chapter ten

Drug delivery industry and the global outlook

According to Find/SVP market reports, U.S. sales in drug delivery systems surpassed $9 billion in 1999. The development of alternative drug therapies has been a major thrust over the past three decades. Alternative drug delivery devices, which cater to the increasing emphasis on cost-containment through outpatient care, include ambulatory infusion pumps, implanted infusion pumps, inhalers, other nasal delivery systems, injector pen systems, needleless systems, and transdermal systems. Emerging alternative drug delivery systems throughout the world include aerosol macromolecule and protein delivery systems, biologic and molecular systems, electrotransport and iontophoretic transdermal systems, and gene therapy.[1–8]

Despite the significant advances in the industry, it is estimated that fewer than 30% of the drugs currently on the market involve alternative drug delivery systems. Development has been slowed by the high costs of research and development of new technologies and by the lengthy procedures needed to secure approval from the regulatory agencies. Nonetheless, increasing concern over the high level of health care expenditures is expected to support the growth of cost-effective novel drug delivery systems.

While a few companies have addressed the demand for more convenience through the miniaturization of infusion pumps, other manufacturers continue to investigate ways of improving the administration of drugs. Companies such as Dura Pharmaceuticals have marketed completely novel systems for dry compounds, while others are advancing dissolution, electrotransport, liposome, and soft gelatin encapsulation technologies. However, most have focused on the lucrative area of sustained-release and transdermal patches, technologies with demonstrated capacities to extend product life and improve the therapeutic effectiveness of the active ingredient.[9–15]

Reasons for intense interest in developing new drug delivery systems have been improving conventional dosage forms, exclusivity for existing drugs, high cost for developing new drugs with new molecular entities, delivery of bioengineered compounds, and enhanced efficacy and safety. Market share

for conventional dosage forms, controlled-release, and novel delivery systems has been 90%, 10%, and less than 1%, respectively. However, in the future, for cost-containment and fast approval for marketing, controlled-release formulations with both rate-modulation and targeting capabilities will prove to be an essential component of effective therapeutic regimens.

According to Freedonia Group, Inc. reports, during the past decade, in a 5-year time period, drug delivery systems demands increased by 5% annually and drug delivery system end uses increased by 12%. This prospectus clearly demonstrates the judicial use of drug delivery systems as a valuable decision-making tool for the pharmaceutical industry.[16–19] Business strategies and market drivers from an industry perspective include a list of items, such as negotiating licensing agreements for new drug delivery technologies; forming strategic partnerships; watching market and consolidation trends in the drug delivery industry; leveraging a technology platform into a commercial strategy; targeting a pharmaceutical product pipeline, capitalizing on new drug delivery technologies, novel technologies, partnering in research and development, portfolio management, pricing, reimbursement and regulatory implications of novel systems within managed care, and government programs; and scrutinizing drug delivery companies from a Wall Street perspective.[20–24]

The global outlook for the development of drug delivery systems appears to be encouraging. This observation is supported by the numerous drug delivery systems listed in the following table. The developers and manufacturers of these delivery systems (see Table 10.1) are located throughout the world,[23,24] although concentrated in the U.S., Europe, and Japan. The data presented here is partial, but representative of the current status of drug delivery systems.[25–28]

In addition to these drug delivery systems, there are several other novel delivery systems that have been simultaneously developed. The categories of these systems are the following:

1. Controlled drug delivery systems, such as Snaplets, Eucaps Multipor, AdMMS, Angie, BioSert, submicronized fat emulsion delivery system, SES formula, Detach, Flo-tab, Flui-Dose, IPDAS, MICROCAP, microCRYSTAL, MicroDROPLET, Micro-Release, MOSTS, NANOZOME, OLipHEX, Oncholab, pHEMS, POLiM, ProLease, Pulsincap, fat-dissolving dosage form (FDDF), site-specific targeted delivery in the colon (STDC), Emisphere, Pegnology, HALO, and HIPN (heterogeneous interpenetrating polymer networks).
2. Transdermal drug delivery systems, such as Pediapatch, Plantar-Patch, Trans-Plantar, Trans-Ver-Sal, Dermaflex, Powerpatch, and cation-activated topical delivery systems.
3. Dental drug delivery systems, such as transoral mucosal anesthetic delivery system (TMADS) and PT-system (an acryl film).
4. Miscellaneous drug delivery systems, such as chemical delivery system for taste masking, immunoliposomes, osmicated liposomes,

