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Introduction to Life Sciences Technology Transfer

Background material for HMI Technology Transfer podcast series: The current state of the life sciences innovation

This is the abridged first section of a teaching case that has been prepared by Leonard Lerer and Nicholas Rowell of the INSEAD Healthcare Management Initiative. The full case was written by Leonard Lerer, Senior Research Programme Manager, Douglas Schein, Associate Research Programme Manager and Professor Thomas D'Aunno, Novartis Professor of Healthcare Management, INSEAD, of the INSEAD Healthcare Management Initiative.

Defining Life Science Technology Transfer

The term ***technology transfer*** describes the means by which the right to use an invention is transferred from the inventor to the market. It includes disclosing and managing inventions, evaluating, protecting, and marketing the invention, and then negotiating and managing licenses for use[1]. The term ***life science*** broadly describes research, development and commercial activities focused on the understanding, prevention, and cure of disease and the promotion of well-being.

In the life sciences, the transfer of technology from university-based research outwards is critical to industry growth. It generates value by taking an invention from research through to clinical development and ultimately to the market. In doing so, it generates substantial societal benefits. Determining which inventions can, and should, be commercially nurtured and financed through to successful and sustainable companies is problematic; a range of scientific, governance, ethical and valuation issues emerge at each stage of the technology transfer process. Technology transfer is therefore regarded as an integral part of the activities of many academic institutions and its usefulness has increased due to changes in intellectual property legislation, relaxation of rules concerning the commercialization of government funded research, growing entrepreneurship in the biotechnology sector and the need to generate revenues in the face of diminishing public sector subsidies.

Does society pay twice for its medicines?

The majority of research done at universities is 'basic'. It is not, however, simple. It is aimed at creating knowledge without being focused on a specific application.[2] This research is driven by an understanding that expanding the greater body of knowledge is beneficial to humanity. It has a public value. However, it is quite a costly process to take a piece of knowledge and turn it into a marketable product. In fact the current cost for a pharmaceutical manufacturer to bring a new drug to market is now estimated at over $800 million.[3] Moreover these costs only represent the portion of the R&D that companies are willing to support; there is another costly part - at the early stage of fundamental science and discovery - that companies have proven unwilling to fund. This is where governments have a role to play.

Governments use a portion of their tax money to fund scientific institutions. In turn, these institutions then create their own labs or fund research performed elsewhere. The United States is currently the largest spender on R&D and the National Institute of Health's support of research programs has increased dramatically. The proposed budget for 2007 spending is over $28 billion.

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[1] "Bringing Technology to Market" Kathleen Allen, International Journal of Entrepreneurship Education, Ref. No.:IJEE1 – 3LA2

[2] National Science Board, "Science and Engineering Indicators", National Science Foundation, 2000.

[3] "The Price of Innovation: New Estimates of Drug Development Costs" J DeMasi, R Hansen, H Grabowski, Journal of Health Economics 22 (2003)

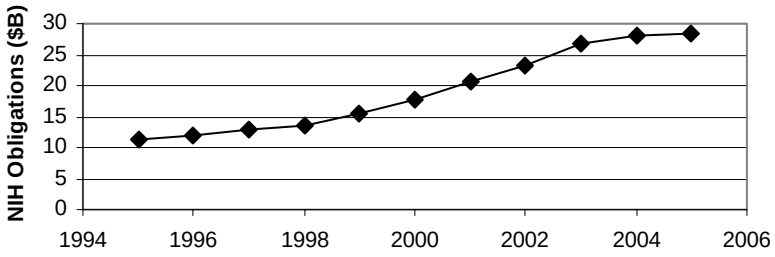

Exhibit 1: *United States National Institutes of Health, Actual Research Obligations*[4]

