds of the drugs in preclinical studies have the same issue.

The nanotechnology-based drug delivery market has so far been led by Elan Corporation, a Dublin-based company that has developed a highly successful nanocrystal platform technology. The technology has been incorporated into five launched products with a total of US\$1.8B+ annual in-market sales and over 1000 patents/patent applications in the US and rest of the world. Licensees include Wyeth (Rapamune (sirolimus)), Merck (Emend (aprepitant)), Abbott Laboratories (Tricor (fenofibrate)), Solvay (Lipanthyl (fenofibrate)) and Par Pharmaceuticals (Megace (megestrol acetate)). Megace sales of €130 million were expected by 2010. The sales of Rapamune are reported to be growing at 4% per year, Tricor has an estimated growth rate of 10% until 2010 and Emend has been growing at an average rate of 14% per year.

### **Drivers and barriers**

The complexity of the pharmaceutical industry is increasing year by year with changes accelerating on an international scale. Along with increased costs and changing demographics, the potential opportunities in emerging markets and competition from generic manufacturers are challenging the traditional major drug companies. This following section examines some of the most important factors that are expected to shape the drug industry in the coming years.

### **Funding issues in R&D**

A particular problem, particularly for smaller companies or university spinouts in Europe, may be the availability of suitable funding mechanisms or partnering opportunities, following the initial research stage, in order to bring the drug to the stage of proof of feasibility where major investors or larger companies may begin to take interest.

### **Development timescales**

On average it takes over nine years for a drug to reach the market from the start of its development. Once the product reaches the market, the traditional model comprises management of the drug life cycle, which involves developing and implementing strategic options that will add value. The traditional pharmaceutical operating model normally goes through the following steps between drug development and life-cycle management<sup>2</sup>.

- identifying the therapeutic agent
- generating active molecules and patenting them
- developing formulations and products
- proving efficacy and safety
- licensing the technology
- marketing the product
- building value through use and indications

Biopharmaceuticals generally fit well with this model, as the novel molecules developed by small companies can be considered as “new chemical entities” which are frequently acquired by large pharmaceutical companies through the processes of licensing, merger or acquisitions. However, the problem with novel drug delivery technologies is that there are no well-defined formulation processes. In addition, there are problems due to the lack of new molecules and delays in implementing new technologies.

To add to the problem, novel technologies frequently suffer from issues regarding intellectual property rights, uncertainty surrounding risks and crucial problems such as saleability and sterility. Large pharmaceutical companies often consider new drug delivery techniques as an add-on to solve specific formulation issues or to increase the lifecycle of the drug (see figure 5).

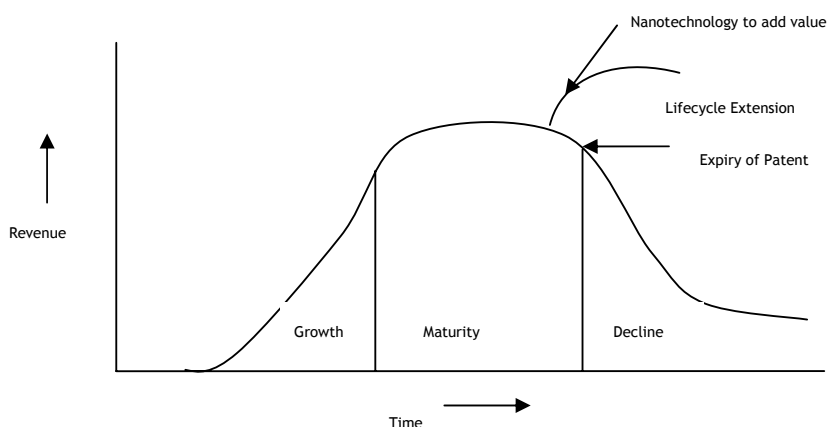


Figure 5. Extending the drug life-cycle

### New drug approvals and the rise of generics

In 2009, the FDA approved 34 new drugs and biologics, three more than in 2008. Across all the drugs in the pipeline, an average of 30 to 40 new drug and biologic approvals are possible in each of the next 3 years.<sup>3</sup>

In 2007, the number of billion-dollar blockbuster drugs fell from 52 to 48 because of the introduction of first-time generics for some major drugs moving out of patent protection. This pattern is expected to continue as many more blockbuster drugs lose their patent protection over the next few years.

Although many current blockbusters will become available in generic form, this trend is expected to be partially offset by the introduction of a number of new drugs that may have the potential to become blockbusters.

However, the pharmaceutical market is tightly regulated worldwide resulting in long approval times for new drugs. Many products lose their patent exclusivity each year and “blockbuster drug” revenue loss can cause serious gaps in revenue streams for major players.

However, this particular situation at the same time creates opportunities for generic manufacturing, which is one of the fastest growing drug sectors. The global generic products market is expected to be around \$75 billion up to 2012<sup>4</sup>. This will increase competition and blockbuster manufacturers will consequently need to find new ways to generate revenue. This is just one example of how generic

products are squeezing the profit margin of established players and making the market place highly competitive. Drug approval is also becoming increasingly difficult in the US and Europe with new requirements implemented by the FDA and EMEA, e.g. for advanced therapy medicinal products in Europe.

In a similar way to the costs of drug development, the costs of securing patents have also dramatically increased in the past few years. This is expected to have a negative effect on the emergence of small companies. Another difficulty faced by the leading pharmaceutical manufacturers with a base in Europe and the US is the shortage of skilled professionals in R&D activities. Immigration restrictions and opportunities in home countries enabled by high economic growth have reduced the flow of scientists and professionals to locations previously considered as elite.

The economic downturn facing the global economy may have a knock-on effect on nanotechnology start-ups and other early stage companies. The difficulty in raising capital may hamper or prevent future growth. Some of the venture capital companies that have previously been active in the start-up market have already altered their strategy. An example is the strategic decision by 3i to move away from early stage to later stage investment.

As regards nanotechnology-enabled products, ethical concerns, health and safety issues, and lack of standardisation are considered to be key issues. There is also considerable uncertainty surrounding the toxicity of nanoparticles and their distribution and fate in the body. Lack of public awareness about nanotechnology is another factor which could potentially inhibit future growth potential.

Issues regarding scalability of new nano-enabled drug delivery technologies and the problems inherent in molecular manufacturing will also remain as key inhibitors in the future growth of nanomedicine.

### **Changing demographics**

According to the US Census Bureau, the total world population, which is growing at an annual rate of approximately 1.2%, stood at 6.66 billion in April 2008 and is expected to grow to 9.2 billion by 2050<sup>5</sup>. In the developed regions, 7.9% of the population was 65 and over in 1950: by 2050 24.7% of the population is expected to be in this age group<sup>6</sup>. The implications of this change are wide-ranging with a growing older population increasingly reliant on the tax and national insurance contributions of a percentage-wise decreasing working population in countries with a publicly-funded healthcare system. The increase in chronic illnesses, due to demographic shift and changes in lifestyle, together with a gradual shift towards more personalised medicine, are also changing the face of the industry. The number of people in the US with a chronic illness is expected to grow from 118 million in 1995 to 157 million in 2020.

### **Increasing costs**

National health expenditures in the US increased 4.4% to \$2.3 trillion in 2008 which accounted for 16.2% of US GDP. Projections for 2010 estimate a 5.7% increase corresponding to an increase to 17.3% of GDP.<sup>7</sup> Increasing costs have sometimes created problems of access to treatment; for example, in the UK, the publicly funded National Health Service (NHS), was reported in the media to have denied drug treatment for some patients with prostate cancer on the basis of high costs<sup>8</sup>. The World Health Organisation expects the worldwide spending on healthcare to increase from 9% of worldwide GDP to 15% by 2015<sup>9</sup>.