Table 10.1 Developers/manufacturers of drug delivery systems

Drug	Drug delivery system	Developer/manufacturer
Ibuprofen	EUCAPS	Euderma, Ciba-Geigy Sankyo
Ibuprofen	Synchron technique	Forest Labs.
Ibuprofen	Liquitard sustained	Eurand Release Technique
Ibuprofen	MICROCAP multiparticulate dosing system	Eurand
Ibuprofen	Softgel (Scherersol) formulation	R.P. Scherer
Indomethacin	IV	Dumex
Indomethacin	Transdermal	KOWA
Indomethacin	Repro-Dose	Hafslund Nycomed
Ketoprofen	Transdermal	Hisamatsu
Ketoprofen	INDAS	Elan
Piroxicam	Topical gel	KRKA, Hyal Pharm
Lithium	Synchron technology	Forest Labs, Johnson & Johnson
Glucagon	Intranasal	Akzo, Novo-Nordisk
Testosterone	Sublingual transdermal	Gynex, TheraTech, CEPA
Contraceptive	Transdermal	Warner Lambert
Estradiol	Transdermal	TheraTech, Solvay
γ-Interferon	Erythrocyte delivery	Novacell
Immunomodulators	Erythrocyte delivery	Novacell
Glucosamyl Muramyl analogs	Liposomes	Immunotherapeutic
Hexamethylmelamine	Microemulsion	Biotech Develop Corp.
Lomustine	Redox drug delivery	PharmTec
Methotrexate	Biodegradable gel-like matrix	Matrix Pharma
Carbamazepine	Molecusol cyclodextrin delivery	PharmTec
Dexmedetomidine	Transdermal	Cygnus
Dihydroepi-androsterone	Transdermal	Pharmedic
Inositol hexaphosphate	Erythrocyte delivery	Novacell
Alprenoxine-HCl	Site-specific delivery	Xenon Vision
Ketoprofen	INDAS	Elan
Diclofenac	Ophthalmic	Wakamoto Pharm.
Diclofenac	Topical	Hyal Pharma
Flurbiprofen	Ophthalmic	Boots, Allergen
Hyaluronic acid	Ophthalmic	Seikagaku Kogyo
Lovobunolol	Ophthalmic	Warner Lambert, Allergen
Ofloxacin	Ophthalmic	Daiichi, Allergen, Bausch & Lomb
Pilocarpine	Soluble ophthalmic delivery	Diversified Tech.
Suprofen	Ophthalmic	CuSi
Metoclopramide	Nasal	Nastech, Rugby

Table 10.1 Developers/manufacturers of drug delivery systems (Continued)

