

Challenges and Opportunities in Emerging Drug Delivery Technologies

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The challenge of identifying and managing complex technology and intellectual property (IP) portfolios, such as those found in the drug delivery arena, and successfully leveraging these assets to create new opportunities is a critical element in the success of the modern, technology and IP driven firm. In today's hyper-competitive environment, it is not enough for firms to focus only on short-term technology development based on existing core competencies and IP; they must be able to place long-term technology bets, based on the convergence of trends in the stakeholder value chain, user base and technology development.

A structured methodology for the integration and infusion of trend mining and convergence analysis (from emerging technology development, market dynamics, and user and stakeholder needs) into the technology portfolio planning process allows organizations to more effectively leverage their investments in innovation while increasing the probability of major opportunity creation – ultimately translating these discrete wins into overall firm success.

The challenges and opportunities created by emerging technologies within the drug delivery landscape are surveyed in this context.

Introduction

The drug delivery technology landscape is highly competitive and rapidly evolving. The market involves both numerous startups and major players in the medical device, pharmaceutical and biotechnology industries. This is a market with intensive intellectual property protection. Products that have been brought to market or that are in clinical trials often involve combinations of technologies from multiple players, with complex licensing and strategic partnering relationships.

New classes of pharmaceuticals and biologics (peptides, proteins and DNA-based therapeutics) are fueling the rapid evolution of drug delivery technology. These new drugs typically cannot be effectively delivered by conventional means. Additionally, it has been determined that, for many conventional pharmaceutical therapies, the efficacy may be improved and the side effects reduced if the therapy is administered continuously (although potentially variable rate), rather than through conventional burst release techniques (oral ingestion, injection, etc).

The benefits from targeted, localized delivery of certain therapeutic agents are another driving force in this market. Additional drivers include the desire to eliminate or minimize the danger of needle stick injuries (and blood-borne pathogens) to healthcare workers, increase patient compliance by simplified or reduced stigma delivery methods, reduced healthcare worker involvement and reduced health care costs.

Increasingly, delivery devices and drugs will be more tightly coupled. In some cases, device development is beginning as early as the discovery phase of the pharmaceutical development process. To compete in this arena companies must be able to demonstrate the value that their combination of drugs and delivery devices and/or systems bring to the market. To improve the odds of a successful product introduction, companies must be implementing advanced development and technology portfolio plans that define the technologies and delivery devices that will be funded. Because drug development can be a 10-year undertaking, advanced development and technology portfolio plans need to be concerned with market requirements and value propositions more than a decade into the future. Short-sightedness in focusing only on near-term shareholder needs in the face of

numerous drug patent expirations while neglecting the emerging delivery trends will fail to maximize the value potential of these opportunities.

Challenges

Historically, drug delivery has taken the form of injection, infusion, ingestion, and inhalation, with additional variations of each category. For example ingestion may be in tablet, capsule or liquid form; inhalation may be via use of a dry powder inhaler, an MDI, or a nebulizer. The challenge for both drug and drug delivery companies is to deliver both existing and emerging drug technologies in a manner that improves the benefits to the patients, healthcare workers and the healthcare system. Areas that are being targeted for improvements through device development include:

- Improved efficacy
- Reduced side effects
- Continuous dosing (sustained release)
- Reduced pain from administration
- Increased ease of use
- Increased use compliance
- Improved mobility
- Decreased involvement of healthcare workers
- Improved safety for healthcare workers
- Reduced environmental impact (elimination of CFC's)

To provide these benefits, a number of approaches are being (or in some cases have been) developed. The common thread running through the approaches is the concept of self-administered, targeted, sustained release with increased bioavailability. Determining which of the emerging approaches best meets stakeholder needs is a complex, multifaceted problem.

