TVM Capital

TVM Capital Life Sciences

Spotlight on

Early Stage
Life Science Investing

Smarter Venture - Growth Strategies - for the New Pharmaceutical Ecosystem

The pharmaceutical 'ecosystem' is transforming. Current merger and acquisition activity in the industry aims to optimize current product pipelines, replenish R&D programs with innovative and differentiated products, and reduce structural costs through economies of scale and increases in global presence. Early stage investment strategies also must change to meet these new objectives.

A changing pharmaceutical ecosystem

The pharmaceutical industry is currently responding to increasing cost pressure, a significant number of blockbuster drug patent expirations and related revenue loss. The resulting consolidation through mega-mergers like Merck and Schering-Plough, Roche and Genentech, and Pfizer and Wyeth is rapidly transforming the pharmaceutical 'ecosystem'.

Global Pharmaceutical Mega-Mergers

Source: BioCentury, TVM Capital

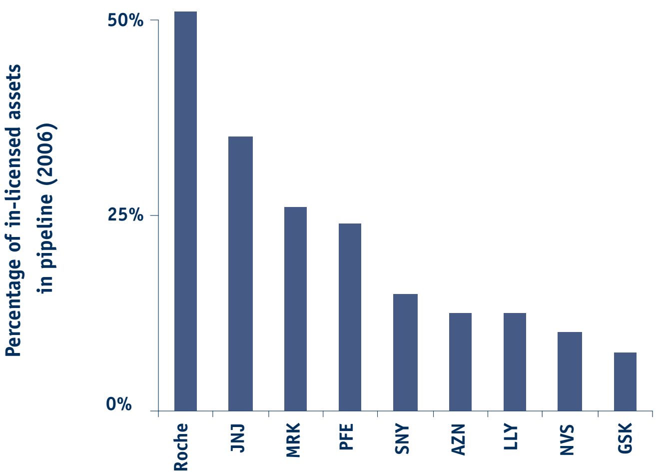
Pending Mega-Mergers of Pharmaceutical Companies in 2009

Target	Acquirer	Deal Value (US$ bn)
Wyeth	Pfizer	68.3
Schering Plough	Merck	41
Genentech	Roche	46.8

Still, demand for higher capital efficiency has to be balanced with the necessity for industry innovation. This is best provided by a vibrant venture-backed biotech industry with the agility, courage for risk and funding to transform disruptive technologies. Undeniably, innovation in healthcare is being increasingly driven by the biotech industry as evidenced by the growing contribution of biotech drugs to the pipelines of the big pharmaceutical companies.

In-licensed Assets Continue to Increase in Large Pharmaceutical Pipelines

Source: Tufts CSDD, Windhover Information, Nature Review

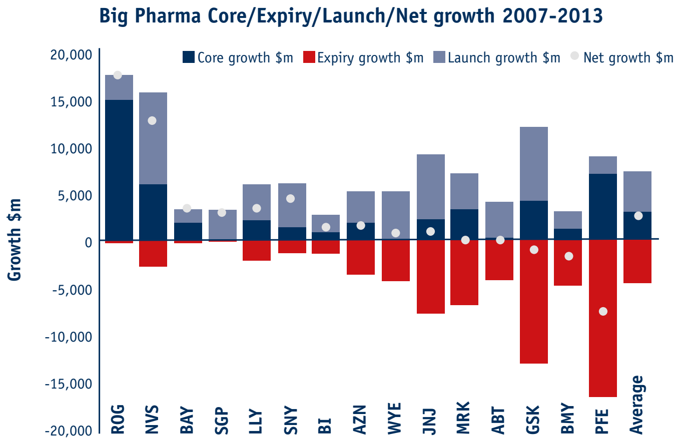


In addition to cushioning patent expirations through mega-mergers and product diversification, pharmaceutical companies are extending their global reach. The slowing growth of markets in Western Europe and the U.S. caused by government policies aimed at curtailing raising healthcare costs can be counter-balanced by expansion into Asia, South America, the Middle East and North Africa. There also is growing interest from Indian and Japanese pharmaceutical companies to acquire players in Europe and the U.S. to achieve and accelerate entry into the world's largest markets.

Overall, current merger and acquisition activity in the industry aims to establish synergies by combining or optimizing current product pipelines, to replenish R&D pipelines with innovative and differentiated programs, as well as to reduce structural costs through economies of scale and increased global presence.

