

# Nanotechnology for Drug Delivery: a Validated Technology?

**Kevin Bottomley**

Managing Consultant, PharmaVentures Ltd, Magdalen Centre, Oxford Science Park, Oxford OX4 4GA, UK



**Kevin Bottomley** has over 25 years of experience in the pharmaceutical (Roche & sanofi-aventis) and biotech (Inpharmatica) industry, involving senior positions in research, alliance management and business development. He has extensive experience of the drug R&D process, as well as participating in compound licensing and all aspects of biotech business development activities. Kevin has contributed to numerous successful projects, including product licensing and company fund raisings. Kevin has authored many peer-reviewed original articles and reviews.

## Introduction

First references to nanotechnologies and drug delivery date back to the late 1970s, as a means of improving drug bioavailability, either by enhancing aqueous solubility, prolonging exposure and/or targeting drug compound delivery. When a technology is determined as validated is often a debatable point but, for nanotechnology and drug delivery, evidence supports both the technical and commercial validation of this technology, both for

improving active ingredient exposure and targeting delivery of therapeutics. So what is the evidence supporting validation of nanotechnology for drug delivery and what are the prospects for this technology?

Nanotechnology refers to the generation of therapeutic relevant matter of between 1 and 100 nanometers. For drug delivery this includes generation of small crystalline drug forms, enhancing the exposed crystalline surface area and thereby improving aqueous solubility. Nanotechnology can also improve delivery of the active drug ingredient to the site of therapeutic action. This can either be by associating drug nano-particles with a carrier such as plasma albumin to improve organ targeting, or by encapsulating the active material in liposomes, to enhance compound half life and improve targeting.

## Nanocrystals

The market leading technology for the production of nano-crystalline drug forms is **Elan Corporation's** NanoCrystal<sup>®</sup> technology. NanoCrystal<sup>®</sup> particles are small particles of drug substance, produced by milling the drug substance using a proprietary, wet-milling technique.

To date, there are four drugs on the market which have specifically exploited NanoCrystal<sup>®</sup>.

- **Rapamune<sup>®</sup>** (sirolimus) from **Wyeth** received marketing approval from the US Food & Drug Administration (FDA), in 2000.
- **Emend<sup>®</sup>** (aprepitant) **Merck**, approved by the FDA in 2003
- **TriCor<sup>®</sup>** (fenofibrate) **Abbott Laboratories**, launched in December 2004
- **Megace<sup>®</sup> ES** (megestrol), **Bristol-Myers Squibb**, approved in July 2004 by the FDA

This is evidence of the technical validation of this technology and its contribution to providing effective therapeutics. With respect to commercial validation, in total there are 25 published references to deals involving third party access to this technology (both while owned by Elan and when the technology was developed by **Nanosystems LLC** (of **Eastman Kodak Co.**) (Table 1).

There is little information about individual deal values but

Year	Companies
2006	Abbott Laboratories, Inc.
2006	AstraZeneca Pharmaceuticals LP (of AstraZeneca plc)
2006	EntreMed, Inc.
2005	MAP Pharmaceuticals, Inc.
2004	EntreMed, Inc.
2004	F. Hoffmann-La Roche Ltd
2003	Janssen Pharmaceutica NV (of Johnson & Johnson)
2003	Bristol-Myers Squibb Co.
2001	NewBiotics, Inc.
2001	Verion, Inc.
2000	Lytropic Therapeutics, LLC
2000	Targeted Molecules Corporation
2000	Cytokine PharmaSciences, Inc.
2000	Atrix Laboratories, Inc.
1999	Sheffield Pharmaceuticals, Inc.
1999	Merck & Co., Inc.
1998	Merck & Co., Inc.
1998	Boehringer Ingelheim GmbH
1998	Rhône-Poulenc Rorer, Inc.
1997	Merck & Co., Inc.
1997	Wyeth-Ayerst Laboratories (of American Home Products Corp.)
1997	Warner-Lambert Co. (now Pfizer, Inc.)
1997	Astra Draco AB (of Astra AB)
1997	Merck & Co., Inc.
1996	Mimetix

Table 1 – Deals involving third party access to NanoCrystal<sup>®</sup> technology.

a pointer is the deal between NanoSystems and Merck in 1998, which has the potential for NanoSystems to receive US\$30 M in development payments, in addition to unspecified royalties.