Despite all the research that this spending supports, technology at the academic laboratory level is still far removed from the market. A substantial investment, most of the $800 million quoted above, is still needed to bring a product, based on an academic invention, to market. Private organizations are reluctant to spend extensive amounts to commercialize public technologies when the fruits of their efforts could then be exploited by other players. A few private corporations have attempted to run basic research centers. Two of the best known were Bell Labs, credited with the laser and fiber optics, and Xerox PARC, credited with the computer mouse and Ethernet. These initiatives, and indeed most other privately funded basic research laboratories, have now stopped their efforts. The lab-to-market path was an intolerable burden to shareholders; increasing investor emphasis on short term results generally prevents most private companies from making such much longer term investments.[5]

Facing the dilemma of the public value of the research dollar not finding its way to the public, in 1980 the United States passed the Bayh-Dole Act giving intellectual property rights - ownership of the inventions from publicly funded research - to the universities from which research originated. Patents and copyrights allow for limited term monopolies, which in turn offset research expenditure. The Bayh-Dole Act allowed universities to protect their inventions and to license them for use. Moreover the act stipulated that inventions must be licensed according to market demand and that there should be a strong preference for small businesses.[6]

The Bayh-Dole Act, alongside similar legislation in other countries, has had a profound effect on the number of inventions prepared for commercialization. For example, before 1980, fewer than 250 patents were issued to U.S. universities each year and discoveries were seldom commercialized for the public benefit. In contrast, in 2002, 5,327 new license agreements were signed. Between 1991 and 2004, annual invention disclosures increased more than 290%, new patents increased nearly 450% and new licenses and options increased about 510%.**Error! Bookmark not defined.** Europe has seen a similar, but far smaller, boom in university technology transfer activity.

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[4] National Institute of Health Website, http://officeofbudget.od.nih.gov/KFactFY06/Actual%20Obligations%201995%20-%202005.pdf, accessed 19 January 2007

[5] University Research and Offices of Technology Transfer, Gregory Graff, Amir Heiman, David Zilberman, California Management Review, Vol. 45, No 1.

[6] AUTM Website, http://www.autm.net/aboutTT/aboutTT_bayhDoleAct.cfm

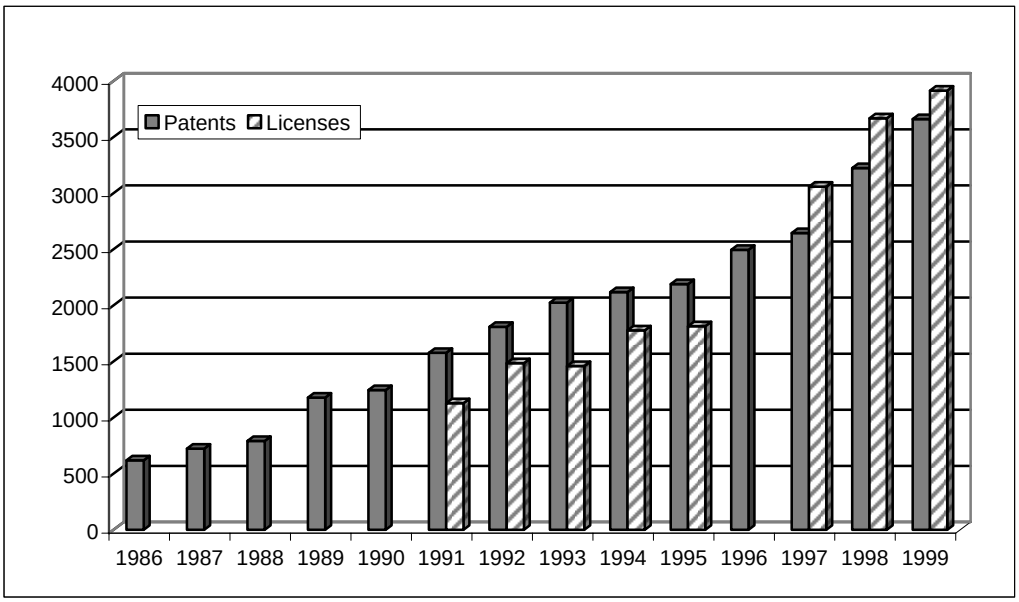

Exhibit 2: *US University and Hospital Patents Awarded and License Agreements*[7]

With proper incentives in place, there was thus created a mechanism for the ownership of inventions discovered with public funding, to move into the hands of for-profit companies. The same mechanism gave the company purchasing or licensing the technology, limited protection from competition when developing and selling the product based on the invention. It is through the sale of the product that the public value recognized by academia finally reaches the public. Nevertheless such an opportunity comes with a price tag - many criticise the profits being made by companies that license government funded research. If the public paid for the original invention, why do they have to pay a second time? Why pay a price that includes a significant margin to the seller? And if competition would lower the price, why is the seller granted a monopoly? As it stands, public policy must strike a balance between the profits of private companies and the need to fulfil the original government mission of improving the wellness of its people.