Projected Growth of Large Pharmaceutical Companies through 2013

Source: Datamonitor



An important upshot of industry consolidation is an increasing pool of experienced managers available to join young start up companies. As such, today, management teams in young bio-tech companies are better equipped to address the requirements of multi-regional drug development strategies, financings, and ultimately market entry. Sophisticated in-licensing, creatively structured partnerships and strategic corporate acquisitions continue to offer new and excellent opportunities for nimble companies and to enter into and expand markets in the future.

New economic realities after the financial meltdown

Undoubtedly, the current financial crisis has left its mark on life sciences companies. The biotech sector is experiencing pressure from both the private and public capital markets. In follow-on financings, neither private nor public investors are offering a premium on development milestones met since the last private round.

Venture firms are more fastidious about funding existing private portfolio companies. As a result, venture-backed companies are cutting spending, reprioritizing pipelines, and shelving projects to extend life. Similar strategies have been implemented by public biotech companies running low on cash. Despite best efforts to implement cost savings measures, some companies have been built using business models that are unsustainable in the current environment, and thus, are likely to go bankrupt.

However, this inevitable attrition will improve the overall quality of the industry. Furthermore, sluggish public markets, scarcity of capital, and depressed valuations have created new and attractive business opportunities for both the investors and pharmaceutical companies.

When stock values plunged, several pharmaceutical executives vowed to go on a 'shopping spree' while prices were low. Cash-rich specialty pharmaceuticals and large biotechnology companies started to see more attractive opportunities in companies with depressed valuations. As a consequence, a hotter 'deal-making' climate was created. This environment is expected to continue; allowing biotech companies to extend their runways and, in the case of acquisitions, return money to investors for new opportunity deployment.

New Economic Realities have Created a 'Hot' Acquisitions Market

Source: Company Disclosures, TVM Capital

Recent Pharma-Biotech M&A
(TVM Capital companies shown in red)

Buyer	Aquired Company	Purchase Price US$, millions
Roche	Genentech	90,516
Takeda	Millenium	8,800
Eli Lilly	Imclone	6,500
Novartis	Speedel	970
GSK	Sirtris Pharma	720
Shire	Jerini	515
Boehringer Ingelheim	Actimis	515
Viropharma	Lev	433
BTG	Protherics	273
Daichi	U3 Biotech	234
Bayer	Direvo	300
BMS	Kosan	190

Additionally, lower valuations for quality companies are favorable for venture investment as well. However, TVM Capital predicts that investors will continue to look for higher quality opportunities and improved business models before backing a company. The importance of deep-pocketed and aligned investor syndicates is more important than ever before.

The 'Innovation Gap': It is noteworthy that governments around the globe have identified the so called 'innovation gap'. This gap results form the lack of funding for translational medicine which bridges the path from the scientist's lab bench to clinical development and the patient. Not only in the U.S. and Europe, but also in Asia this recognition has led to high-level funding initiatives with the strategic goal to progress scientific projects further and closer to clinical development. TVM Capital views these initiatives as important nuclei for venture funding. Companies formed on the foundation of these programs should be ideally positioned for early partnerships with the innovation-hungry pharmaceutical industry, and add yet another layer of risk mitigation for the venture investor.

There is opportunity in every crisis - adapting to the new ecosystem

The changes in our ecosystem have led to innovative and more cost effective therapeutic development. As an industry, we have begun to establish growth and exit strategies that are independent of the public markets. Typically, only a fraction of private investment in biotechnology is spent on the development of the products that determine the value of the entire corporation. Therefore, building fully-integrated R&D operations is not the only answer for driving future innovation - especially in times when there is no value assessed in the build-up costs of a 'risk-mitigating' pipeline.

At TVM Capital, we have identified two strategies for our earlier stage investments that are better suited for this new environment:

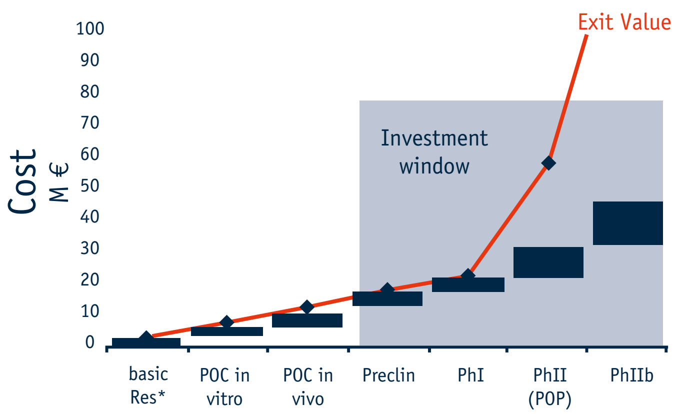
One possible solution for the development of early stage bio-pharmaceutical assets is what we have coined 'Virtual Asset Development' (VAD). The other is the identification and industrialization of 'bona fide' disruptive product platforms.