The US, at \$7,681 per capita, spends up to double that in most other industrialised countries. According to a CNN report in 2009<sup>10</sup>, in Denmark for example, the figure for expenditure is \$3,362 per person (9.8%

of GDP). These escalating costs partially arise from rising chronic disease rates but are, in part, also attributed to inefficient drug delivery. Recent estimates suggest that 75% (at the time of the survey \$1.7 trillion) of the total US healthcare costs was spent on treating chronic and complex diseases. The US is estimated to spend more than twice as much on healthcare as compared to food (\$1 trillion).

### **Risk, characterisation and measurement issues in nanoscale drug delivery**

Any new technology brings some degree of risk with it, and to bring a product to market based on that technology entails characterizing and quantifying that risk as far as possible, reducing it to an acceptable level, balancing any remaining risk against benefit, and communicating effectively on such “residual” risks.

The application of nanotechnology to products brings a new series of challenges in relation to risk management. While novel properties and characteristics at the nanoscale can endow products such as drugs with very many useful new benefits, those same properties and characteristics may introduce novel, and sometimes poorly understood, risks. Equally, the therapeutic mode of operation at the nanoscale is, in some cases, still poorly understood and requires further study to characterise the metabolic mechanisms involved. The overall quantity of materials may often be much decreased and while this may have benefits, both for the patient and the environment, more sensitive and in some cases novel *in-vivo* measurement methods may be required. In order to take nanotechnology-based medical products forward to the clinic it is, therefore, necessary to address these issues during development of the product, including any novel risks resulting from the nanoscale properties of the materials used.

In relation to pharmaceuticals, the European Medicines Agency (EMA) published a Reflection Paper on nanotechnology-based medicinal products for human use in June 2006 (EMA/CHMP/79769/2006, London, 29 June 2006). This Reflection Paper includes the following statements:

*“Although the existing toxicological and ecotoxicological methods are appropriate to assess many of the hazards associated with the products and processes involving nanoparticles, they may not be sufficient to address all the hazards. Existing methodologies will need to be adapted and new methods will need to be devised.”*

*“Before marketing, toxicology and ecotoxicology for a specific nanomedicinal product, as well as the methodologies used for the evaluation of toxicity, would be assessed in the context of the evaluation of the Marketing Authorisation Application, which foresees evaluation of benefits and risks to patients as well as an environmental risk assessment. A description of the pharmacovigilance system will be submitted and, where appropriate, an EU risk management plan will be required.”*

It can, therefore, be seen that regulatory approval will imply an assessment of novel risks, in addition to normal medicinal products assessment, and possibly a risk management plan.

In relation to this, EMA has also published a “Guideline on risk management systems for medicinal products for human use” (EMA/CHMP/96268/2005, London, 14 November 2005) which sets out guidance on how applicants should

*“... meet the requirements for a description of a risk management system that they will introduce for an individual medicinal product, or a series of medicinal products, in line with new Community legislation. The guideline also describes how such a risk management system can be presented to Competent Authorities in the form of a Risk Management Plan.”*

and which provides some specific risk management recommendations. In addition, the European Medicines Agency organised its 1<sup>st</sup> *International Workshop on Nanomedicines* in London on 2/3 September 2010 to examine risk and other challenges associated with the development of nanomedicines<sup>11</sup>.

Risk management is a very complex subject and, as such, is not dealt with in detail in this report. It is generally considered to comprise a number of essential interrelated components, some of which are technical such as hazard identification, risk estimation and risk reduction, and others which comprise senior management responsibilities such as the development and maintenance of a risk management policy, training of personnel and risk communication.

There is a growing body of literature addressing some of the risk issues associated with nanoparticles and nanosystems, including some that may be used for drug delivery. However, much of the literature addresses risks associated with naturally-occurring nanoparticles. To date, most of the risk research concerning manufactured nanoparticles has been with carbon nanotubes (CNTs).

While there is some accumulated knowledge on the toxicology of some nanomaterials that have already found use as drug delivery vehicles, e.g. liposomes, and other materials such as colloidal gold that have been in medical use for many years, for others there is currently little toxicological data available.

This suggests strongly that, in parallel with research on finding new nanoscale drug-delivery vehicles and systems, concomitant research is required on characterizing the properties of, and risks, including potential toxicity, associated with these novel materials.

## **Boundary conditions**

### **Patent landscape**

Effective management of patents with adequate protection is an important part of the pharmaceutical industry, as the estimated cost of developing a new chemical entity has skyrocketed to over \$700 million. This also reflects the decrease in the number of approved chemical entities (16 in 2007<sup>12</sup>) by the FDA in the US. In order to maximise the profit potential from a new drug, it is very important that the drug is effectively protected and the life cycle is extended to sustain revenues.

Over 70% of the revenues of major manufacturers like AstraZeneca, Amgen, and Johnson & Johnson derive from “blockbuster” streams. Only five of the top twenty companies do not generate at least 40% of their revenues from such “blockbuster” products and two of these companies (Teva and Novartis) are the world's leading generic pharmaceutical companies<sup>13</sup>. Figures available suggest that the revenue from blockbusters for some of the major companies doubled over a five year duration. Key issues are that patents will only provide protection for 20 years, and generic products will take a substantial market share once the patent protection is over. Nanotechnology may be valuable in such instances as it may enable unique new properties, capable of adding value and patent extension to existing high-value drugs.

This has created new opportunities for small companies developing novel nanotechnology-based drug delivery systems. Some of these novel systems and platform technologies can be used by the big pharmaceutical companies to enhance existing products and to extend patent life.

A brief analysis of the patents granted for different delivery technologies, using the European Patent Office website, provides an insight into the most important nanotechnology-based drug delivery platforms.

Liposomal drug delivery applications, one of the most established platforms, have the largest number of patents. A search using the keyword liposom\* together with “delivery”, “nano”, “therapy” and “targeted” resulted in a list of over 800 issued patents and liposome/liposomal drug delivery listed 223 patents. The other two technologies which topped the list are nanoparticle- and micellar-based technologies. The search identified over 182 patents in the nanoparticle category and 99 in micelles. The analysis furthermore shows that nanoparticle based research has increased over the last few years and is one of the fastest growing delivery modes along with micelles.

## Economic information and analysis

### Selected product examples

The following table is intended to provide a non-exhaustive snapshot of some important nanotechnology-based drug delivery platforms or nanotechnology-enabled drugs that are currently in the market or which are currently in drug pipeline development.

