

Drug Delivery Technology: Revolutionizing CNS Therapies

Use the incisive analysis, commentary, opinions and forecasts provided in this note to:

- gain an in-depth understanding of the technology landscape for invasive, minimally invasive and non-invasive delivery of CNS therapeutics and regenerative therapies
- assess the options available for the invasive delivery of small molecules, peptides, proteins, gene therapies and stem cells now & in the future
- assess the potential delivery options available for emerging non-invasive formulations including transdermal, intranasal, oral and buccal melts
- evaluate the use of ultrasound and convection enhanced delivery as alternative methods for CNS delivery
- gauge the current & future technology requirements of pharma, biotech & medical device companies developing CNS products & devices
- analyze how the market is evolving & the influence that drug delivery may have on pharma CNS pipelines
- identify key pharma & delivery companies focusing on the improved delivery of existing & novel CNS agents



Providing Independent, tailor-made, pharmaceutical thematic research

PharmaVision.co.uk

KEY FINDINGS:

- 2006 global CNS market worth over US\$100 billion

- The CNS market has attracted attention of specialty pharma and big pharma players such as Abbot, Astellas, AstraZeneca, Biogen, Boehringer Ingelheim Bristol-Myers Squibb, Dianippon Sumitomo, Eisai, Eli-Lilly, Forest Laboratories, GlaxoSmithKline, Lundbeck, Johnson & Johnson, Merck & Co., Novartis, Otsuka, Pfizer, sanofi-aventis, Schering AG, Merck Serono, Shire, Takeda, Tanabe, UCB and Wyeth

- Challenges remain to ensure the efficient and targeted delivery of agents across the blood brain barrier by invasive and non-invasive delivery methods to a provide flexible, reproducible and cost-effective method of managing CNS disorders

- Specialists are applying a plethora of platforms to deliver CNS agents and regenerative therapies, including needle free delivery, transdermal, intranasal, pulmonary, oral & buccal delivery

- Many new classes of drugs will reach the market over the next 6 years, driving future market growth including small molecules, peptides and regenerative therapies (stem cells and gene therapies). Their success is analyzed in detail and case studies provided to highlight the progress of each technology.

- The application of nanotechnologies including micellar nanoparticles, nanoparticles, nanocells and lipobridge systems offers significant opportunities for selective and targeted delivery of CNS products. A number of nano-enabled delivery systems are evaluated in this report.

- As the CNS market evolves new approaches to treatment of CNS are emerging utilizing stem cells and gene-based therapies. Several companies are working towards this goal including: Copernicus Therapeutics, Genzyme, Oxford Biomedica, NeuroGeneration and Pharmidex. A number of delivery options are currently being evaluated to optimize the clinical utility of these regenerative therapies and are analyzed in detail in the report.

Introduction

“The World Health Organization has indicated that CNS disorders are the major medical challenge of the 21st Century, yet treatments for most CNS disorders are either inadequate or absent. The CNS is the most challenging frontier for drug discovery largely because of the complexity of the brain and the existence of the BBB”

Alan Palmer, Chief Executive of Pharmidex, UK

The revenue derived from Central Nervous System (CNS) drugs is vast, in that such a large number of diseases and disease processes are grouped under the CNS “umbrella”. These include acute organic conditions, such as infection, pain (both acute and chronic); chronic organic conditions such as neoplasms, seizure disorders; chronic degenerative disorders such as multiple sclerosis, Parkinson’s disease, Alzheimer’s disease, and other dementias, as well as the range of functional disorders classified as mental illnesses: schizophrenia, affective and anxiety spectrum disorders, attention deficit hyperactivity disorder (ADHD), sleep disorders and addictions.

The CNS has always posed problems in terms of drug delivery, drug efficacy and safety/ tolerability because of the presence of the blood brain barrier (BBB). The BBB is composed of a layer of extremely tightly packed epithelial cells, saturated with enzymes designed to protect the brain by

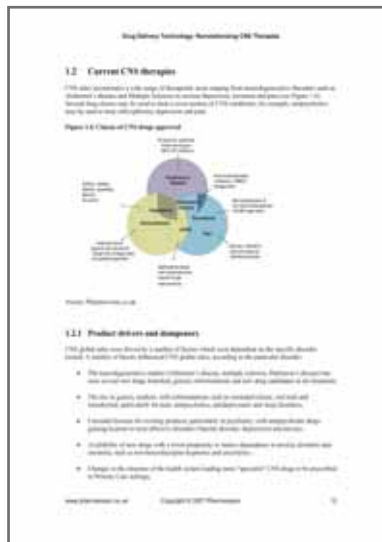
disallowing the entry of noxious substances via the bloodstream. The unfortunate by-product of this has been the problem of delivering beneficial drugs to the CNS in sufficient quantities to effectively treat the targeted condition without causing unacceptable systemic adverse reactions.