Did anything break? Life Science's Need for Technology Innovation

Rising costs of healthcare and reduced efficiency in drug development are placing new strains on the life science industry. Traditional pharmaceutical companies are finding themselves under pricing pressure from governments and having their products attacked earlier and earlier by generic drug manufacturers. They are struggling to keep their pipelines full; the *pipeline* refers to the portfolio of drugs that a pharmaceutical company has at various stages of development. Life science companies must look to new technologies to help along the innovation pathway and bring new efficiencies to discovery, development, service, product manufacturing and distribution.

[7] Howard Bremmer, Presenation to the National Association of State Univerisites and Land Grant Colleges; Nov. 11, 2001, Washington, D.C.

The major pharmaceutical players have been struggling to show they are capable of meeting these challenges. The blockbuster model (drugs with sales exceeding $1 billion per year) might not be dead, as some critics suggest, as effective drugs for common illnesses will always be sought after and granted patent protection from competition. However, life science companies are facing increasing R&D budgets and a number of late stage pipeline failures. The number of approved new drugs dropped from a high of 56 in 1996 to 30 in 2004, while during the same period, total R&D spend more than doubled to $38.8 billion.

Current Events:

In late 2006, increased mortality in a phase III trial caused Pfizer to shelve a molecule after spending close to $1 billion in R&D. The cholesterol lowering drug, Torcetrapib, was aimed at a pathway first identified in 1989 was on track to replace Lipitor, which provides Pfizer $12 billion per year in revenues, almost a quarter of its total revenues. Lipitor goes off patent in 2010 and Pfizer was touting Torcetrapib as its replacement until studies showed a statistically significant increase in patient mortality. Investors price in the returns from expected pipeline products and the market capitalization of Pfizer dropped 11% on the news, a drop of over $21 billion.[8]

The risk of failure along the development path will always exist. New technologies like in-silico testing can mitigate some of the risks, but drug development will always be fraught with failure. Coping with the new development environment, life science companies are busy rationalizing their processes and pipelines. Many are increasing activity in newer products such as biologicals (such as antibodies), either directly through development alliances. The traditional small molecule drugs are still dominate, but many firms are betting that biological products can turn the industry around. Early promises have yet to be achieved, but biologicals are starting to deliver. In 2004, biological products accounted for 10% of the $550 billion spent in the total drug market and 11 of the 76 blockbuster, drugs with annual revenues over $1 billion. Within clinical trials biologicals account for 67% of the drugs being tested, yet account for only 3% of the total R&D expenditure.[9]

There are promising signs that some of the efforts by the pharmaceutical companies are starting to produce results. For example, Novartis and Pfizer, released date that estimate a significant increase in new entities being submitted for approval or entering phase III testing. However, each product in development represents a discrete bet on success and even having over a large number of 'shots on goal' is no guarantee of success.

[8] "Pfizer Shares Plummet on Loss of a Promising Heart Drug", Alex Berenson, Andrew Pollack; The New York Times, 5 December 2006

[9] "The Biotechnology Market Outlook", Boston Consulting Group, Datamonitor, November 2005