Drug	Drug delivery system	Developer/manufacturer
Ribavarin	Brain-specific carrier system	Pharmos
Gentamicin	Liposomes	The Liposome Co., 3M
Zidovudine	Redox delivery	Pharmos
Asparaginase	Erythrocyte delivery	Novacell
Daunorubicin	Liposome	Vestar
Butorphenol	Nasal	Nastech, Bristol-Myers Squibb
Diazepam	Rectal solution	Dumex
Tetrahydroacridine	Redox brain delivery	Pharmos
Tetrahydrocannabinol	Molecusol cyclodextrins	Pharmos
Valproate sodium	Brain-specific delivery	Pharmos
Amphotericin	Liposome	Vestar, Fujisawa
Histamine H2-receptor antagonists	Nasal	Nastech
Antiemetics	Nasal	Nastech
Doxorubicin (Evacet)	Liposome	The Liposome Co.
CDP870	Pegylation technology	Inhale Therapeutics
Insulin (Exubera)	Inhalation	Aventis/Pfizer
Neulasta	Inhalation	Amgen
Pegasys	Inhalation	Roche
Somavert	Inhalation	Pharmacia
Risperidol (antipsychotic)	Oros	J & J (Alza)
Topamax (antiepileptic)	Oros	J & J (Alza)
Ortho Evra	Contraceptive patch	Ortho-McNeill
Lotemax (loteprednol)	Ophthalmic	Bausch & Lomb
Alrex	Ophthalmic	Bausch & Lomb
Singulair (montekulast)	Inhalation	Merck
Nasonex (mometasone)	Inhalation	Schering-Plough
Beconase (corticosteroid)	Inhalation	GSK
Vancenase (corticosteroid)	Inhalation	Schering-Plough
Pulmicort respules	Inhalation (Budesonide)	AstraZeneca
Flonase (fluticasone)	Inhalation	GSK
Azmacort triamcinolone)	Inhalation	Rhone Poulenc Rorer
Climara (estradiol)	Transdermal	3M-Berlex
Zomig (Zolmitriptan)	Nasal spray	AstraZeneca
Interferon beta-1a	Inhalation	Inhale Therap
Spiros	Aerosol	Dura
Pulmosol (proteins)	Inhalation	Inhale Therap
Larger particles	Inhalation	Alkermes
Therap. agents	Inhalation	Aradigm
Powder formulations	Transdermal	Powder Tech
E-Trans	Iontophoresis	Alza
Macroflux	Transdermal	Alza
Sono-Prep Syst	Ultrasound-transdermal	Sontra Medical
Therap. agents	Microchip drug delivery	MicroCHIPS
Depofoam	Extended release	Skye-Pharma

Table 10.1 Developers/manufacturers of drug delivery systems (Continued)

Drug	Drug delivery system	Developer/manufacturer
Concerta	OROS-Tech	Alza
Duros/Alzamer	Implant	Alza
Proteins	ReGel/Oligosphere	MacroMed
Medisorb/Prolease	Microspheres	Alkermes
Macromolecules	Carrier Tech	Emisphere
Vaccines, insulin, proteins	Orasomes	Endorex
Macromolecules	Oral/Promdas/Locdas	Elan
Rapamune (immunosuppressant)	Nanocrystal Tech	Elan

stealth liposomes, pyran oil as diluents, caragennan complexes, collagen-based liposomes and the use of HYAFF membranes, and TOGA gene delivery.

Drug delivery is playing a significant role in the pharmaceutical industry such that new drug delivery systems and a diverse range of technology options have emerged. The drug delivery market is currently estimated to be worth approximately $50 billion, and worldwide sales could reach as much as $100 billion by 2005. Big pharmaceutical companies, unfortunately, are experiencing "dry" product pipelines. Consequently, they are looking to acquire drug delivery companies as a means of filling their gaps.

A recent industry survey estimated that there are more than 300 companies engaged in the development and licensing of drug delivery technology. By merging with a drug delivery company, the big pharmaceuticals add to their core business by extending the exclusivity and life cycle of a marketed product, enhancing patient compliance, improving the biopharmaceutical properties of a new chemical entity, or enabling delivery via a new route.

Sometimes, a higher risk is worth taking in areas of high unfulfilled medical need, where the new delivery technology can potentially enable the innovative NCE to significantly advance the current standard of care and become a commercial blockbuster medicine.

The final goal has been winning in the marketplace, which is where we ultimately want to get to first and quickly. These products have to be developed and launched before loss of exclusivity. For a product (either old or new) in a drug delivery system, the same "Go/No-Go" rules apply for its development for the market. The attraction of increased revenues through product sales is likely to lead to numerous mid-sized drug delivery companies becoming fully integrated pharmaceutical companies. A recent survey has estimated that, on average, big pharmaceuticals have about five drug delivery deals per year and smaller pharmaceuticals have about two delivery deals per year.