Administering drugs directly into the CNS e.g. intrathecally or intracerebrally, is an effective method of delivery but carries significant risks in terms of infection as well as being invasive and unpleasant for the patient. In recent years, methods of by-passing the BBB have been proposed, trialed and are now available, such as osmotic permeability, the use of nanoparticles small enough to penetrate the

BBB, ultrasonic adjunctive drug treatment, and stem-cell and gene therapy, which effectively provide a “self-cure” by promoting neuroplasticity and cell regeneration within the central nervous system itself.

New delivery methods such as transdermal drug delivery which can employ nanotechnology to increase absorption and bioavailability, as well as being non-invasive and simple to use are on the rise, and seem set to be used for a wide range of CNS disorders, including psychoses, pain and neurodegenerative disorders.

SAMPLE PAGES



SAMPLE PAGES FROM THE REPORT



EXPERTS FROM LEADING ORGANISATIONS CONSULTED:

Alan Palmer, Chief Executive of Pharmidex, UK

Arthur Tipton, President and CEO of Brookwood Pharmaceuticals

Charles Potter, Founder and Chief Executive Officer, Glide Pharmaceuticals

Robert Moen, M.D., Ph.D, President & CEO, Copernicus Therapeutics, Inc.

SEVEN QUESTIONS THIS NOTE ANSWERS:

1. How will the drug delivery technology drivers change in the CNS arena during the next decade and beyond?
2. What are the key delivery technologies and devices in the CNS field?
3. When are products and medical devices which utilize these key delivery technologies likely to reach the market?
4. Which drug delivery technologies are likely to win in the near-term and the long-term, and why?
5. Which companies are the winners in each technology category?
6. How are drug delivery technologies evolving to meet the demands of the CNS market?
7. Where are the market opportunities now and in the future?

COMPANIES MENTIONED:

Aastrom, Ablynx, Abbott Laboratories, Acadia Pharmaceuticals, Actelion, Alkermes, Alseres Pharmaceuticals, Altea Therapeutics, ALZA Corporation, Anesiva, Amarin, Arena, AstraZeneca, ArmaGen Technologies, Astellas, Axonyx, Biogen Idec, Boehringer Ingelheim Bristol-Myers-Squibb, Boston Life Sciences, Brookwood Pharmaceuticals, Cenomed BioSciences, CeNeRx, Ceregene, Clinical Data Online, Inc., Corcept, Cortex Pharmaceuticals, Copernicus Therapeutics, Cyberkinetics, Dainippon Sumitomo, Dermatrends, D-Pharm, DOV Pharmaceuticals, Durect, Elan Corporation, Eli Lilly, EKOS, Endo Pharmaceuticals, Epix, Esai, Fabre-Kramer, Forest Laboratories, GlaxoSmithKline, GPI Pharma, Generex, Genzyme Corporation, Glide Pharma, GW Pharmaceutical, Janssen, Juvantia Pharma, Johnson & Johnson, Inflazyme Pharmaceuticals, Ipsen, Ivax, Intranasal Therapeutics, King Pharmaceuticals, Kurve Technologies, Kyowa Lundbeck, Medtronic, MediciNova, Memory Pharmaceuticals, Midatech, MAP Pharmaceuticals, Medical technologies, Merck & Co., Merck Serono, Migenix, Myriad Genetics, Nabi Pharmaceuticals, Nanopharm, NeuroWave, Neuro3d, Neurocrine, Neurogen, Neurologix, NiTi Medical Technologies, NeoPharm, NeuroSearch, Neurocrine, Northwest Biotherapeutics, Novartis, NPS, Ono Pharmaceuticals, Otsuka Pharmaceutical, Organon, Ovation Pharmaceuticals, Oxford BioMedica, Pain Therapeutics, Pharmidex UK, Pharms, Perfusion Technology, Pfizer, Phase 2 Discovery, Potomac Pharma, Predix Pharmaceuticals, Prescient, Repligen, Roche, Saegis Pharmaceuticals, sanofi-aventis, Schering-Plough, Schering AG, Schwarz Pharma, Sepracor, Servier, Shire Pharmaceuticals, New River Pharmaceuticals, SK Pharmaceuticals, Solvay Pharmaceuticals, Sosei, Spherics, SurModics, Tanabe, Takeda, Teikoku Pharmaceuticals, Tissue Repair Cell Technology, Transpharma Medical, Targacept, Tetragenex, Teva Pharmaceuticals, Tikvah Pharmaceuticals, Titan Pharmaceuticals, Torrey Pines Therapeutics, Toyama Chemical, Trans-Tech Pharma, UCB, Valeant Pharmaceuticals, Vanda Pharmaceuticals, Wyeth, Xytis, Zogenix

