The contribution of venture business in DDS research and development

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Drug delivery systems date back to the ninth century A.D. when Abu Bakr Mohammad Ibn Zakariya al-Razi, known as Al-Razi, or Rhazes, discovered gum and pear seed mucilage could be used to mask the taste of medicines. Twelve centuries later, we still define DDS as including taste-masking as a component in orally disintegrating tablets and oral thin films, and DDS includes many other technologies which can be classified in the following way according to its market value:

- Oral: Delayed, Extended or Sustained Release, Modified Release (Chronotherapy, Pulsed Release, Colon Targeted Release), Fixed Dosage Combination IR/SR, Fast Dissolve Tablets, Oral Thin Films or Wafers, Taste-Masked Chewables
- Trans-membrane: Ocular, Nasal, Pulmonary (Nebulizer, Soft-Mist, MDI, mDPI, CFC-Free, HFA), Buccal, Rectal, Vaginal
- Parenteral: 30, 60, 90 Day SR Depots, Implants, PEGylated Proteins, Microneedles, Drug Polymer Conjugates, Fusion Proteins, Formulations Using Functional Particles
- Dermal: Topical (Gels, Skin Permeation Enhancers), Transdermal, Electro-Transport, Iontophorosis, Microporation (Thermal Pulses), Needle-free Delivery (Jet Injectors)

Venture capital provides a source of funds through investment, usually in companies or projects that are start-up or at a very early stage of product development. These projects and organizations usually would not attract sources of finance such as loans and could not raise money in the major public stock markets. The usual mechanism for venture investment is through the formation of a new company. The company will own rights to the intellectual property that originate from earlier research activities and will probably employ or have contracts with the scientists behind the research work. The venture

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capital firm buys a shareholding in the new company, thereby providing the company with money for development work. Frequently, more than one venture capital firm may invest in a company. Venture capital firms add value to the new business by strengthening the management team by recruiting individuals with specific expertise; working with the management team to raise further finance from other investors or by listing on a stock exchange; combining specific technologies or projects to expand the company’s portfolio. Venture capital firms focus on investments that have a high degree of risk. Investing in research-based activities is intrinsically risky because, by definition, one is dealing with the unknown or barely known. Compounding that risk are the uncertainties of product development, of healthcare markets, of the law (regulatory and patents), of economic cycles (generic erosion) and of management.

Even if a company succeeds, the venture capital firm’s money could be tied up in the company for many years. Venture capitalists need high returns on those projects that do succeed because not all projects they back will succeed. Venture firms normally manage money that originates in investment institutions, such as those which manage pension funds. The venture capital companies need to deliver a good rate or return to those investors. In evaluating investment prospects, the venture capital firm will evaluate the risks, length of time their money is likely to be tied up, and the level of return they need to deliver to their investors. Venture capital firms are investors in people. Early in their lives, the most valuable assets venture-backed new companies have are intellectual property and the people needed to develop it. In structuring a new company, venture professionals ensure that the researchers and management have shares or share options that will grow in value if the company develops. Venture firms invest in a diverse portfolio of companies to spread risk. This cushions the impact of failure by any one company in their portfolio. In drug delivery, a portfolio might include companies involved in medical devices, gene therapy, inhalation, prodrugs or drug-delivery platforms. Usually if a venture firm has already invested extensively in a particular type of company, it may be less willing to raise funds for a directly competitive company. Conversely, if a venture investor sees synergies with a company already in its portfolio, it may have an additional reason to back a new project. Venture capitalists will need to be satisfied with a company’s management or potential management and their plans. In the event that there are gaps in the management team, the venture capital firm may provide assistance with recruiting additional team members. The management must also have the right resources available, such as strong patent position, access to skilled employees and facilities, and a technological or product advantage that addresses ideally a substantial unmet market need.

Venture firms generally seek to sell most of their shares within about five to seven years of their initial investment; typically, they will sell after the company floats its shares on a public stock market.

This article traces capital formation for the DDS entrepreneur leading to a contract development business, and an internal DDS product business, and how pharmaceutical companies access the DDS technology through drug delivery collaborations⁴.