A related but competing technology is **Dow Pharma's** Bioaqueous Solubilization Service, based on technology licensed from the **University of Texas at Austin** in 2002. This allows generation of small crystalline forms of drugs using non-milling approaches, specifically SFL (Spray Freezing into Liquid) and EPAS (Evaporative Precipitation into Aqueous Solution). In 2004, Dow Pharma announced a technology access deal with **Bristol-Myers Squibb**, which included fees, milestones and royalties contingent on the development of markets drugs availing of the technology. **Baxter** and **SkyePharma** (Dissocubes® and NanoEdge® respectively) and other service providers also offer proprietary technologies for the preparation of nanocrystals.

## Targeting Drug Therapies

Nanotechnology can provide a technical solution for delivering effective anticancer agents. Liposomes: phospholipid bilayers which encapsulate a drug, can ensure both effective exposure and targeting of the chemotherapy agent (*Table 2*). These structures provide a wrapper for hydrophilic drugs, reducing metabolism. The first examples of this class of therapy were licensed in the mid 1990s and, since then, there have been a large number of drugs which

Year	Companies combined
2006	Brookwood Pharmaceuticals, Inc., Genzyme Corp.
2006	Alnylam Pharmaceuticals, Inc., Inex Pharmaceuticals Corp.
2005	Defence R&D Canada, Hemispherx Biopharma, Inc.
2005	Bioxalis Medica, Inc., Procyon BioPharma, Inc.
2005	Immuno-Designed Molecules SA (IDM), Cambridge Laboratories Ltd
2005	Dr. Program Co. Ltd, Kyorin Pharmaceutical Co. Ltd
2005	Polymun Scientific Immunbiologische Forschung GmbH, Sanochemia Pharmazeutika AG
2004	Vectron Therapeutics AG, Pharmexa AS (formerly M&E Biotech AS)
2004	Zilip-Pharma, Bayer HealthCare LLC (of the Bayer Group)
2004	NeoPharm Ltd, Nippon Genetics Co. Ltd
2004	Inex Pharmaceuticals Corp., Enzon Pharmaceuticals, Inc.
2001	Endovasc Ltd, Inc., CytoGenix, Inc.
2001	Peregrine Pharmaceuticals, Oakwood Laboratories LLC
2001	Georgetown University, NeoPharm, Inc.
2001	Celsion Corp., National Institutes of Health (US NIH)
2000	CytRx Corp., Undisclosed
1998	Therapeutics 2000, Inc., Adams Laboratories, Inc.
1997	Sequus Pharmaceuticals, Inc., Bayer, Inc.
1997	Tel Aviv University Authority for Applied Research and Industrial Development Ltd (Ramot), Medis El Ltd
1996	MEHL/Biophile International Corp., Applied Genetics, Inc.
1996	Massachusetts Institute of Technology, Endorex Corp. (formerly ImmunoTherapeutics)

Table 2 – Selected liposome drug delivery deals.

use this nanotechnology to enhance their therapeutic effectiveness. These include DaunoXome®, Caelyx® and Myocet®, liposome formulated versions of daunorubicin. Since the first introduction of these drugs, the liposome technology has developed and matured to include surface presented polyethylene glycol (PEG) to reduce metabolism of the therapeutic, thereby increasing the half-life of the therapeutic and exposure to the drug. Typical deal structures include fees, milestones and in a low minority of examples undisclosed royalties. As with nanocrystals, liposomes are a mature validated technology.

## Abraxane®

Another clinically validated nanotechnology is exemplified by Abraxane from **Abraxis**. Abraxane (paclitaxel), approved by the FDA in January 2005 for the treatment of chemotherapy refractory metastatic breast cancer, uses drug nano-particles stabilised by albumin, to enhance the exposure of the active compound, at the tumour. This drug is the product of Abraxis' nanoparticle albumin bound technology and provides clinical validation of nanotechnology to both target and enhance the exposure of the drugs. Targeting of drugs using nanotechnology techniques by limiting systemic exposure can also reduce general drug induced toxicities.

## Summary and Potential future developments

Drug delivery nanotechnologies exemplified by nanocrystals, liposome and nano-particle-protein conjugates are mature technologies clinically and commercially validated. From the assembled evidence, nanotechnologies are a valuable adjunct to the development of new therapeutics. While nanotechnology is a buzzword which suggests exciting need developments in clinical therapies, it is clear that in the context of drug delivery, this is now a successfully validated technology, both therapeutically and clinically.

The future is exciting, not only with respect to the continued development and maturation of these established technologies, but there is also the prospect of new technologies which promise enhanced benefits in both control of drug targeting and exposure by enhancing both efficacy and safety. Currently in clinical trials are technologies which exploit micelles, monolayer equivalents of liposomes; dendrimers, regularly branched water soluble nanoparticles which can act as a carrier for hydrophobic active compounds; and nanoshells, nanoscale partials, which can be used to actively or passively target pathologies (such as cancers) within the body, and then release therapeutic agents.