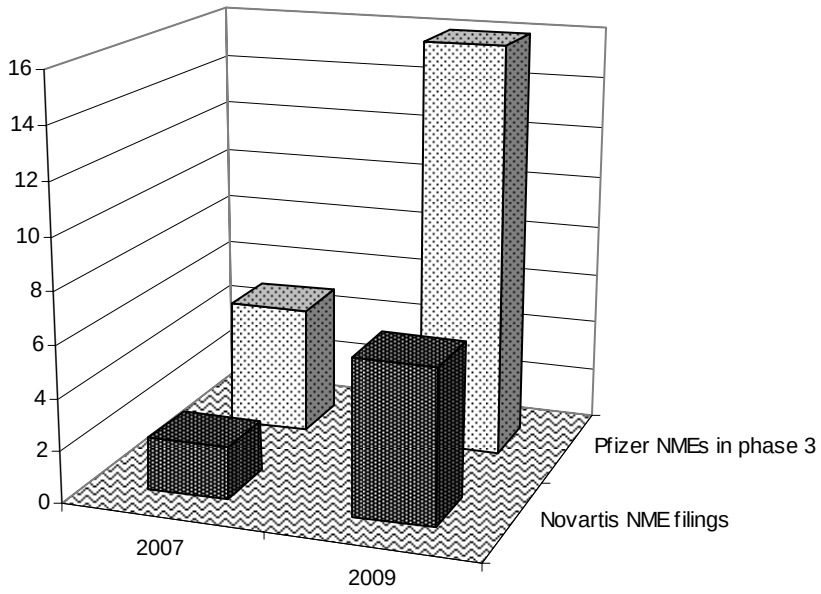

Exhibit 3: ***Product development at Novartis and Pfizer***[10]

Getting public value from new technologies is not only a problem in the drug discovery arena. Within healthcare delivery, recent studies show that only 5% of hospitals have centralized ordering systems and 25% of physician offices use electronic records. These are information technology systems that have become pervasive and commonplace in most other industries. These applications have been slow to take off in this one due to high cost of implementation and uncertainty in their efficacy.[11]

These systems are seen as critical to improve the transparency and cost of delivering health services. To make up for a lack of private spending to implement such systems, public policy is beginning to shift. In the United States, new policies like 'The Wired for Health Care Quality Act of 2005' have reduced a number of legal and organizational barriers for implementing these types of systems. Technological innovation in security, interoperability, and life cycle management could reduce financial barriers to implementing and running these systems.[11]

Demographic changes, such as an aging population and the growing prevalence of lifestyle-related disease are growing demand for health products and services. Across the globe, populations are aging and the longer people live, the more of healthcare they consume. Researchers have estimated that people over 65 years of age consume 4 times as much healthcare than those under 65.[12] Similarly, a rise in disposable income has triggered, either through need or desire, an increase in personal spending on healthcare. With that spending, consumers are beginning to demand more for their healthcare dollar and their growing power is reshaping the healthcare industry. Consumers are also beginning to demand more

[10] "Promising More Shots on Goal", Michael Flanagan, BioCentury, 4 December 2006
[11] "Health Information Technology in the United States: The Information Base for Progress", Robin Wood Johnson Foundation, 2006
[12] "Short Term Pain", Vicky Meek, Real Deals, 24 February 2005.

transparency and choice. Their demand for transparency has been backed up by the US federal government which passed the "Health Care Price Transparency Act of 2006" demanding that private and public entities make pricing details available on websites or by request. Similar efforts are focused on quality reporting and move toward a pay-for-performance type systems. Some of the system discussed go as far as a 'No Cure, No Pay' arrangement which aim at preventing the cost from consumers being prescribed ineffective drugs.[13] Drug manufacturers recognize this power and in 2006 spent around $4.5 billion on direct to consumer advertising.[14]

Life Science Finance is Active, but Ignoring the Roots of Innovation

Business models are evolving, driven by the transforming life science industry. Companies are creating business models that concentrate on a limited range of core competencies. While fully integrated companies continue to exist, the value creation is being maximized through the creation of companies that concentrate on limited core competencies; some examples being contract research organizations (CRO), no research, development only companies (NRDO), contract sales and marketing organizations (CSO), and discovery tool developers.