More than half of the current drug delivery market is based on technologies for the oral delivery of drugs. Oral dosage forms will remain as the primary dosage form; however, in the future, alternative routes of adminis-

tration are likely to increase in prominence. Development and adoption of delivery technologies will be influenced by trends in pharmaceutical discovery portfolios, therapeutic area focus, and patient demographics. Increased prominence of biotechnology-derived products in the marketplace will play a major role in shaping drug delivery technologies. Current estimates are that biotechnology products will contribute $120 billion by 2010, and needleless delivery systems are predicted to increase to about $1 billion by 2005. However, just as any conventional drug could be recalled or removed from the market, either NCE or an established drug in a drug delivery system could experience a similar fate. For example, Wyeth recently discontinued production of Norplant, a levonorgestrel implant for contraception, as women and health care professionals continued to report adverse effects with this product.

It is likely that during the next several years, extensive work on these delivery systems or those that are similar to these will be continued. Additional drug delivery systems and methods may include, for example, refinements in timed-capsule delivery, contact lenses soaked with antibiotics, plastic wafers that can convey medications into the bloodstream quickly, and a powder consisting of microsponges that transmit antibiotic transdermally where they are sprinkled.[29,30]

New drugs will continue to be developed, but at a slower pace due to higher costs and government regulations. However, the advent of drug delivery systems — that is, more patches and specific chemical compounds (e.g., liposomes, cyclodextrins, etc.) designed to extend the life of drugs — may well enhance the future of the research-based pharmaceutical companies. Through these systems, products can have extended patent life and be produced at lower cost, and products that have not been commercially available due to high production costs will now be commercially viable.[31–35]

References

1. Madley, S.W., Oral delivery of macromolecules and continued movement shape the drug delivery industry, *Contract. Pharma.*, April/May 2002, 36–44, 2002.
2. Roth, G.Y., Delivering profits, *Contract. Pharma.*, April/May 2000, 50–54, 2000.
3. Henry, C.M., *Special Delivery C&E News*, Sept. 18, 2000, 49–65.
4. Henry, C.M., *Drug Delivery, C&E News*, August 26, 2002, 39–45.
5. Horspool, K.R., Future strategies for the drug delivery industry, *Am. Pharm. Rev.*, 5, 20–24, 2002.
6. Charlish, P., *Scrip Magazine*, May 2000, 27–32.
7. Drews, J., *Drug Discovery Today*, 2000, 5, 2–4.
8. Jain, K.K. in *Drug Delivery Technologies and Markets*, Informa Publishing Group, Ltd., 2000, 144.
9. Kermani, F. and Findley, G., in *The Application of Drug Delivery Systems: Current Practices and Future Strategies*, CMR International, Epsom, U.K., 2000.
10. Langer, R., Drug delivery and targeting, *Nature*, (Suppl. 6679) 1998, 392, 5–10.
11. Pulazzinnini, A. and Segantini, L., *Scrip Magazine*, May 2001, 7.
12. Putney, S.D., *Pharmaceutical News*, 1999, 6, 7–10.