Virtual Asset Development (VAD): The VAD approach is an extension of the incubation concept. A single asset is developed in a virtual biotech company to value-creating proof of concept with a defined investment amount - ideally not more than $20m in total – and involving not more than 2 or 3 major institutional shareholders who all share the same path to exit vision and have the 'will to kill' if a milestone is not met.

The structure of a VAD offers maximum flexibility with regard to an exit route. Ideally, the company would be sold at proof of concept. However, the shareholders might decide to broaden the scope around a VAD or combine assets if warranted. In order to remain nimble, VAD companies must have a simple governance structure to allow swift and efficient decision-making. The management team, founders and originators of such a project (i.e. academic institutions, biotech companies or pharma) have a clearly defined equity participation, because the capital required to exit the project is committed upfront and initially is not dependent on future financing rounds with unpredictable dilutive effects.

Value Inflection Points for Virtual Asset Development

Source: TVM Capital



To further enhance cost efficiency efforts, VAD programs are managed by a small team comprised of highly experienced individuals, the development steps are governed by clearly defined 'go/no-go' decision points and the development activities are not undertaken by full-time employees, but are contracted to fully integrated service providers such as contract research organizations (CROs), medicinal chemistry service providers or regulatory consultants.

The economic outcome of such a program is dependent on the need of potential buyers to own this program after proof-of-concept and their willingness to pay a substantial price (ideally all upfront). Thus, strong business development know-how, applied when assessing the commercial attractiveness of an asset prior to funding, as well as prior to auctioning it after the completion of milestones, is critical for success. These skills can either sit directly with the management team or could be outsourced to high profile business development service organizations.

Product Platform Development: Contrasting the VAD model are product platforms. In recent years, some of the most successful venture-backed exits fall into this category.

TVM Capital applys a very high standard to this type of investment by seeking opportunities which are truly disruptive, broadly applicable, and reasonably scalable. The proof of concept of a disruptive platform involves two aspects:

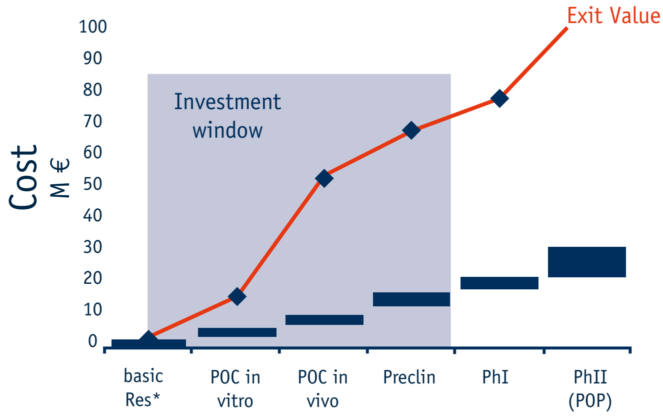
- Demonstration of the ability to create novel drug candidates that can be brought into clinical development and
- industrialization of the technology, i.e., the platform becomes a product engine and is successfully repeatable.

To achieve this, one needs a team of dedicated scientists, a fully functional management team, and a well equipped infrastructure. This does, of course, translate into larger amounts of funds to realize the real value of the technology and a longer time horizon.

However, history has shown that there is limited opportunity to invest in truly revolutionary new platform technology companies with the broad product potential that we require. Thus, TVM Capital believes that a diversified portfolio of VAD and product platform companies represents a good balance in required fund allocation, risk profile, as well as time horizon to exit.

Value Inflection Points for Product Platforms

Source: TVM Capital



As demonstrated in the previous two charts the idealized investment windows for VAD and product platform companies differ. The cost for a distinct step according to the pharmaceutical value is indicated through the height of the blue bar, the upper end of the blue boxes indicates total cost. The red line shows a hypothetical exit value after the indicated step has been successfully concluded.

In the case of a pure product development, it is well accepted that the exit value often only exceeds the amount of development expenses after reaching a statistically significant milestone in the clinic which is usually the successful conclusion of a Phase IIb study.