As these organizations seek their niche on the value chain, they sell products and services to each other, create alliances, cross license, consolidate, and divest. Corporate finance in the life sciences is undergoing one of its busiest periods. There has been significant activity in the public markets, in mergers and acquisitions, and private equity. However, with all this activity and new capital available, there is a dangerous trend that is ignoring the roots of innovation and a smaller and smaller portion of available capital is being devoted to seed and early stage companies.

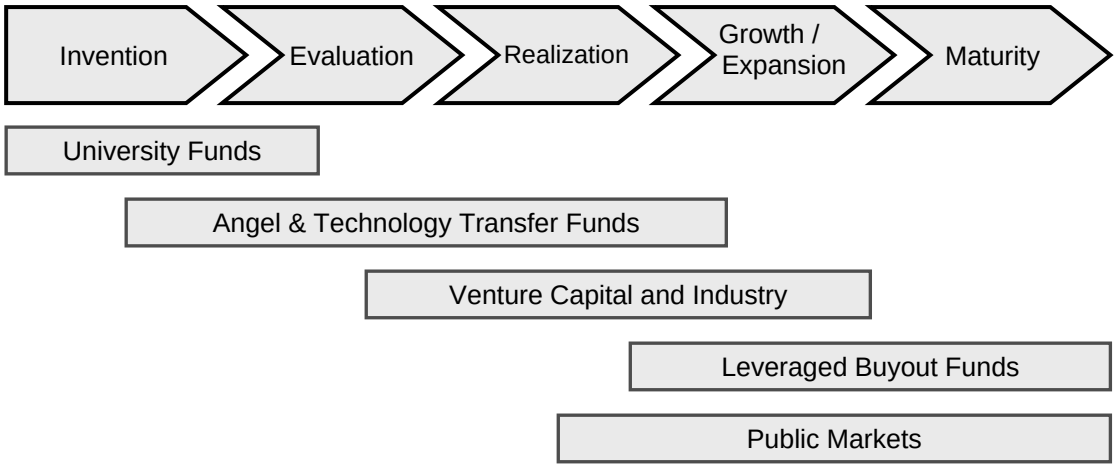

Exhibit 4: *Stages of Corporate Growth and Sources of Funding*

[13] Møldrup C, No cure, no pay. BMJ 330:1262-1264, 2005.
[14] "Drug Ad Spending Up Significantly", Jim Edwards, BrandWeek, 28 December 2006

Private Equity

Private equity re-emerged as a powerful force in corporate finance in the recent years. Buoyed by a willingness of financial market players to absorb increasing amounts of high yield debt, almost any company in any industry is considered a take-private candidate. A record $215.4 billion was raised by 322 firms in 2006 for private equity investments. According to Dow Jones' Private Equity Analyst, this is the largest annual amount ever raised and is 22% greater than the previous record year, 2000, and a 33% increase on the previous year.[15] And while this represents funds for all types of private equity deals in all industries and includes buyout, venture capital, and mezzanine, and funds of funds, the driver of this growth has been the big buyout funds who raised 70% of the total. Venture capital funds actually lost ground in 2006 dropping 2% from the previous year to $25.1 billion.

In life science private equity, the focus has shifted toward later stage deals. These deals are getting attention due to lower risk profiles associated with their product or market development. The lower risk is often associated with a quick exit, but also brings lower returns. In the current funding environment, this appears to meet the needs of most investors.