<b>Table 1. Overview of some delivery platforms and nanotechnology-enabled drugs on the market or in pipeline</b>			
<b>Product</b>	<b>Drug Application</b>	<b>Method</b>	<i>Licensed to /Technology</i>
Vivagel®	Microbicide/Virucide	Dendrimer	Starpharma
Doxil®	Doxorubicin, anticancer	Liposomes	Centocor Ortho Biotech Inc
DaunoXome®	Doxorubicin, anticancer	Liposomes	Gilead Sciences/Diatos
AmBisome®	Amphotericin B, antifungal	Liposomes	Gilead Sciences/Astellas Pharma
Amphotec®	Amphotericin B, antifungal	Liposomes	Three Rivers Pharmaceuticals
NeoLipid®	Delivery platform; anti-cancer drugs	Liposomes	Neopharm
Superfluids™	Delivery platform	Liposomes	Aphios Corporation
Taxosomes™	Paclitaxel	Liposomes	Aphios Corporation
ALERT	Delivery platform	Liposomes	Azaya Therapeutics
FluidCrystal®	Delivery platform	Lipid nanoparticles	Camurus AB
Estrasorb	Transdermal delivery	Micelle	Graceway Pharmaceuticals
Nanocarrier®	Delivery platform	Micellar nanoparticles	Nanocarrier
Nanoviricide/TheraCour	Antiviral drugs	Micelle	Nanoviricides Inc
Medusa® platform	Delivery platform/various drugs	Nanogel	Flamel Technologies
Rapamune®	Sirolimus	Nanocrystal	Wyeth/Elan
Emend™	Aprepitant	Nanocrystal	Merck/Elan
TriCor®	Fenofibrate	Nanocrystal	Abbott/Elan

Megace® ES	Megestrol acetate	Nanocrystal	Par Pharmaceutical Inc/Elan
Abelcet®	Amphotericin B	Nanocrystal	Sigma-Tau Pharmaceuticals/Elan
Triglide™	Fenofibrate	Nanocrystal	First Horizon Pharmaceutical/Skyepharma
Bioral®	Delivery platform; Amphotericin B,	Nanocrystal	BioDelivery Sciences International
BioSilicon™	Delivery platform; antifungals (Amphotericin B)	Nanoporous silicon	pSivida Corp
BioAir™, BioOral™ BioVant™, BioLook™	Delivery platforms	Calcium phosphate (CaP) nanoparticles	BioSante Phamaceuticals
NanoDRY™ NanoCOAT™ NanoQUAD®	Delivery platforms	Nanopowders	Nanotherapeutics
Protein Stabilized Nanoparticles	Delivery platform	Polymeric nanoparticles	Azaya Therapeutics
Abraxane®	Paclitaxel	Polymer nanoparticles	Abraxis Biosciences Inc
<b>Transdrug®</b>	Delivery platform; Doxorubicin Transdrug®	Polymeric nanoparticles	BioAlliance Pharma
<b>Paclitaxel (Genexol-PMP), protein delivery and others</b>	Delivery platforms	Polymeric micelles (Genexol-PM) Polymeric nanoparticles	Samyang
Biorise®	Delivery/drug bioavailability platform	Polymeric network	Eurand
ONCASPAR®	Pegylated L-asparaginase for treatment of acute lymphoblastic leukaemia	Polymeric nanoparticles	Sigma-Tau Pharmaceuticals
<b>Various drug applications</b>	Delivery platforms	Solid lipid nanoparticles (SLN) and hybrid lipid-polymer nanoparticles (HLN)	AlphaRx

In 2008, the nanotechnology-enabled drug delivery market was estimated at \$4.1 billion, or 4% of the global drug delivery market. However, at a very conservative estimate it is expected that this will have a cumulative growth rate of 48% over the next four years to increase to \$20.1 billion by 2012, an 11% share of the global drug delivery market.

Elan's nanocrystal-delivery based drugs are expected to have a consistent growth up to 2012.

Vaccines against fungal infections like Bioral and AmBisome are expected to have a solid growth during this period. Ambisome, which was growing at 18% per year up to 2008, is expected to have a growth rate of over 20% by 2012. A pipeline of products under different stages of development by Nanotherapeutics is expected to reach the market by 2012.

Other prospective drug nanotechnologies with huge market potential expected within 5 -10 years include nanoviricides against H5N1 bird flu viruses from Nanoviricides Inc., BrachySil from Psivida for brachytherapy (makes use of nanostructured silicon, which is biocompatible), cancer therapy using

magnetic nanoparticles by Magforce Nanotechnologies, and HIV treatment from Dendritic Nanotechnologies.

There are several other companies working in the field, particularly small start-ups and spin-offs, which have developed platform technologies for drug delivery applications. Detailed descriptions of the main players are presented in the Appendix.

### **Commentary from some industry insiders**

Adriana Vela of NanoBioNexus estimates that nanotechnology is now playing a part in helping to solve delivery problems in around 40%+ of drugs that have poor solubility. Elan Drug Technologies has led the way in this field with its exploitation of NanoCrystal® technology which offers, among other benefits, improved biocompatibility, increased absorption rates, dose reduction, faster formulation of compounds, and increased performance through various administration routes.<sup>14</sup> Elan had its fifth product approved in late 2009 and has also licensed this technology to a number of companies including J&J, AstraZeneca, Roche and Bristol-Myers Squibb with annual in-market sales of more than \$1.8 billion according to its Chief Technology Officer, Dr. Gary Liversidge. Dr. Liversidge suggests also that pharmaceutical companies to look at their inventory of pipeline products to see if there are any hidden gems that were discarded because of their inherent poor water solubility properties, reporting that Elan has worked with a client on such a product that is now a blockbuster selling in excess of \$1.2 billion in annual sales in the US alone.

Vela also considers that the notion that companies must innovate to survive has become more commonplace as “competitive pressures and economic volatility define the business landscape” and suggests that action must be taken in three areas; intellectual property issues, regulatory issues and pharmacovigilance which, combined, have the potential to create real difficulties for the industry if not properly addressed.

Vela estimates that, by 2011, the pharmaceutical industry will face the potential loss of approximately \$70 to \$80 billion of drug revenues as various blockbuster drugs go off-patent. With pharmaceutical companies reducing headcounts by around 69100 in 2009, up 60% from 2008 figures, some are even changing their business model to include outsourcing of various functions to stay competitive.

Vela considers that this is where leading biopharmaceutical or specialty pharmaceutical companies may have a slight advantage. In particular, those focused on nanotech-enabled discovery, development or platform technologies that increase benefits while reducing costs are now in a position of strength for licensing, outsourcing or other collaborative opportunities with “big pharma” whose challenge for “big will be to swiftly adapt to a new business model that has the right balance of in-house and outsourced processes. They will also need to make efficient use of resources to identify and incorporate nanopharmaceuticals and processes into their pipelines. To achieve this small and medium-sized biopharmaceutical and speciality pharmaceutical companies will need to be prepared with ample data in the light of stagnancy in the venture capital markets.

According to Vela, nanotechnology also has the potential to move us closer to personalised medicine. Targeted therapeutics with smart drug delivery devices and theranostics will drive this trend forward. On the surface, these two trends are not likely to have a favourable impact on pharma's current business

model, but they could if the pharmaceutical industry adapts its business model to align more closely with scientific and market trends. The market will demand these technologies based on benefits and costs as compared to today's alternatives. Areas of nanotechnology advances with a direct benefit to pharma and biopharma are those that will not only further improve efficacy and reduce side effects of existing drugs, but that will enable a faster discovery process to eliminate non-efficacious drugs much earlier and with less investment. Similarly, there are nanotechnologies that will shorten the drug development process and get more drugs to market quicker.

According to Dr. Mike Eaton, Executive Board Member of the European Technology Platform on Nanomedicine, the pharmaceutical sector is adaptable and can accommodate incremental changes. However, nanotechnology could enable radical innovation and open up new modalities for patients and the sector. Progress on nucleic acid based therapeutics, for example, has been slow because of delivery problems. Similarly, biologicals cannot address intracellular targets; neither can they enter the CNS. Progress here would challenge current thinking. He suggests that improving the transport of therapeutic macromolecules is an area of potential interest; progress here would open up new markets and help treat patients in a new way. Eaton noted also that such changes do not come overnight but, provided companies welcome open innovation, suggests that they still have plenty of time to adapt.