13. Shi, M. et al., *Modern Drug Discovery*, July 2001, 27–32.
14. Tinebo, K. and Siebert J.M., Presentation at the Sixth Annual Drug Delivery Partnerships Meeting, Los Angeles, January 28–30, 2002.
15. Park, K. and Mresny, R.J. Eds., Controlled drug delivery: designing technologies for the future, *ACS Symposium Series 752,* American Chemical Society, Oxford University Press, New York, 2000.
16. Shao, J. et al., A cell-based drug delivery system for lung targeting, I. Preparation and pharmacokinetics, *Drug Deliv.*, 8, 61–69, 2001.
17. Pignatello, R. and Amico, D., Preparation and analgesic activity of Eudragit RS100 microparticles containing diflunisal, *Drug Deliv.*, 8, 35–45, 2001.
18. Singh, M. and Kosoon, N., Receptor-mediated gene delivery to HepG2 cells by ternary assemblies containing cationic liposomes and cationized asialoorosomucoid, *Drug Deliv.*, 8, 29–34, 2001.
19. Quadir, M. et al., Development and evaluation of nasal formulations of ketorolac, *Drug Deliv.*, 7, 223–229, 2000.
20. Sinha, J. et al., Targeting of liposomal andrographolide to *L. donovani*-infected macrophages *in vivo*, *Drug Deliv.*, 7, 209–213, 2000.
21. Risbud, M.V. and Bhonde, R.R., Polyacrylamide-chitosan hydrogels: *in vitro* biocompatibility and sustained antibiotic release studies, *Drug Deliv.*, 7, 69–75, 2000.
22. Dass, C.R. and Walker, T.L., A microsphere-liposome (microplex) vector for targeted gene therapy of cancer, II. *In vivo* biodistribution study in a solid tumor model, *Drug Deliv.*, 7, 15, 2000.
23. Petrikovics, I., McGuinn, W.D., et al., *In vitro* studies on sterically stabilized liposomes (SL) as enzyme carriers in organophosphorous (OP) antagonism, *Drug Deliv.*, 7, 83–89, 2000.
24. (a) Dass, C.R. and Jessup, W., Apolipoprotein A-I, phospholipid vesicles and cyclodextrins as potential anti-atherosclerotic drugs: delivery, pharmacokinetics and efficacy, *Drug Deliv.*, 7, 161–182, 2000; (b) Mishra, P.R. and Jain, N.K., Reverse biomembrane vesicles for effective controlled delivery of doxorubicin HCl, *Drug Deliv.*, 7, 155–159, 2000; (c) Allen, C. et al., PCL-b-PEO micelles as a delivery vehicle for FK506: Assessment of a functional recovery of crushed peripheral nerve, *Drug Deliv.*, 7, 139–145, 2000.
25. Wechsler, J., Harmonizing clinical trials, *Applied Clinical Trials*, 1, 14–22, 1992.
26. Reinhart, S.P. and Trotter, J.P., Incorporating economic analysis into clinical trials, *Applied Clinical Trials*, 1, 46–50, 1992.
27. (a) The businessman's guide to EC legal developments, InterPharm Press; (b) Future system for the free movement of medicinal products in the European community, InterPharm Press; (c) Product liability in Europe, InterPharm Press; (d) EC drug registration, notes for guidance, InterPharm Press; (e) Guide to working in a Europe without frontiers, InterPharm Press; (f) EC Pharmaceuticals after 1992, InterPharm Press; (g) 1992 and the European pharmaceutical industry, The EC directives, InterPharm Press; (h) EUCOMED harmonization of medical device regulation in Europe, InterPharm Press; (i)Therapeutics in Australia, InterPharm Press; (j) Guide to medical device registration in Japan, InterPharm Press; (k) The Japanese pharmaceutical challenge, InterPharm Press; (l) Pharmaceutical innovations: recent trends, future prospects, InterPharm Press; (m) Multinational drug companies: issues in drug discovery and development, InterPharm Press.
28. Stephenson, J., Who gains, who loses from a European formulary?, *Pharm. Tech.*, 15, 26–29, 1991.