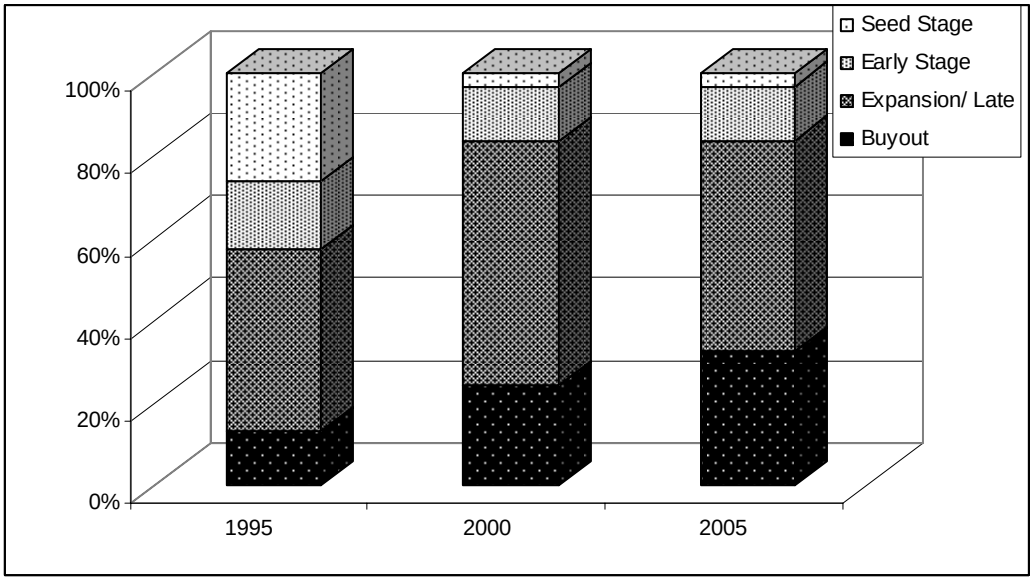

Exhibit 5: *Distribution of Life Science Private Equity Investments by Stage*[16]

Historically, the majority of buyout funds have avoided the life science industry. While tempted by the upside of high margins, patent protection, and recurring revenues for chronic medications, private equity funds were deterred by the downside risk associated with drug development, regulatory issues, government oversight, and patent challenges.[17] The large pharmaceutical companies have until recently not been on the radar of the private equity giants. However, perhaps due to the amount of money now positioned for buyout deals and

[15] Dow Jones Private Equity Analyst, Press Release, 11 January 2007.
[16] Thompson Financial, Investment Analytics
[17] "Private Equities Growing Role in the Generics Industry" Thimo L. Sommerfeld, Journal of Generic Medicines, Vol 3. No 1., October 2005

the need to find less crowded markets, there has been increasing later stage private equity activity across the industry. This interest has focused on those brands that have proven to be able to sustain high margins and market share and companies that are exposed to little development risk. Some private equity firms are attracted to the recurring revenues of hospitals and other health service providers, as we witness in the $32.7 million deal ($11.7 million in debt) deal for hospital operator HCA by Bain Capital LLC, Kohlberg Kravis Roberts & Co and Merrill Lynch Global Private Equity. Biomet, Inc., a leading player in orthopaedic products, agreed to be taken private for a total equity value of approximately $10.9 billion by a consortium of investors including The Blackstone Group, Goldman Sachs Capital Partners, Kohlberg Kravis Roberts & Co. and Texas Pacific Group.[18] A number of deals have also taken place for generic drug manufacturers after they have proven their ability to deliver solid returns.

PE investor	Investment	Country	Year of investment	Year of exit	Form of exit
GTCR	GeneraMedix	USA	2004	–	NA
3i	Betapharm	Germany	2004	–	NA
Advent International	Terapia	Romania	2003	–	NA
RoundTable Healthcare	Sabex	Canada	2002	2004	Trade sale
Advent International	Fada Pharma	Argentina	2001	–	NA
Advent International	Alcalá Farma	Spain	1999	2003	Trade sale
Warburg Pincus	Zentiva	Czech Republic	1998	2004 (partial)	IPO

Exhibit 6: *Private Equity Deals for Generic Drug Manufacturers*[17]

As increasing capital flows towards buyout and expansion deals, there is growing controversy about the risks and benefits of private equity in health care. Although private equity has an investment time frame longer than the public markets, it is argued that the new capital flowing into the sector is doing little neither to fund early stage companies nor to promote R&D. In the venture capital space, the number of deals has been relatively flat over the recent past and the percentage of seed and early stage deals has decreased, from 39% in 1995 to 16% in 2006.