## **Selected company and product profiles**

### **Abraxis Biosciences Inc.**

Abraxis Biosciences Inc. has developed the drug Abraxane<sup>®</sup>, an albumin-based nanoparticle formulation of paclitaxel for the treatment of metastatic breast cancer. It uses Abraxis' proprietary nab<sup>™</sup> technology platform to allow the delivery of a drug from the vascular space across the blood vessel wall to the underlying tumour tissue using a natural pathway, the gp60 pathway, where biomolecules can be transported across the endothelial barrier when attached to albumin<sup>15</sup>. Abraxane has the ability to slow or to temporarily stop tumour growth by stopping cancer cells from growing and dividing by interfering with certain cell structures. Abraxis Biosciences was spun-off from APP Pharmaceuticals Inc. and has headquarters in Los Angeles.

Website: [www.abraxisbio.com](http://www.abraxisbio.com)

### **Access Pharmaceuticals Inc.**

Access Pharmaceuticals Inc. is an emerging biopharmaceutical company specialising in products for the treatment of cancer and for supportive care. Its lead oncology drug is ProLindac<sup>™</sup> which has recently completed a Phase 2 monotherapy study in patients with ovarian cancer. This product utilises a water-soluble nanoparticulate system to deliver DACH platinum to tumours. The company also has other advanced drug delivery technologies including Cobalamin<sup>™</sup>, an absorption enhancement system, which may be combined with nanoparticulate delivery.

Website: [www.accesspharma.com](http://www.accesspharma.com)

## **AlphaRx**

AlphaRx, headquartered in Hong Kong, has developed solid lipid nanoparticle (SLN) and hybrid lipid-polymer nanoparticles (HLN) drug delivery platforms that are intended to enhance the bioavailability of drugs towards targeted diseased cells, and promote the required response while minimizing side-effects. The two class of particle are made of FDA approved polymers or lipids that, because of their size and chemical composition, permit systemic and local treatment. The technologies are intended to address a range of drug delivery applications and could, potentially, solve the problem of the *in vivo* delivery of biomimetic molecules such as nucleic acids, proteins, peptides and other very insoluble drugs, which is very difficult by current technological means. AlphaRx's lead product candidates include Zysolin™, an inhaled formulation of Tobramycin nanoparticles, intended for the adjunctive treatment of Pseudomonas aeruginosa pneumonia in intubated and mechanically-ventilated patients (VAP); Vansolin™ and a Vancomycin compound encapsulated in the company's Nano Drug Delivery Platform intended for the treatment of nosocomial pneumonia due to methicillin-resistant Staphylococcus aureus (MRSA).

Website: [www.alpharx.com](http://www.alpharx.com)

## **Aphios Corporation**

Aphios Corporation, uses its patented SuperFluids™ liquid-liquid technology to disaggregate or comminute protein crystals and amorphous protein powders into monodisperse nanoparticles that can be used to improve the delivery and therapeutic efficacy of poorly water-soluble drugs while reducing their toxicities. The technology can be utilized to enhance the oral bioavailability of therapeutic proteins and as controlled release vehicles for potent viral antigens against extreme infectious diseases<sup>16</sup>. Using these technologies the company has developed and patented a cremophor-free nanosomal formulation of paclitaxel called Taxosomes™.

Website: [www.aphios.com/](http://www.aphios.com/)

## **Artificial Cell Technologies**

Artificial Cell Technologies, an early-stage company based in the US, designs peptides and polypeptides to mimic naturally occurring structures in the human body. These are assembled into multilayer nanofilms by a method called layer-by-layer self-assembly. Such films can be used to coat surfaces or generate capsules (an 'artificial cell'). The nanofilm fabrication process enables a high level of control over film and capsule properties such as thickness (at the nanometre scale), porosity, permeability, density, surface charge, roughness, and suitability for integration with pharmacological agents<sup>17</sup>. The company currently has 7 issued patents and a further 5 patent applications pending covering the technologies, and has vaccines utilising the technology in development against respiratory syncytial virus (RSV) and dengue fever, two infectious diseases for which there is currently no effective vaccine.

Website: [www.artificialcelltech.com/](http://www.artificialcelltech.com/)

## **Azaya Therapeutics**

Azaya Therapeutics, Inc, is an emerging pharmaceutical company with a novel drug delivery platform technology. Its proprietary Protein Stabilized Nanoparticles (PSN) technology platform addresses the significant toxicity problems associated with delivery of cancer treatments. The company is applying its

PSN technology to produce a targeted, safer and more efficacious formulation of a marketed chemotherapy drug for the improved treatment of cancer. It has also licensed a breakthrough technology now known as ALERT (Azaya Liposomal Encapsulated Radiation Therapy) from the University of Texas Health Science Center that uses liposomes to deliver radiation through direct injection into head and neck tumors, shrinking the tumor, delaying recurrence and avoiding the collateral tissue damage that often accompanies all other forms of radiation therapy. The company planned to begin a phase I clinical trial in early 2010.

Website: [www.azayatherapeutics.com/](http://www.azayatherapeutics.com/)

### **Baxter Healthcare**

The dispersion technology NANOEDGE™ developed by Baxter is designed to provide filling and formulation services to companies with insoluble drugs. The technology is used to solve formulation problems by reducing the size of particles to 100 nanometres and coating them with a thin layer of proprietary excipient to create drug particles which are capable of dissolving quickly<sup>18</sup>. Baxter is using this technology to develop anti-infective and anti-cancer drugs through oral delivery which are now in their early development stages.

Website: [www.baxterbiopharmasolutions.com/](http://www.baxterbiopharmasolutions.com/)

### **BioAlliance Pharma**

BioAlliance Pharma, a French company with a focus on developing therapeutics for cancer and HIV, has developed a patented polymer polyisohexylcyanoacrylate (PIHCA) nanoparticle-based drug delivery system called Transdrug® for the treatment of advanced hepatocellular carcinoma and other cancers<sup>19</sup>. The company's lead product, Doxorubicin Transdrug®, utilizes the chemotherapy agent, doxorubicin. BioAlliance announced positive survival data in phase II clinical trials of the drug in December 2009 and the drug has been granted orphan drug status by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

Website: [www.bioalliancepharma.com/](http://www.bioalliancepharma.com/)

### **Biodelivery Sciences International**

BioDelivery Sciences International (BDSI®), a biopharmaceutical company based in North Carolina, has developed a platform technology called Bioral® which encapsulate drugs in alternating layers of lipids, potentially protecting it from degradation by acid or digestive enzymes in the stomach, for effective oral delivery. The technology was developed in collaboration with the University of Medicine and Dentistry of New Jersey (UMDNJ) and Albany University, each of which has granted BDSI® exclusive worldwide licenses under applicable patents. The company's lead product is based on the antifungal agent Amphotericin B. Collaboration with the National Institutes of Health has supported, in part, the Bioral® preclinical program, and a collaboration with the US Walter Reed Army Institute of Research is currently exploring the use of Bioral® technology in difficult to treat parasitic infections. According to data sources, the global antifungal market was approximately \$3 billion in 2006 and was projected to grow to \$4 billion by 2009. BDSI® market research indicates that Bioral® Amphotericin B may be able to achieve peak sales of approximately \$400 million annually.

Website: [www.bdsinternational.com/](http://www.bdsinternational.com/)

### **Biophan**

Biophan, a New York-based company, currently holds intellectual property around two core areas of nanotechnology-based drug delivery. In guided drug delivery: nanomagnetic carriers offer the possibility of improved drug efficacy and reduced toxicity by delivering pharmaceuticals to the exact location of need and releasing them at the appropriate time. The targeting of the drug can be followed using MRI imaging. In nanomagnetic drug-eluting devices, by means of the use of nanomagnetic particles and coatings, Biophan's technology offers the possibility of improved drug-elution for medical devices such as stents and orthopaedic implants, with greater control over the release of drugs. Biophan currently owns or has exclusive license to over 40 US patents, with more than 60 patent applications pending in the US and worldwide. Biophan entered into a license agreement with Boston Scientific Corporation in 2005, and sold some of its MRI safety patents to Medtronic for \$11 million in 2007.