Although ingestion is probably the most widely accepted form of delivery it presents difficulties for a number of important classes of drugs. Many drug delivery scientists view oral delivery as the ideal drug delivery method. In the case of proteins and peptides, historical oral delivery mechanisms can only deliver bioavailabilities of a few percent. In some cases, dose limiting toxicity levels are caused by lack of selectivity. Although oral delivery meets the need for self-administered drugs, targeted, sustained release and increased bioavailability present the areas of difficulty in meeting the emerging value proposition.

To address this difficulty, companies are developing micro-fabricated drug delivery systems. Technologies such as nano-pore membranes and micro-particles enable the drug to survive stomach acids and be released at specific targeted areas of the gastrointestinal tract. These technologies are being developed to provide more efficient drug absorption and enhanced bioavailability.

Pulmonary delivery provides a number of benefits particularly with regard to absorption area and avoidance of first pass metabolism in the liver. However, meeting the sustained-release goal is somewhat problematic. The lungs tend to expel materials that are introduced and it is therefore difficult to keep the drug in the lung long enough for the sustained release to be effective. Additional challenges revolve around elimination of excipient (enabling delivery of a neat drug), elimination of CFC propellants (in the case of MDI), reduction of the stigma associated with inhalers, and ease of use. A number of companies are working in this arena with technologies varying from ultrasonic de-aggregation, to heat vaporization of the drug.

Transdermal patches have been used for a number of years. To improve their effectiveness for a broader range of drugs, devices are being developed that disrupt the skin barrier to allow drug transfer to the interstitial fluid. Technologies are being developed that range from ultrasonic disruption of the skin, to micro-projections, to using

electro-transport to drive molecules through the skin barrier. These technologies are being developed individually and in various combinations.

Although from a patient standpoint the elimination of injections is ideal, indications are that injection will remain a necessary means of drug delivery. To minimize the pain, biohazard, cost and inconvenience associated with injections, companies are working to reduce the negative aspects of this delivery method. Along these lines, advances in needle-free injection, micro needle injection and MEMS syringes are under development. To minimize the number of injections required new implants and time release approaches are in development.

Meeting the need for better bioavailability and reduced side effects is not being left only to the mechanical delivery systems; methods are being developed to better target the drug once it is introduced into the body. Ultrasound or other energy sources are being used to activate the drug once it reaches the targeted location. Receptors are being used to target specific cells, and in the event that a targeted cell does not have a required receptor, methods for adding receptors for a specific drug are being developed.

Competitive Landscape:

A top-level view of the competitive landscape and some of the companies involved in various areas has been developed as follows:

Sustained Release Technology

- Injectable: MacroMed (Oligosphere); Alkermes (ProLease, Medisorb)
- Oral: (MacroMed (SQ2Gel); Altus Biologics (Crystalized proteins); Alkermes (PLG microspheres); Spherics (sticky spheres); DepoMed (GR System)
- Ocular: InSite Vision (Durasite polymer eye drops)
- Pulmonary: Acusphere (microspheres); Alkermes (AIR microparticles)

Targeted Delivery Technology

- Ultrasound activated: Point Medical (biSpheres); ImaRx (NanoInjection)
- RF activated: Scintipharma (Intelesite capsule)

Enhanced Absorption/Transport Technology

- Enhanced transmucosal absorption: Genex Biotechnology (oral mucosa target); Anesta Corp. (OTS oral mucosa target)
- Enhanced transdermal absorption: Sontra (ultrasonic); Antares (CombiGel – transdermal gel); Altea (micropore technology); TransPharma Medical; Norwood Abbey (laser)

Implantable Technology

- Constant release: Alza (DUROS Implant); Guilford Pharmaceuticals (polymer wafers)
- Controllable release: MicroCHIPS (programmable MEMS implant)

Pulmonary Systemic Delivery

- Dry Powder: Nektar Therapeutics (formerly Inhale Therapeutic Systems (inhance, PulmoSpheres)); Alkermes (AIR); Meridica (Xcelovair); GlaxoSmithKline (Diskus, Advair)
- Liquid Aerosol: Aradigm (AERx); Evit Labs (Sonik, LDI); Meridica (Xcelovent); Chrysalis Technologies ; GlaxoSmithKline (non CFC MDI's)