[18] Biomet, Inc., Corporate Press Release, 18 December 2006

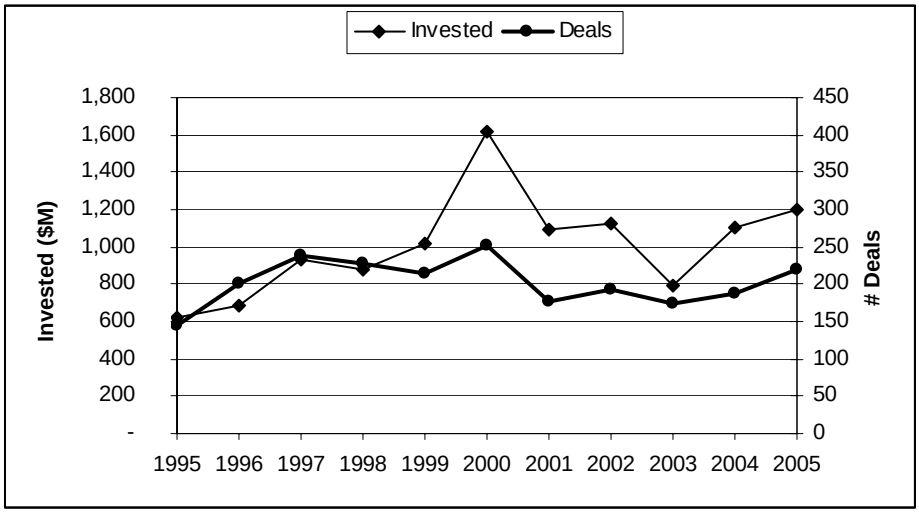

Exhibit 7: *Biotechnology, Health Services, Medical Device and Equipment Venture Investments in the United States*[19]

As the number of deals aimed at seeding companies get less, supply at the beginning of the innovation pipeline gets smaller. While active M&A players and public markets may do well over the short and medium term while through shifting around the value of current inventions, the healthcare industry cannot flourish by simply reshuffling the same deck over and over.

Shifting ownership of Companies, Technologies, and Molecules

Three categories of M&A activity drive changes in the ownership of life science inventions. The first is robust companies combining their products, revenues and new markets for competitive advantage. The second is cash rich, but product poor companies looking to purchase smaller technology rich businesses. And the third trend is the defensive posturing of weaker companies merging in an attempt to become sustainable. All three types of transactions do not greatly contribute to developing the most efficient mechanism for bringing health innovation profitably to market.

After earlier consolidation by the big pharmaceutical companies, the middle market (mainly established European pharmaceutical companies and stronger US biotechnology players) has seen increasing activity. In 2003, 150 biotechnology companies ceased to operate independently[20]. 2007 begins with $19.6 billion in biotech acquisitions waiting to close. According to BioCentury, the two primary reasons for the surge in activity were cheap equity prices in late 2006 and a 'rational panic' from the number of mainstream drugs coming off patent and a reduction in internal productivity[21].

The robust M&A returns have been driven mainly by the larger pharmaceutical corporate buyers who need to fill the pipeline and already have the infrastructure in place to manage drug development. When doing their valuations, financial investors in smaller companies

[19] PWC MoneyTree, Historical Trend Data
[20] "Biotechnology in Europe: A 2005 Comparative Study", Critical I, Branbury, UK. 13 April 2005
[21] "M&A Upside", Steve Edelson, Mike Ward; BioCentury, Vol. 15, No. 1, 1 Jan 2007

must discount their ownership stake with the potential that additional dilution can occur in order to fund additional development and its associated capital investment. A strategic investor, such as a fully integrated pharmaceutical company, focuses on the potential value of the products that come with the aquisition. Strategic buyers are aware of this arbitrage but have different timelines, needs and information than the financial investor.

A number of life science companies looked towards the public markets to fund their purchasing of companies, technologies, and molecules. In 2006, there were 45 US and European life science IPOs, raising more than $2 billion and representing $9.5 billion in market capitalization.[22] Follow on funding in the public markets raised another $5.5 billion for 51 firms. Life science companies have also benefited from a robust public debt market; over $43 billion was raised in 2005.[23]

[22] BioCentury Financial Center, market capitalization data from closing prices on 29 December 2006.
[23] Thomson Financial, Investec Database, accessed 22 October 2006.