Website: [www.biophan.com](http://www.biophan.com)

### **BioSante Pharmaceuticals**

BioSante Pharmaceuticals of Illinois, USA, has developed a calcium phosphate nanoparticle (CaP) platform that can be applied to a number of therapeutic areas such as vaccine adjuvants (BioVant™), drug delivery (BioAir™/BioOral™) and aesthetic medicine (BioLook™). The company has completed pre-clinical tests showing that its biodegradable calcium phosphate nanoparticle vehicles enhance and extend the hypoglycemic effect of proteins when administered subcutaneously, buccally and pulmonarily. It believes that CaP can be used to deliver many proteins (such as human Factor IX for haemophiliacs, Interferon alpha-2b for chronic hepatitis B treatment, a1-antitrypsin for the prophylaxis of venous thromboembolism) and peptides.

Website: [www.biosantepharma.com/About-Us.php](http://www.biosantepharma.com/About-Us.php)

### **Calando Pharmaceuticals**

The RONDEL (RNA/oligonucleotide nanoparticle delivery) technology developed by Calando Pharmaceuticals, a subsidiary of Arrowhead Research Corporation, is being used in novel siRNA-containing therapeutics. When mixed with small interfering RNA (siRNA), the system's cyclodextrin polymers bind to the siRNA. The polymer and siRNA self-assemble into nanoparticles of approximately 50 nm diameter. CALAA-01, Calando's leading drug candidate, is a combination of RONDEL and a patented siRNA targeting the M2 subunit of ribonucleotide reductase, a clinically-validated cancer target. Ribonucleotide reductase catalyzes the conversion of ribonucleosides to deoxyribonucleosides and is necessary for DNA synthesis and replication; it is a critical component in the proliferation of cancer cells. Calando's siRNA and CALAA-01 have demonstrated potent anti-proliferative activity across multiple types of cancer cells.<sup>20</sup>. Calando also owns the CycloSert™ delivery platform for the delivery of small molecule drugs which provides many of the same benefits as the RONDEL™ system.

Website: [www.calandopharma.com/](http://www.calandopharma.com/)

### **Camurus AB**

Camurus AB, based in Lund, Sweden, provides innovative nanoscale drug-delivery systems for the development of high-value therapeutics. Its delivery solutions range from long-acting depots to lipid nanocarriers designed for improved intravenous, transdermal and oral delivery. These are used in partner projects with biotech and pharma companies worldwide for enabling and improving delivery of a wide range of difficult drug compounds, including peptides, proteins, and insoluble small molecules. Its FluidCrystal® delivery technology has been adapted for the delivery of drug carrying nanoparticles orally, transdermally and by injection. The company currently has a number of in-house and partner products in preclinical and clinical trials.

Website: [www.camurus.com/index.asp](http://www.camurus.com/index.asp)

### **Capsulation Nanosciences AG**

Capsulation NanoSciences is a nanotechnology company focusing on the development of tailor-made drug delivery systems and other innovative life science products based on nano-sized capsules and nanocomplexes. Their patented layer-by-layer technology (LBL-Technology®) produces capsules containing between 4 and 20 polymer layers, which can contain a solid core or be rendered hollow for inclusion of a desired molecule. Biochemical, electrical, optical and magnetic properties can be altered to suit different applications.

Website: [www.capsulation.com/en/home.html](http://www.capsulation.com/en/home.html)

### **Centocor Ortho Biotech Inc.**

Centocor Ortho Biotech Inc., part of the Johnson and Johnson family of companies, manufactures the anticancer drug Doxil®. Doxil® is a liposomal formulation of doxorubicin, an intravenous chemotherapy agent indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after prior platinum-based therapy. The liposomes in the Doxil® formulation are coated with methoxypolyethylene glycol, which gives them 'stealth-like' properties (i.e. they can evade detection and destruction by the immune system). At least 90% of the drug remains inside the liposome while it is in the blood, the slow release means less frequent dosing and greater take-up by tumour tissue<sup>21</sup>.

Website: [www.centocororthobiotech.com/cobi/oncology\\_doxil.html](http://www.centocororthobiotech.com/cobi/oncology_doxil.html)

### **Elan Corporation**

Elan Drug Technologies (EDT) is a leading drug delivery company and is a business unit of Elan Corporation, based in Dublin, Ireland. It is estimated that in excess of 40% of compounds in development suffer from poor solubility, making them difficult to develop and resulting in a significant number of potentially beneficial compounds being discarded in development each year. Elan Drug Technologies' NanoCrystal® technology is intended to provide a solution to this problem. NanoCrystal® particles are small particles of drug substance, typically less than 2,000 nanometres (nm) in diameter, which can be produced using various approaches such as wet milling, homogenisation, precipitation and supercritical fluid techniques. The NanoCrystal® particles of the drug are stabilised against agglomeration by surface adsorption of selected GRAS (Generally Regarded As Safe) stabilisers. The result is an aqueous dispersion

of the drug substance that behaves like a solution - a NanoCrystal Colloidal Dispersion<sup>®</sup> composition, which can be processed into finished dosage forms for all routes of administration<sup>22</sup>. The technology has the potential to be incorporated into many delivery forms, e.g. parenteral and solid, liquid, fast-melt, pulsed release and controlled release oral dosage forms. The technology has been incorporated into a number of commercialised products from companies such as Wyeth, Abbott Laboratories, Merck, Par Pharmaceuticals and Janssen, and several others are in the pipeline.

Website: [www.elandrugtechnologies.com/nanocrystal\\_technology](http://www.elandrugtechnologies.com/nanocrystal_technology)

#### **Enzon Pharmaceuticals Inc.**

Abelcet, a lipid complex formulation of Amphotericin B, is used primarily in hospitals to treat immunocompromised patients with invasive fungal infections and is marketed by the Enzon Pharmaceuticals Inc...

Website: [www.enzon.com/](http://www.enzon.com/)

#### **Eurand**

Eurand is an Amsterdam, Netherlands-based company that has developed several drug bioavailability enhancement (Biorise<sup>®</sup>) and drug delivery platforms (DiffuCaps<sup>®</sup>, DiffuTabs<sup>®</sup>). With the Biorise<sup>®</sup> platform new physical entities (NPEs) are produced by breaking down the crystalline drug into nanocrystals and/or amorphous (noncrystalline) drug that is stabilized in a carrier system to maintain the drug in its activated form for the duration of its shelf life. This approach creates a greater surface area to volume ratio that increases the intrinsic solubility and dissolution rate of poorly water-soluble drugs, thereby enhancing their rate and extent of absorption. The Biorise technology can be applied to Class II compounds with solubilities in the range of <10 to 500 µg/mL.

Website: [www.eurand.com/](http://www.eurand.com/)

#### **Exilica Ltd**

Exilica Ltd., a spin out company from Coventry University in the UK, has two core products: spherical polymer micro-beads, called µ-Sq Beads, and hollow silica nanoshells which are prepared by over-coating µ-Sq beads with a liquid silicon precursor. Hollow silica shells are currently being developed as potential drug delivery vehicles. The release of chemical agents from the shells can be controlled by over-coating the shells with other molecular materials such as polymers. For example, if the shells are over-coated with poly-L-lysine then they can be endocytosed (taken up) by cells. Preliminary results have also demonstrated that the contents of the shells can be delivered into cells.