Transdermal/Intramuscular Technology

- Bolus injection: Becton Dickenson etc.
- Gas-based injection: Bioject (Biojector 2000); PowderJect (powder-based injection)
- Mechanical injection: Bioject (Vitajet 3); antares/Medi-Ject (Vision – Insulin injector, ZomaJet, SciToJet); Norwood Abbey

- Micro needles: Altea/Elan (MEDIPAD); BioValve; Alza (Macroflux); MEMS Syringe (Berkeley); Norwood Abbey
- Electrotransport (Iontophoresis): Alza (E-Trans); Hisamitu Pharma; Iomed Clinical Systems; Vyteris; 3M Drug Delivery Systems
- Ambulatory “Wearable/Reusable” Infusion: Abbott (AIM); Medtronic (MiniMed); PRO-MED (Smart Dose); Electronic Infusion Systems (I-Flow, VIVUS 4000); I-Flow (Homepump Eclipse and C Series, Paragon); Animas (IR 1200 insulin pump)
- Ambulatory “Disposable” Infusion: Insulet (Insulin, basal and bolus)

Meeting the Challenge:

Meeting the challenges that are presented by emerging drug technologies and the requirement for improved stakeholder benefits, including the impact of the aging population, will require some combination of drugs, delivery devices and mechanisms currently underdevelopment, as well as the identification and integration of new yet to be defined technologies. Complicating the need for self-administered, targeted, sustained release with increased bioavailability, is the need to improve patient compliance. To achieve improved compliance will require further simplification of the user experience. The next step can easily be envisioned as involving further integration of devices and drugs to provide means to deliver multiple therapies in a simple, pain free, unobtrusive, and targeted sustained release device. The proper combination of technology portfolios, intellectual property, market and stakeholder understanding required achieve this next step is the challenge on the horizon.

Making sense of this complex interaction of competing companies, intellectual property, core competencies, stakeholder needs, and technology trends, in a manner that will meet the corporate goals requires a structured methodology, such as the Innovation Genesis framework, to drive corporate planning and decision-making. Based on the corporate strategies, portfolio investments can be managed to meet the appropriate mix of high and low risk activities for the company. By establishing a deep understanding of convergent trend (and the conditions and drivers underlying the trends), and by maintaining knowledge of emerging technologies outside the core competencies of the firm, IP and technology portfolio strategies can be optimized. Visibility of long-range evolution scenarios enables actionable short and mid range activities, and decisions that are aligned with the long term goals. In short, this structured methodology enables Strategic Innovation. The approach enables informed technology investments that deliver meaningful business consequences, and the development of new ideas that fundamentally change the basis of competition within the drug delivery industry.

Conclusion

The expanding arena of emerging drugs combined with increased sensitivity to clinical outcomes and healthcare costs are driving the need for alternative drug delivery methods and devices. More and more, the development of drugs and the development of delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. As new methods are developed and patented, the intellectual property landscape becomes congested. Some companies may find themselves locked out and in a position of having few attractive paths to market. Possibly worse, is the potential for a pharmaceutical company to find itself in the unenviable position discovering a potential blockbuster drug that requires a delivery method that is thoroughly protected by a competitor’s patents.

For the companies in the drug development and delivery business, Strategic Innovation is required to ensure complex and competing technology investments are aligned with emerging market needs and support corporate goals. Gaining an understanding of long-term trend convergence in drug development and delivery methods, the intellectual property landscape, and emerging technologies will position a company to make the best possible investment decisions. Through the rigorous application of a Strategic Innovation analysis framework, actionable investment criteria may be identified that both support the short-term financial responsibilities to shareholders while securing the future potential for the firm to participate in major growth opportunities.

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