How DDS companies were formed and kept in operation

The most famous DDS company is ALZA, founded by Alejandro Zaffaroni in 1968, based on an idea he had as a student at the University of Rochester studying biochemistry. He noticed that in the science of endocrinology, small amounts of hormones are dispersed to the body, but their release is controlled by a gland, and only delivered under a set of controlled conditions. At the time, he believed that conventional oral delivery and in-
jections were the wrong way to deliver drugs, but no one in the pharmaceutical industry believed him, much less bankers willing to lend money to develop drug delivery systems. He turned to Steve Burrill at Ernst & Young who helped Zaffaroni write a prospectus seeking venture capital in the amount of $10 million. After numerous presentations, including a memorable one at Johnson & Johnson, which ironically declining to invest the money in ALZA, but 23 years later acquiring the company for $13 billion, Zaffaroni put $3 million of his own savings to start the company, and recruited the best people he could find, including their first CFO, Martin Gerstel a 28 year old MBA student from Stanford. Gerstel took ALZA public, and sold stock to 20,000 stockholders, showing no revenues. Since Zaffaroni left Syntex, a company he co-founded, he was compelled by his departure agreement to give Syntex 25% of ALZA's initial stock which went to Syntex's stockholders. Thus, ALZA became the first publicly traded venture business, a model that opened the floodgates of investment in early stage companies with similar financing models.

ALZA developed products that made very little money, and by 1977, ALZA was out of money, owed $20 million, and its stock was selling below $1 per share. Ciba Geigy then bought a controlling interest in ALZA which it kept for five years, but sold its shares in return for license agreements in 1982, when ALZA convinced Ciba that it could not grow because competitors to Ciba were reluctant to provide contracts for applying ALZA's DDS to their own molecules. In 1983, ALZA still owed $20 million and had no revenues, but it was free to work with the pharmaceutical industry in research and development collaborations in drug delivery. Zaffaroni placed part of the stock in an employee stock plan, which would activate if ALZA ever made a profit. This kept the employees at ALZA, because they believed in DDS. The turnaround came that year on the launch of Transderm-Nitro (transdermal nitroglycerine), and within one year, ALZA made its first profit. Had the ALZA employees held the stock and sold it when it was acquired by J&J, the value would have been $500 million.

Throughout the following decade, ALZA used a number of ways to obtain a continuous flow of capital it needed to fund the development of 60 products, including a financial instrument called the SWORD, stock/warrants for off-balance-sheet research and development, invented by Martin Gerstel, ALZA's CFO. On March 11, 1993, Gerstel created the first SWORD, by spinning-off a company called Therapeutic Discovery Corporation. ALZA invested $250 million in TDC, which then hired ALZA to develop DDS products, largely first-time DDS products of off-patent drugs, now known as DDS Supergenerics. ALZA showed this investment on its balance sheet as an asset, instead of an R&D expense deducted from earnings. TDC paid ALZA $275 million over five years, and ALZA booked the revenue as income, artificially inflating its balance sheet. TDC was dissolved and acquired by ALZA for $100 million, along with a portfolio of DDS Supergeneric products. Had the SWORD not been created, ALZA would have just recorded R&D expenses, dismal earnings, and not have enough capital to continue developing DDS products.

However, a few DDS companies recently abused the SWORD model, and have been investigated by the Securities and Exchange Commission, notably Elan Pharmaceuticals in many of their DDS research ventures. The abuse occurred when the research venture paid a license fee to use Elan's DDS technology, and the fee came from Elan itself. This is known as "round trip revenue" and has lead to a restatement of Elan's balance sheet, forcing the company to divest many of the DDS ventures it created.

ALZA and Elan are extreme cases for studying the contribution of the venture business on DDS research and development, but are necessary to present as cases, because without them, we all may not be here today. Other successful DDS companies with products on the market founded
by entrepreneurs using their own funds for seed capital, and later entering the public market are:

- R. P. Scherer (Robert Pauli Scherer)
- TheraTech (Dinesh Patel and William Higuchi)
- KV Pharmaceuticals (Victor Hemerlin)
- Biovail (Eugene Melnyk)
- DebioPharm (Rolland-Yves Mauvernay)
- SkyePharma (Jacques Gonella)
- Ethypharm (Patrice Debrageas and Gerard Leduc)
- Kos Pharmaceuticals (Michael Jaharis)
- Nastech Pharmaceuticals (Nicholas Amendola)
- Noven Pharmaceuticals (Steven Sablotsky)
- Key Pharmaceuticals (Phil Frost and Michael Jaharis)
- ANDRx (Elliott Hahn, Alan Cohen and Chih-Ming Chen)
- IMPAX (Chih-Ming Chen after leaving ANDRx)

In all cases (except R.P. Scherer acquired by Cardinal Health in 1996, and TheraTech acquired by Watson in 1985), the company started by these entrepreneurs has remained independent so far, and all are on the public stock markets. Other DDS companies with products close to market are funded with traditional venture capital, corporate venture capital, and sponsored research in the form of drug delivery research and development collaborations.