Website: [www.exilica.co.uk](http://www.exilica.co.uk)

#### **Flamel Technologies**

Flamel Technologies of France has developed the Medusa<sup>®</sup> drug delivery platform, a self-assembled poly-aminoacid nanogel system, which is a versatile protein carrier for the development of novel and second-generation long-acting native protein drugs. The Medusa<sup>®</sup> platform is being used as the delivery system for a number of drug candidates that are in clinical trials including: a long-acting interferon alpha-2b (IFN Alpha XL), a long-acting basal insulin for the treatment of type 2 diabetes (FT-105) and a long-acting interleukin-2 for the treatment of renal cell carcinoma.

Website: [www.flamel.com/](http://www.flamel.com/)

### **Fresenius Kabi**

Nanoxel is a novel cremophor-free paclitaxel formulation in which the drug is delivered as nano-micelles using polymeric carriers<sup>23</sup>. The technology was originally developed by Dabur Pharma Ltd, a pharmaceutical manufacturer based in India with expertise in cytotoxicity and targeted oncology and was acquired by Fresenius Kabi in 2008. The technology is claimed as an effective and safe therapy for advanced breast, non-small-cell lung, and ovarian carcinomas. The technology has been available in India for specialist cancer therapy providers and healthcare institutes for cancer treatment since January 2007.

Website: [www.fresenius-kabi.com/4393.htm](http://www.fresenius-kabi.com/4393.htm)

### **Gilead Sciences, Inc**

Gilead Sciences has two products on the market – DaunoXome<sup>®</sup> and AmBisome<sup>®</sup>. DaunoXome<sup>®</sup> is a liposomal formulation of daunorubicin, a widely used generic anti-cancer chemotherapeutic agent, and its commercialisation and development is licensed to the Paris-based pharmaceutical company Diatos S.A. DaunoXome was approved in 1996 for HIV-related Kaposi's sarcoma and is currently sold in more than 20 countries. AmBisome<sup>®</sup> is a liposomal formulation of amphotericin B and is licensed to Astellas Pharma US, Inc., and is used to treat serious, life-threatening fungal infections, including a certain form of meningitis in people infected with HIV. AmBisome is a true single bilayer liposomal drug delivery system containing liposomes that are less than 100 nm in diameter.

Websites: [www.gilead.com/](http://www.gilead.com/)    [www.ambisome.com](http://www.ambisome.com)

### **Graceway Pharmaceuticals, LLC**

In 2008, Novavax Inc. sold its assets related to Estrasorb<sup>®</sup> in the US to Graceway Pharmaceuticals, LLC. Estrasorb<sup>®</sup> was developed for the reduction of vasomotor symptoms such as moderate to severe hot flushes as a result of menopause. Estrasorb<sup>®</sup> encapsulates oestrogen in micellar nanoparticle delivery system providing 'patchless' transdermal delivery.

Website: [www.estrasorb.com/index.htm](http://www.estrasorb.com/index.htm)

### **ICeutica**

The SoluMatrix™ platform developed by ICeutica is a drug reformulation and delivery technology especially for poorly water-soluble compounds which is simple, scalable and cost effective to: improve bioavailability; open up novel delivery methods such as direct particle injection. Particle size reduction increases surface area and in-vivo dissolution rate. Drug product produced using the platform comprise very small particles of drug (typically less than 2000nm diameter), which are produced by milling the drug substance together with conventional pharmaceutical excipients (matrix materials) using a proprietary, dry-milling technique. The particles of the drug are stabilized against agglomeration by the unique matrix, which can also provide other beneficial pharmacokinetic properties. The resulting dry powders can be processed into finished dosage forms for all routes of administration.

Website: [www.iceutica.com/](http://www.iceutica.com/)

### **ImuThes Ltd**

ImuThes Ltd is a London-based biotech company that was formed in November 2005. A key feature of ImuThes' nanoparticle delivery technology is the proprietary concept of post-coupling that allows for highly reproducible, homogenous particle fractions (the formation of the liposome - payload complexes and subsequent addition of PEG or ligands can be carried out in the absence of organic solvents), and shedding of the stealth and targeting layer upon cell entry, as triggered through the drop in pH during endosome uptake, which is a requirement for efficient delivery of the payload to the cytosol or nucleus. Applications for ImuThes' nanoparticle technology comprise delivery of siRNA (for example in the indications of oncology and hepatitis and other viral infections), delivery of plasmid DNA (for therapeutic vaccines against life-threatening infectious diseases) and targeted delivery of cytostatic agents (in the indications of cancer and chronic inflammatory conditions).

Website: [www.imuthes.com/](http://www.imuthes.com/)

### **Intezyne Technologies**

Intezyne Technologies' proprietary IVECT™ (polymer micelle technology) drug delivery platform reduces drug toxicity by securely encapsulating the active therapeutic agent in the IVECT micelle, a polymeric nanoparticle that minimizes drug exposure to healthy tissues as well as increasing solubility. The IVECT micelle shields its contents from the body's natural defences, allowing higher concentrations of the active drug to reach the tumour without being excreted or degraded. Additionally, proprietary cross-linking technology can provide enhanced protection and increased anti-tumour activity by creating a triggered release mechanism, which actively dispenses the drug payload only at the tumour site. The IVECT copolymer is equipped with proprietary means of attaching cell targeting groups, which anchor the IVECT micelle to the tumour, both quickly and easily.

Website: [www.intezyne.com/our\\_technology.asp](http://www.intezyne.com/our_technology.asp)

### **IOTA NanoSolutions Limited**

Based in Liverpool, UK, IOTA NanoSolutions Limited specialises in enabling and enhancing the application and activity of poorly soluble and insoluble materials. IOTA NanoSolutions' ContraSol™ technology produces dry, solid blends (e.g. powders, granules, beads or tablets) of soluble matrices with insoluble compounds. The techniques do not involve chemical modification of the insoluble compound. When added to liquid that dissolves the matrix, the insoluble API is released to form a dispersion with mean particle size typically between 100 and 500nm. Solids and liquid dispersions produced using ContraSol™ have demonstrated: enhanced bioavailability, activity and efficacy in a range of *ex vivo* and *in vivo* models; 'tunable' particle size with high consistency; dispersions in water, hydrophilic liquids and hydrophobic liquids; particle dispersions of hydrophilic, hydrophobic and reactive materials; water-clarity for many dispersions; long shelf life for solid formats; high powder loadings of insoluble APIs (up to 85 w/w %). ContraSol™ formulations can be used in tablet, gel, powder and liquid formats for parenteral, inhalable, ocular, oral and topical administration. APIs including anti-hypertensives, anti-lipidemics, NSAIDs, anti-infectives, anti-virals, hormones and vasodilators have been successfully processed.

Website: [www.iotanano.com](http://www.iotanano.com)

## **Keystone Nano**

Keystone Nano has an exclusive license to Penn State University patented technology that allows the creation of stable, non-toxic, 5 to 50 nm-composite nanoparticles termed NanoJackets™. These can be used to encapsulate drugs and/or fluorescent molecules. Key technological advantages include: use of several non-toxic materials, homogeneous and non aggregating, maintenance of specific control over the size and size distribution of particles, synthesis approach is suitable for chemotherapeutics and pro-apoptotic lipids, the suspensions are stable for long periods of time, surfaces can be modified to provide for cell type, specific targeting using a variety of targeting techniques, fluorescent nanoparticles are highly resistant to photo-bleaching and photo, the nanocomposites can be designed to dissolve at a specific pH to facilitate intra-cellular delivery.