About the author:



Ruth Ohlsen is trained as a general and psychiatric nurse in Australia, and has been a researcher at the Institute of Psychiatry, King's College London, since 1998. She has extensive experience of managing psychopharmacology and adverse events in mental health patients, and an interest is in antipsychotic induced weight gain and related metabolic effects, in which she is completing a PhD. She has lectured and published widely, both nationally and internationally extensively, and is the author of the Maudsley Antipsychotic Medication Review Service Guidelines.

purchase online NOW at www.pharmavision.co.uk

FUTURE TOPICS:

Drug Delivery Technology: Revolutionizing CNS Therapies is the fifth in a new series of ground breaking therapy-specific drug delivery market analysis notes. Each provides in-depth commentary, scientific technical and commercial analysis, opinion and market forecasts for the applications of drug delivery within a specific therapeutic area.

Previous titles include:

- **May 2007 Drug Delivery Technology: Revolutionizing Cancer Therapies**
(<http://www.pharmavision.co.uk/article84-drugdeliveryrevolutionizingcancertherapies.php>)
Author: Dr Cheryl L Barton
- **July 2007 Drug Delivery Technology: Revolutionizing Cardiovascular Therapies**
(<http://www.pharmavision.co.uk/article87-drugdeliverytechnology.php>)
Author: Dr Cheryl L Barton
- **September 2007 Drug Delivery Technology: Revolutionizing Diabetes Treatment**
(<http://www.pharmavision.co.uk/article90-drugdeliverytechnology.php>)
Author: Paul Evers
- **November 2007 Drug Delivery Technology: Revolutionizing Vaccine Development**
(<http://www.pharmavision.co.uk/marketingbrochures/paper94.pdf>)
Author: Dr Sara Sleigh

PURCHASE THIS REPORT NOW

Drug Delivery Technology: Revolutionizing CNS Therapies

PUBLICATION DATE: December 12th, 2007

NUMBER OF PAGES: 101

FORMAT: PDF (download direct from web or order CD-ROM)

PRICE: £945 / \$1,835.19 (approx) / €1,411.46 (approx)

How to order:

- 1) Purchase securely online at: www.pharmavision.co.uk
OR
- 2) Place your order by telephone. Call PharmaVision on +44 (0) 1243 785 496

CONTACT

Justin Anwyl, Purchasing
T: +44 (0) 1243 785 496
E: info@pharmavision.co.uk

www.pharmavision.co.uk

Registered in England Number 4598078
VAT Registration Number 801 1969 47

Nurses Cottage
Post Office Lane
North Mundham
Chichester
West Sussex
PO20 1JY
United Kingdom