### Traditional venture capital

Traditional venture capital was used to fund the start-up of some familiar DDS companies as shown in Tab. 1 above. Traditional venture capital favors drug delivery companies, because it reduces risk by selling productivity (improved versions of existing drugs) to established pharmaceutical companies. After the DDS technology is developed enough to begin drug delivery research collaborations, some licensing is accomplished, and after a few years the DDS firm is acquired, either by its drug delivery research collaborator, another DDS company to expand its DDS “toolbox”, or

<table>
<thead>
<tr>
<th>Company</th>
<th>Acquired by/date</th>
<th>Key DDS product/technology</th>
<th>Venture investor(s)</th>
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<tr>
<td>Aerogen</td>
<td>Nektar 2005</td>
<td>AeroNeb®</td>
<td>US Venture Partners</td>
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<td>Alkermes</td>
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<td>Nutropin Depot®</td>
<td>Cardinal Partners, New Enterprise Associates</td>
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<td>Anesta</td>
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<td>Actiq®</td>
<td>Flagship Capital, Columbine Ventures</td>
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<td>Aviron</td>
<td>Medimmune 2002</td>
<td>FluMist®</td>
<td>Arch Venture Partners</td>
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<td>Aradigm</td>
<td></td>
<td>Intraject®</td>
<td>Versant Ventures, Frazier Healthcare, New Enterprise Associates</td>
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<tr>
<td>DepoTech</td>
<td>Skypharma 2000</td>
<td>DepoCyte®</td>
<td>Sorrento Ventures, Brentwood</td>
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<td>Epic Therapeutics</td>
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<td>J &amp; J 2004</td>
<td>Crystal-Solubility Enhancement</td>
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<tr>
<td>Xenopert</td>
<td></td>
<td>Active Transport®</td>
<td>Frazier Healthcare</td>
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by a pharmaceutical company desiring internal DDS capability (innovator or generic companies). Therefore, traditional venture capital provides the initial ability for a DDS company to position itself for drug delivery research and development collaboration, and eventual acquisition by the collaborator or licensing partner.

### Corporate venture capital

Venture capital from corporations has been created successful DDS companies which are later acquired by their research drug delivery sponsor, as shown in Tab. 2. SR One, a subsidiary of GSK was the first corporate venture capital fund to invest in DDS, and its most successful investment was Inhale Therapeutics, now known as Nektar Therapeutics. Other corporate venture capital funds include J&J Development Corp. and the Novartis Venture Fund.

#### Drug delivery research and development collaborations

Once the capital formation phase has been completed DDS companies enter into research and development collaborations with the goal of commercializing products. TCI has tracked DDS research collaboration since 1979. For this review article, we present the trends of these collaborations over the past 10 years.

Since 1995, venture-driven research collaborations in the drug delivery industry have changed in terms of their purpose. For many years the focus had been with Pharma Innovator companies using drug delivery as a life cycle management tool to protect against generic sales erosion. Though the number of collaborations has remained relatively steady at 90~130 collaborations annually, the focus of the collaborations and the companies involved have changed significantly.

As can be seen from Fig. 1, the number of

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<td>Adhesives Research</td>
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<tr>
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<td>Wyeth</td>
<td>Oral DDS</td>
<td>Warburg Pinkus/1999</td>
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<td>Eyetech Pharmaceuticals</td>
<td>Novartis Venture Fund</td>
<td>PEGylated Drugs Macugen®</td>
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<td>Merck/1981</td>
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<td>LTS</td>
<td>Lohmann</td>
<td>Transdermals and Oral Thin Films</td>
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<td>Stolle Medical</td>
<td>Risperdal Consta®</td>
<td>Alkermes/1996</td>
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<td>Meridica</td>
<td>PA Consultants</td>
<td>Inhalation</td>
<td>Pfizer/2004</td>
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<tr>
<td>Nektar</td>
<td>SR One (GSK)</td>
<td>Exubera®</td>
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<tr>
<td>Shire Laboratories</td>
<td>Shire Pharma</td>
<td>Oral DDS</td>
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Tab. 2 Selected DDS companies started with corporate venture capital
collaborations with large innovator pharmaceutical companies ("Big Pharma") has decreased from a high of 58 percent of all collaborations in 1998, to 25-35 percent since 2001. Drug delivery companies are more likely to be collaborating with specialty pharmaceutical companies or other drug delivery companies, than with large pharmaceutical companies.