Website: [www.keystonenano.com/](http://www.keystonenano.com/)

## **Labopharm**

Labopharm has developed a Polymeric Nano-Delivery System™ (PNDS). PNDS comprises a library of block copolymers designed to address the unmet needs of insoluble drug delivery. Comprising hydrophobic and hydrophilic GRAS (generally recognized as safe) subunits fused as novel molecular entities, PNDS can be simply manufactured to form stable nano-vehicles or micelles that entrap insoluble drugs, making them available for oral or parenteral administration in safe and convenient forms. PNDS technology has been used by the company to increase the rate of oral absorption and extent of oral bioavailability of fenofibrate to more than 80%. The company has also identified a series of stable, solvent-free cytotoxic drug formulations using PNDS with very high maximum tolerated doses compared to current products. Website: [www.labopharm.com/](http://www.labopharm.com/)

## **Magforce Nanotechnologies AG**

Magforce Nanotechnologies' Nano-Cancer® therapy is a new way of treating tumours locally by hyperthermia and thermoablation. The principle behind the method is the direct, minimally invasive introduction of magnetic nanoparticles into the tumour and their subsequent heating in an alternating magnetic field. The nanoparticles comprise particles of iron oxide with a diameter of approximately 20nm (including the covering) which are suspended in a liquid. The particles are made to vibrate by a magnetic field which alters its polarity up to 100,000 times/min and, in response, they generate heat. This technique makes it possible to fight the tumour from the inside out. Through their application, the particles are placed directly in the tumour and their coating allows them to penetrate into the tumour cells. Due to this coated design, they remain in the tumour and are not ejected, so that the treatment is limited solely to the tumorous tissues while surrounding healthy tissues are spared. On 28 June 2010 MagForce Nanotechnologies received European regulatory approval for its Nano-Cancer® therapy.

Website: [www.magforce.de/english/home1.html](http://www.magforce.de/english/home1.html)

## **Nanocarrier®**

NanoCarrier's micellar nanoparticles technology was developed by researchers at the University of Tokyo and Jikei University in Japan. The micellar nanoparticles are composed of biocompatible block copolymers, comprising of hydrophilic polyethylene glycol (PEG) and hydrophobic polyamino acid. The formation of micelles, aggregates of 20-100 nanometre-size spheres, occurs when the block copolymers

diffuse in water. Drugs and biologically active substances can be stably encapsulated in the hydrophobic inner core of the micelles. This technology can be applied to various types of compounds by modifying amino-acid side chains, etc. PEG coating on the surface ensures the micelles' stability in the bloodstream and the drugs are then released slowly<sup>24</sup>. The company currently has three anticancer drugs in clinical trials. NanoCarrier has been working with Debiopharm S.A. of Switzerland, which developed oxaliplatin, to develop DACH-Platin micelles (a new platinum compound). DACH-Platin is an active metabolite of oxaliplatin, which shows stronger anticancer activity.

Website: [www.nanocarrier.co.jp/en/index.html](http://www.nanocarrier.co.jp/en/index.html)

### **Nanocopeia**

Nanocopeia is a drug delivery company developing a nanotechnology-enabled portfolio of therapeutic products. It has developed a proprietary technology ElectroNanospray™ for producing nanoparticles between the ranges of 2-200 nm. The technology is capable of transforming drugs and polymers into many nanoscale material states including powders, liquids, encapsulated particles, and coatings.

The company intends to utilise ElectroNanospray™ to create new proprietary products by enhancing the value and performance of off-patent, already proven drugs and taking advantage of the efficient FDA 505(b) (2) regulatory pathway for minimizing the time to market. ElectroNanospray™ also enables novel nanoformulations of those drugs optimized for delivery to and through the skin.

Website: [www.nanocopeia.com/](http://www.nanocopeia.com/)

### **NanoBioMagnetics**

NanoBioMagnetics (NBMI) is a nanobiomaterials company pioneering an emerging area of nanomedicine referred to as organ-assisting-device (OAD) technologies, in which magnetically responsive nanoparticles (MNP) under the influence of external shaped magnetic fields, are magnetically vectored to cause or drive a desired physiological event. OAD healthcare applications are being developed under two proprietary platforms for which patents are pending: *Site-Specific Drug Delivery*- MNP-therapeutic constructs, under the influence of external shaped magnetic fields, are vectored to a target site, followed by cell uptake; *Biostable Implants* - MNP, implanted in tissue, nanomechanically drive tissue movement or vibration under the influence of an external oscillating magnetic field. The company was awarded US patents in 2008 for hearing amplification and in 2010 for the targeted delivery of bioactive compounds and has a further 8 patent applications under review.

Website: [www.nanobmi.com/](http://www.nanobmi.com/)

### **Nanobiotix**

Nanobiotix, based in Paris, France, has developed NanoXray™ technology, designed to resolve cancer therapy's biggest drawback, namely destruction of healthy tissue and its subsequent deleterious side effects when a high dose of X-ray is necessary. The core of a NanoXray™ nanoparticle is an inactive and inert substance—not a drug—that can subsequently be activated in order to locally (intratumour) increase the dose of a standard X-ray, which is then expected to lead to higher efficiency. NanoBiotix is

also currently working on two further nanoparticle technologies: nanoMag™ - magnetic particles for treatment and diagnostic of cancer; and nanoPDT™ - laser activated nanoparticles for cancer treatment

Website: [www.nanobiotix.com/](http://www.nanobiotix.com/)

### **Nanotherapeutics**

Nanotherapeutics, a Florida-based company specialising in drug delivery solutions, has three different nanotechnology-based drug delivery platforms:

- The NanoDRY™ process uses a low-shear method of rapidly forming particles of controlled size and shape in batch sizes ranging from a few grams to kilograms. The process is well-suited to form nanoparticles or microparticles of low molecular-weight compounds, insoluble drugs, drug salts, peptides/proteins and DNA.
- In the NanoCOAT™ process a core nanoparticle/microparticle is encapsulated with a thin layer of a coating material, such as a surfactant or a biodegradable polymer. The coating may be applied to slow the rate of release of an active component, improve the dispersion/flow properties, or increase the absorption into the systemic circulation.
- In the NanoQUAD™ system nanoparticles of typically less than 1000 nanometres in diameter are stabilized against agglomeration by surface adsorption of selected GRAS (Generally Recognized As Safe) stabilizers. The result is a dispersible powder of the drug substance with dramatically improved dispersion and absorption properties, which can be processed into finished dosage forms for various routes of administration.

Nanotherapeutics currently has a number of nano-enabled drugs for different applications in development.

Website: [www.nanotherapeutics.com/](http://www.nanotherapeutics.com/)

### **NanoViricides Inc**

NanoViricides, Inc. currently developing a class of antiviral drugs termed nanoviricides based on a technology it terms TheraCour. TheraCour polymers are patented amphiphilic polymers which form micelles and which can carry certain bioactive materials. These operate in a homologous manner to bactericides and neutralise viruses through blocking cellular uptake (e.g. through coating the virus particle surface). The current generation of nanoviricides are delivered by injection; however the company has plans to develop bronchial sprays (similar to asthma medications), nasal sprays (similar to allergy medications) and oral inhalation formulations (for deep chest cavity inhalation) for greater ease of use. NanoViricides currently has a number of drugs in its development pipeline targeting viral diseases including H5N1 bird flu, seasonal influenza, HIV, rabies, and dengue fever.

Website: [www.nanoviricides.com/](http://www.nanoviricides.com/)

### **Neopharm**

Neopharm, an Illinois-based company, has developed a liposome-based drug delivery platform called NeoLipid® for the delivery of anticancer drugs to tumours. The company currently has a number of drug candidates utilising the NeoLipid® platform in preclinical or clinical trials including formulations of

paclitaxel for metastatic breast cancer, docetaxel for metastatic solid cancers and the active metabolite of Camptosar® (produced by Pfizer Inc.) for colorectal cancers .