purchase online NOW at www.pharmavision.co.uk

Table of Contents

1	The CNS market: opportunities for novel delivery technologies.....	7
1.1	Introduction.....	7
1.2	Overview of the market.....	8
1.2.1	Current market size.....	9
1.2.2	Patient population.....	10
1.2	Current CNS therapies.....	12
1.2.1	Product drivers and dampeners.....	12
1.3	CNS players & product pipeline.....	14
1.3.1	Key pharma players.....	14
1.3.2	Product pipeline.....	14
1.3.3	Product pipelines: neurodegenerative diseases, chronic organic conditions.....	22
1.3.4	Product pipeline: mental disorders, pain.....	23
1.4	Growth areas for CNS drug delivery.....	24
1.4.1	Penetrating the blood brain barrier.....	24
1.4.2	Transdermal delivery.....	24
2	Market drivers and opportunities for drug delivery technologies.....	25
3	Key drug delivery companies and academic researchers in CNS drug delivery.....	27
4	Current CNS drug delivery issues and opportunities.....	33
4.1	Delivery across the BBB.....	34
4.2	Improving patients compliance.....	34
4.3	Harnessing neuroplasticity.....	34
5	Invasive delivery technologies.....	35
5.1	Small molecule nano-enabled delivery.....	35
5.1.1	Case study: Paliperidone palmitate (Johnson & Johnson/Elan).....	35
5.1.2	Case study: DNA nanoparticles (Copernicus Therapeutics).....	35
5.1.3	Case study: Nanocells (Midatech).....	36
5.1.4	Case study: nab technology/Protosphere (Genomed BioSciences).....	37
5.2	Vaccine delivery.....	38
5.2.1	Case study: ProSavin (Oxford BioMedica).....	38
5.2.2	Case study: DCVax (Northwest Biotherapeutics).....	39
5.2.3	Case study: NicVax (Nabi Pharmaceuticals).....	39
5.3	Gene therapy delivery.....	40
5.3.1	Case study: non-viral delivery (ArmaGen Technologies).....	40
5.3.2	Case study: viral vectors (Neurologix/ Cornell Medical College).....	41
5.3.3	Case study: Intracerebral delivery (Genzyme Corporation).....	43
5.4	Stem cell delivery.....	43
5.4.1	Transplantation.....	45
5.4.2	Drug delivery of stem cells.....	45
5.4.3	Case study: NeuroGeneration.....	45
5.4.4	Case study: Neural stem cells (Institute of Cellular Medicine).....	46
5.4.5	Case study: Neural repair cells (Aastrom / Tissue Repair Cell Technology).....	46
5.5	Peptide delivery.....	47
5.5.1	Case study: Lipobridge technology (Genzyme Corporation / Pharmidex UK).....	48
5.5.2	Case study: "Design for Peptides" (Genzyme Corporation/ Brookwood Pharmaceuticals/SurModics).....	49
5.5.3	Case study: Nanobodies (Ablynx).....	50
5.6	Implants, pumps and electrical delivery systems.....	51
5.6.1	Case study: Duros implant (ALZA/NiTi Medical Technologies).....	51
5.6.2	Case study: Intrathecal delivery devices (Medtronic).....	53
5.6.3	Case study: "Brain Gate" implants (Cybernetics Inc).....	54
5.7	Our opinion on invasive drug delivery technologies.....	55
6	Minimally invasive delivery technologies.....	56
6.1	Ultrasound.....	56
6.1.1	Case study: Catheter for stroke & ischemic stroke (EKOS / NeuroWave).....	56
6.1.2	Case study: Ultrasonic delivery device (Perfusion Technology).....	58
6.2	Convection enhanced delivery.....	58
6.2.1	Case study: CED Research (University of California/National Cancer Institute).....	59
6.2.2	Case study: Cintredekin besudotox (NeoPharm).....	60
6.3	Our opinion on minimally invasive delivery.....	61
7	Non-invasive delivery technologies.....	62
7.1	Needle free delivery.....	62
7.1.1	Case study: Intraject delivery (Zogenix Inc).....	62
7.1.2	Case study: Glide solid dose injector (Glide Pharma).....	63
7.2	Transdermal delivery.....	65
7.2.1	Case study: PassPort system (Altea Therapeutics).....	65
7.2.2	Case study: Transdur patch (Durect / Endo Pharmaceuticals).....	66
7.2.3	Case study: Viaderm technology (Transpharma Medical).....	67
7.2.4	Case study: Exelon patch (Novartis).....	68
7.2.5	Case study: Antipsychotic patch (Dermatrends / Teikoku Pharma).....	69
7.2.6	Case study: Zingo (Anesiva).....	70
7.3	Intranasal/pulmonary delivery.....	72
7.3.1	Case study: Vianase - Controlled Particle Dispersion (Kurve Technology).....	72
7.3.2	Case study: Tempo inhaler (MAP Pharmaceuticals).....	73
7.3.3	Case study: Intranasal midazolam (Intranasal Therapeutics).....	73
7.4	Novel oral formulations.....	75
7.4.1	Case study: Remoxy (Pain Therapeutics / King Pharmaceuticals).....	75
7.4.2	Case study: Spheromers (Spherics/Takeda).....	75
7.4.3	Case study: Oros implant (ALZA Corporation).....	76
7.5	Buccal melt.....	77
7.5.1	Case study: Rapidmist (Generex).....	77
7.5.2	Case study: Sativex (GW Pharmaceutical).....	78
7.6	Reformulations.....	79
7.6.1	Extended release.....	79
7.7	Our opinion on non-invasive drug delivery technologies.....	80