These changes have occurred as the pharmaceutical industry has consolidated through M&A. After merging, pharmaceutical companies typically divest a number of product lines to smaller companies with smaller sales forces, known as the specialty pharmaceutical company. Indeed, some of the larger drug delivery companies have evolved in specialty pharmaceutical companies themselves, such as ALZA, Elan, and Biovail. As the specialty pharmaceutical company has evolved, they have established research and development collaborations with the drug delivery industry as a way to continue extending the lives of their product lines.

Moreover, the focus of collaborations with large innovative pharmaceutical companies has also changed for the drug delivery company. Since 2000, collaborations for life cycle management (line extensions) have decreased in their importance. The collaborations are more likely to focus on the development of formulations for pipeline products, or granting the pharmaceutical company access to technology to develop formulations with a number of unspecified molecules. This change is shown graphically in Fig. 2.

This change is a result of the advancement of drug delivery technology to address some of the more difficult problems of pharmaceutical formul-
tion, such as solubility enhancement of poorly soluble drugs.

A second change for the innovator pharmaceutical companies has been in their understanding of the need to develop better formulations at an earlier stage of development, both for product success, and to create a high barrier of entry for generics.

For the specialty pharmaceutical company, their reliance on the drug delivery company is to develop a formulation and do some of the early clinical development. As can be seen from Fig. 3, these companies are more likely to be marketing a product that the drug delivery company has developed internally rather than collaborate for a line extension or development of a formulation for a compound in the pipeline.

The rise of DDS generics

DDS products generally provide for a high barrier of entry to generics, until the generic company acquires its own in-house DDS formulation capability, or licenses a formulation from a DDS company specializing in the development of generic DDS products. Tab. 3 lists major generic firms and how they acquired and accessed their DDS capability.

Generic companies need to become self-sufficient in DDS research and development capability since their market penetration is low. In the USA, generics have only a 6% penetration into the DDS brand market, and 10% in Europe. In the USA, DDS generics represent only 13% of sales, and in Europe, 9%. There are several reasons for this poor performance:

- Difficult Formulations to Copy
- Broad Patent Coverage
  - Blood Level Patent Claims
  - Many DDS Generics Still in Litigation
- Strict DDS Generic Regulations in Effect in Regulated Markets
- Citizen Petitions in USA Block Generic Launches
- Limited Reimbursement in Europe for DDS Products
- Lack of Knowledge of Brand Company Generic Defense Strategies
- Lack of Access to DDS Contractors

The lack of access to DDS contractors is the single reason why generics have limited market share, and this is due to the terms on which DDS companies agree, when they sign agreements for their DDS collaborations with innovator pharmaceutical companies. Many DDS companies agree to license their DDS technology for the entire molecule, which will exclude generic versions, even when the DDS molecule loses patent protection.

Conclusion

Entrepreneur start-up savings or loans, traditional or corporate venture capital, the public stock market and large or specialty or generic pharmaceutical companies have interacted at various stages throughout the life of any novel idea in drug delivery. From the idea to pharmacy shelf, whether a new product introduction or a generic copy, the venture business keeps DDS companies alive, and enable its founders to continue on and start new drug delivery companies. The availability of capital in massive amounts is proportional to the amount of new products which can be commercialized. Almost all of the examples...
given in this article reflect the USA experience where so much capital has flowed to the DDS company in creative ways. The venture business will continue to affect DDS in a positive way, and cushion the impact of DDS generics, which make pharmaceuticals more affordable to those who need it most: patients.

References
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4) Actual data is taken from NDDS Online, a proprietary database created and maintained by Technology Catalysts International 1979 to present.
5) BIO-Europe Dispatch, Nov. 13, 2001, interview with Gary Cleary.
9) NDDS Online, proprietary database containing Drug Delivery Research Collaborations.