Website: [www.neopharm.com/](http://www.neopharm.com/)

### **Novosom**

Novosom is a German biopharmaceutical company that has developed a fully charge-reversible liposomal delivery technology which it has named SMARTICLES®. These particles are negatively charged under normal physiological conditions. However, as the pH drops down to 5 or 4 during endocytosis (the process whereby the cell absorbs the liposome from the outside by engulfing it with its cell membrane), the vector surface becomes neutral and eventually positively charged. This unique property guarantees stable and aggregate-free travel within the bloodstream, but the acidification from endocytosis switches the charge of SMARTICLES®, leading to membrane fusion and the escape of the drug payload from the endosome. Although all SMARTICLES® share the same fundamental biophysical characteristics, the particles can be very diverse chemically. Novosom has tested close to one thousand different SMARTICLES® formulations out of which a small number of lead vectors have been selected for a unique match of stability, efficacy and targeting properties. The company is currently focusing SMARTICLES® technology on the delivery of DNA-based therapeutics, siRNA, antisense and decoy oligonucleotides.

Website: [www.novosom.com/](http://www.novosom.com/)

### **pSivida Corp**

pSivida's portfolio includes its BioSilicon™ technology, a nano-structured porous silicon specifically designed for use as a drug delivery platform. Unlike most polymer-based drug delivery systems, the manufacture of BioSilicon does not require complex chemistry and the final product is pure silicon irrespective of the delivery characteristics imparted by the nanostructuring process. BioSilicon has advantages over some other delivery systems in terms of its heat and radiation stability, simplifying the manufacturing and sterilization process. The platform also offers a high efficiency/capacity of drug loading, the ability to control release kinetics with extended durations (hours/days/weeks/months), the ability to vary nanosized pores to accommodate different molecule sizes, full bioerodibility over range of time periods and semiconductor properties that allow the construction of "smart" processor controlled delivery.

Website: [www.psivida.com/index.html](http://www.psivida.com/index.html)

### **Samyang Corporation**

As a company committed to research in DDS (Drug Delivery Systems), Samyang has developed a number of innovative products, e.g. an analgesic transdermal patch for cancer patients, an anti-emetic transdermal patch, patches for smoking cessation, an anti-inflammatory transdermal patch, and an oral colitis treatment. Samyang Pharmaceutical R & D Centre is developing FDT (fast dissolving tablets) that melt in the mouth without water, making it easy for children and the elderly to swallow medications. In addition, the Genexol-PM® Injection, which greatly reduces the side effects of earlier anti-cancer medications, is being clinically tested in the United States.

### **Sigma-Tau Pharmaceutical Corporation**

Sigma-Tau Pharmaceuticals, Inc. is a corporation dedicated to creating novel medicines for the unmet needs of patients with rare diseases. Truly unique in its field, Sigma-Tau places its considerable scientific resources behind the discovery of compounds that benefit the few. One of its products, ONCASPAR<sup>®</sup> is the only FDA-approved pegylated formulation of L-asparaginase, the enzyme that depletes the amino acid asparagine. For the last 25 years, L-asparaginase has been an important component in the treatment of acute lymphoblastic leukaemia .

Website: [www.sigmatau.com](http://www.sigmatau.com)

### **Starpharma**

Starpharma is an Australian-based company with a number of products and platforms under development using dendrimer technology. Starpharma's dendrimers are precisely defined, synthetic macromolecules, formed primarily from the amino acid lysine, that are well suited to pharmaceutical applications. One important property of dendrimers is "polyvalency" or the presence of multiple active groups on the surface of the dendrimer. This is significant because simultaneous presentation of active groups can yield entirely new or enhanced activity compared to single presentation of the same active group. Starpharma's current development programmes are in the areas of HIV and genital herpes prevention (VivaGel<sup>®</sup> , in clinical trials), other VivaGel<sup>®</sup> indications such as HPV, bacterial vaginosis and contraception, other drug delivery, siRNA delivery, and other life science and industrial applications for dendrimers.

Website: [www.starpharma.com/](http://www.starpharma.com/)

### **Skyepharma**

Skyepharma is a UK-based company with research and manufacturing facilities in Switzerland and France respectively. The company's insoluble drug delivery (IDD<sup>®</sup>), DissoCubes<sup>™</sup> and solid lipid nanoparticles (SLN<sup>™</sup>) technology platforms enhance the uptake and safety of water-insoluble drugs across a broad range of therapeutic classes, including anaesthetics, anti-cancer agents and immunosuppressants. There are currently nine approved products in the area of oral drug delivery that incorporate the Group's proven proprietary technologies. The Group's products are marketed in a number of countries throughout the world by leading and speciality pharmaceutical companies.

Website: [www.skyepharma.com/](http://www.skyepharma.com/)

### **Tekmira Pharmaceuticals Corporation**

Tekmira Pharmaceuticals Corporation, a Canadian biopharmaceutical company, has developed a siRNA delivery technology platform termed SNALP for "stable nucleic acid-lipid particles". SNALP are specialized lipid nanoparticles that fully encapsulate and systemically deliver a variety of nucleic acid molecules such as siRNA. Pre-clinical studies have shown them to be effective in delivering the drug to target organs and into cells where the nucleic acid-based drug can carry out its desired effect while minimizing systemic toxicity. SNALP technology relies on the "enhanced permeability and retention effect", which occurs

because these nucleic acid-containing particles have a long circulation time in the blood, resulting in increased accumulation at sites of vascular leak such as those found at sites of tumour cell growth, infection or inflammation. Once at the target site, cells take up the SNALP through endocytosis and the nucleic acid payload is delivered inside the cell resulting in unparalleled potency. In addition to the delivery platform, Tekmira is developing two lead RNAi products, ApoB SNALP for the treatment of hypercholesterolemia, or elevated cholesterol, and PLK SNALP as a novel, safe and effective anti-tumour drug in the treatment of cancer.

Website: [www.tekmirapharm.com/Home.asp](http://www.tekmirapharm.com/Home.asp)

### **Three Rivers Pharmaceuticals®**

In 2005 Three Rivers Pharmaceuticals® acquired the rights to the broad-spectrum intravenous antifungal AMPHOTEC® (amphotericin B cholesteryl sulphate complex). AMPHOTEC® comprised a lipid-based delivery system. Liver macrophages break down the AMPHOTEC® complex and release amphotericin B, which binds to lipoproteins that carry amphotericin B to the site of infection where the agent binds to ergosterol in cell membranes of infecting fungi. The membranes' permeability is altered and the intracellular contents leak out causing death of the fungi. AMPHOTEC®, originally developed by Sequus Pharmaceutical, Inc., is now marketed in many countries.

Website: [www.3riverspharma.com/products\\_amp.htm](http://www.3riverspharma.com/products_amp.htm)

### **XstalBio**

XstalBio is a Glasgow, UK-based company that specialises in advanced drug delivery. The company's platform technology, protein-coated microcrystals, is applicable to proteins, peptides, nucleic acids and vaccines and has the potential to improve therapeutic value, to strengthen patent cover for new biological entities and to extend product life-cycles. Protein-coated microcrystals (PCMC) are water-soluble micron-sized particles that consist of a core crystalline material, such as an amino acid, sugar or salt on which is coated the therapeutic biomolecule. They are prepared in a 1-step process that simultaneously dehydrates these two components and results in the immobilisation of the protein on the surface of the carrier. Particle morphology, protein payload and particle size can all be tuned *via* the appropriate choice of dehydration conditions. The PCMC technology provides a highly-differentiated method for preparing biomolecules as stable solid-state formulations and the particles may be engineered for a wide range of delivery options including parenteral, pulmonary, sustained release and transdermal.

Website: [www.xstalbio.com](http://www.xstalbio.com)

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