29. Rolf, D., Chemical and physical methods of enhancing transdermal drug delivery, *Pharm. Tech.*, 12, 130–141, 1988.
30. Schlom, J., Monoclonal antibodies in cancer therapy: the present and the future, *Pharm. Tech.*, 12, 56–60, 1988.
31. (a) Pharmaceutical dosage forms: Disperse systems, InterPharm Press; (b) Chien, Y., Novel drug delivery systems: Fundamentals, development concepts, biomedical assessments, InterPharm Press; (c) Drug development: From laboratory to clinic, InterPharm Press; (d) Groves, M.J., *Parenteral Technology Manual*, InterPharm Press, 1989.
32. Hamrell, M.R. and Chew, N.J., New development strategies for life-threatening illnesses., *Bio. Pharm.*, 5, 18–21, 1992.
33. (a) Kydonieus, A., Ed., *Treatise on Controlled Drug Delivery: Fundamentals, Optimization and Application*, Marcel Dekker, New York, 1992; (b) Pardridge, W.M., *Peptide Drug Delivery to the Brain*, Raven Press, 1991; (c) Tomlinson, E. and Davis, S.S., Eds., *Site-Specific Drug Delivery*, John Wiley & Sons, New York, 1986; (d) Juliano, R.L., Ed., Biological approaches to the controlled delivery of drugs, *Annals. of N.Y. Acad. Sci.*, 1987; (e) Shaw, J.M., Ed., *Lipoproteins as Carriers of Pharmacological Agents*, Marcel Dekker, New York, 1991; (f) Chien, Y.W., Su, K.S.E., Chang, S., *Nasal Systemic Drug Delivery*, Marcel Dekker, New York, 1989; (g) Davis, S.S., Illum, L. McVie, J.G., and Tomlinson, E.. *Microspheres and Drug Therapy: Pharmaceutical, Immunological and Medical Agents* Elsevier, 1984; (h) Kydonieus, A.E. and Berner, B., *Transdermal Delivery of Drugs*, Vols. 1–3, CRC Press, Inc., Boca Raton, FL, 1987; (i) Guiot, P. and Couvreur, P., *Polymeric Nanoparticles and Microspheres*., CRC Press, Inc., Boca Raton, FL, 1986; (j) Tyle, P. and Ram, B.P., *Targeted Therapeutic Systems*, Marcel Dekker, New York, 1990; (k) Wise, D.L., *Biopolymeric Controlled Release Systems*, Vols. 1–2, CRC Press, Inc., Boca Raton, FL, 1984; (l) SaeHore, M.E., Bucci, M., and Speiser, P., Eds., *Ophthalmic Drug Delivery: Biopharmaceutical, Technological and Clinical Aspects*, Liviana Press, Springer-Verlag, Padova, Italy, 1987; (m) Roerdink, F.H. and Kroon, A.M., Eds., *Drug Carrier Systems*, John Wiley & Sons, New York, 1989; (n) Rodwell, J.D., Ed., *Antibody-Mediated Delivery Systems*, Marcel Dekker, New York, 1988; (o) Ansel, H.C. and Popovich, N.G., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Lea & Febiger, Philadelphia, 1990; (p) Gregoriadis, G., Senior, J., and Poste, G., *Targeting of Drugs with Synthetic Systems*, Plenum Press, New York, 1986; (q) Krowczynski, L., *Extended-Release Dosage Forms*, CRC Press, Inc., Boca Raton, FL, 1987 (r) Hsieh, D.S.T., *Controlled-Release Systems: Fabrication Technology*, Vols. 1 and 2, CRC Press, Inc., Boca Raton, FL, 1988; (s) Tirrell, D.A., Donaruma, L.G., and Turek A.B., Eds., Macromolecules as drugs and as carriers for biologically active materials, *N.Y. Acad. Sci.*, New York, 1985; (t) Thompson, K. and Burrill, G.S., Pharmacoeconomics and health care reform, *Bio. Pharm.*, January-February, 7, 50–52, 1994; (u) Wechsler, J., Healthcare takes center stage in Washington, *Pharm. Tech.*, 17(1), 16, 1993; (v) Knowles, M.R., Surviving health care system reforms, *Pharm. Executive*, 14(4), 38, 1994; (w) Wagner, J.R., Angst, health care reform and the German market, *Pharm. Executive*, 14(7), 38, 1994.
34. Varma, R.K. and Garg, S., Current status of drug delivery technologies and future directions, *Pharm. Technol. On-line*, 25 (2), 1–14, 2001.
35. Kannan, V., Kandarapu, R., and Garg, S., Optimization techniques for the design and development of novel drug delivery systems, Part 1, *Pharm. Tech.*, February 2003, 74–90.