Contents Cont'd

8	Market trends in drug delivery in CNS.....	81
8.1	Key drug delivery players in the CNS arena.....	81
8.2	Recent partnerships and acquisitions.....	86
8.2.1	Strategic partnerships & joint ventures.....	86
8.2.2	Acquisitions.....	88
8.2.3	Emerging specialty pharma companies.....	88
8.3	Market trends now 2006-2012.....	89
8.3.1	Global drug delivery market 2006-2012.....	89
8.3.2	Pharma drivers and drug delivery trends by 2012.....	90
8.4	Market by 2020.....	91
8.4.1	Pharma drivers and drug delivery trends by 2020.....	96
9	Summary & Conclusions.....	97
10	Bibliography.....	99
11	Acknowledgements.....	100

List of Figures

Figure 1.1:	Schematic of the blood brain barrier.....	7
Figure 1.2:	US\$100 billion global CNS market 2006.....	10
Figure 1.3:	Half a billion people affected with CNS conditions globally.....	11
Figure 1.4:	Classes of CNS drugs approved.....	12
Figure 1.5:	Drugs in clinical development for mental illness.....	14
Figure 4.1:	CNS delivery opportunities.....	33
Figure 5.1:	Mechanism of uptake of compacted DNA nanoparticles.....	36
Figure 5.2:	Gene therapy for Parkinson's disease.....	38
Figure 5.3:	ArmaGen's molecular Trojan horse.....	41
Figure 5.4:	New approaches to Parkinson's disease.....	42
Figure 5.5:	Sources of stem cells.....	44
Figure 5.6:	Applications of stem cells.....	47
Figure 5.7:	LipoBridge technology.....	49
Figure 5.8:	Ablynx's nanobodies.....	50
Figure 5.9:	Duros once-yearly osmotic implant.....	51
Figure 5.10:	Duros system for delivery of antineoplastic agents into the brainstem for brain tumour.....	52
Figure 5.11:	Sagittal CTS of Duros implant.....	52
Figure 5.12:	Medtronic Matric SCS system, percutaneous leads and laminotomy leads.....	54
Figure 5.13:	Cyberkinetics brain gate implant.....	54
Figure 6.1:	EKOS® NeuroWave™ Catheter in stroke.....	57
Figure 6.2:	The NeuroWave catheter.....	57
Figure 6.3:	Convection enhanced delivery image.....	59
Figure 6.4:	CED imaging.....	59
Figure 6.5:	Model of CED.....	60
Figure 7.1:	Intraject delivery device.....	62
Figure 7.2:	Application of interject device.....	63
Figure 7.3:	Glide delivery technology.....	64
Figure 7.4:	PassPort Delivery System - transdermal versus subcutaneous delivery of apomorphine in rats.....	66
Figure 7.5:	Trasndur - transdermal patch.....	67
Figure 7.6:	Viaderm transdermal delivery.....	68
Figure 7.7:	Exelon patch.....	69
Figure 7.8:	Dermatrend's A) transdermal technology and B) HRA molecule.....	70
Figure 7.9:	Anesiva's Zingo.....	71
Figure 7.10:	CPD delivery profile.....	72
Figure 7.11:	Spherics drug delivery technologies.....	76
Figure 7.12:	Oros drug delivery technologies.....	77
Figure 7.13:	Rapidmist device.....	78
Figure 8.1:	Total number of pharmaceutical and drug delivery deals (1997-2006).....	88
Figure 8.2:	Drug delivery deals as a proportion of specialty pharma deals (2000-2007).....	89
Figure 8.3:	Migration of CNS products from invasive to non-invasive delivery.....	91
Figure 8.4:	CNS drug delivery landscape by 2020.....	96

List of Tables

Table 1.1:	Table drug expenditure in 2006.....	9
Table 1.2:	Summary of key CNS drugs in clinical development - by therapeutic category.....	15
Table 3.1:	Leading CNS delivery companies.....	27
Table 5.1:	Medtronic's range of delivery technologies.....	52
Table 8.1:	Summary of leading drug delivery companies and their delivery technologies.....	81
Table 8.2:	Summary of recent alliances, agreements and acquisitions within CNS delivery.....	86
Table 8.3:	Forecasts of approved CNS products 2006-2012 (US\$ billion).....	89
Table 8.4:	Forecasts of pipeline DD driven CNS products 2006-2012 (US\$ million).....	90
Table 8.5:	Leading CNS drug delivery specialist by 2020.....	94