The exit valuation of a platform company surmounts the spending on clinical development much earlier and at lower overall expense because favorable preclinical or early clinical results allow an earlier judgment of the overall value of the product engine.

At TVM Capital, our early stage portfolio has and will continue to utilize both strategies.

New Biotech Financing Models Place Focus on Exits

Pharmaceutical venture partnering models secure positive outcomes

To gain earlier access to innovative products and technology platforms many pharmaceutical companies have increased business development, licensing efforts and M&A activities. Additionally, some have set up corporate venture funds that are both financially and strategically motivated.

Traditionally, corporate venture arms, such as those at Novartis, GSK, Pfizer, Roche, and Merck-Serono have been involved in equity investments and asset spin-outs.

But sensing a win-win opportunity for corporate pharmaceuticals to enhance the narrowly defined role of corporate venture activity and for TVM Capital to develop the long-standing relationships that would create exit opportunities for our portfolio companies, we intensified our relationships with Biogen Idec, Genzyme, Dow Chemical and Quintiles.

All of these corporate partners have subsequently invested in several TVM Capital funds. But more specifically by doing so, TVM Capital helped our pharmaceutical partners invested to access and assess the strategic acquisition value of certain target companies where TVM Capital was NOT invested. This resulted in major deals for these partners.

The strong strategic relationship also allowed TVM Capital to achieve several of its best exits by selling tailored innovative assets and companies, including the:

- SIRNA sale to Merck
- Sirtris Pharmaceuticals sale to GSK
- Jerini sale to Shire
- Direvo sale to Bayer
- Proteon option deal with Novartis
- Developen licensing deal with Boehringer Ingelheim
- Concert Pharmaceuticals development alliance deal with GSK

Moreover, there are currently more than 35 active strategic partnerships, all with major pharmaceutical and biotech companies, within the TVM Capital Life Science portfolio.

Strategic option funds

The next wave of pharmaceutical venture partnerships will be even more formalized through the development of strategic option funds. Investment from these funds will include a traditional equity contribution and an option component from the pharmaceutical partners for certain technology developments of the target company.

The option fund concept is a unique approach to gain early access to promising compounds and technologies at a reasonable price with controllable risk while ensuring adequate financing and preserving the entrepreneurial drive and motivation at the financed company to take the product to the relevant value inflection or option exercise point.

The Proteon Therapeutics option deal

TVM Capital portfolio company Proteon Therapeutics is a good example of this emerging trend. Headquartered in Waltham, MA, USA (near Boston), the company's key (and only) product is a locally acting recombinant human lactase that persistently dilates arteries and veins. The lead indications are for vascular access in hemodialysis.

In September of last year, Novartis became interested in Proteon Therapeutics and option deal negotiations ran in parallel to Series B fundraising for clinical development of the product.

Option Deal

Novartis obtained an exclusive option to acquire product or to obtain a license. If Novartis chooses not to exercise the Option, then Proteon may also offer Novartis an exclusive license to market and sell product, under predefined terms.

Including the initial acquisition payment plus potential additional regulatory milestone payments, the deal could exceed $550 million.

Series B Financing

In March 2009, Proteon completed the first closing of a two tranched $38 million Series B equity financing. A second closing was completed in April bringing the total Series B financing to $50 million and representing one of the largest biotech venture funding rounds in the United States in 2009.

Shared Views from Both Sides of the Pond

Despite the divergent regional focus TVM Capital partners Hubert Birner and Jens Eckstein, both share a consistent philosophy on early stage investment strategies, the rise of pharmaceutical partnerships to meet pipeline needs and future opportunities for exits in the new pharmaceutical ecosystem.

Early Stage Strategy

Q: It is clear that large pharmaceutical pipelines will require supplementation from the venture-backed biotechnology industry. What type of products and indications are of greatest interest to potential purchasers?

HB: Products with large markets, known mechanisms of actions, low cost of goods and royalty free products are particularly interesting to traditional pharmaceutical companies.
JWE: New mechanisms of action and product platforms, truly innovative approaches to achieve differentiation in the market place and premium pricing will always be attractive acquisition targets.

Q: How has TVM Capital shifted to meet the changing demands of the new pharmaceutical ecosystem?

HB: Our investment strategy relies on stronger partnerships and more frequent information exchange with pharmaceutical industry leaders.
JWE: At TVM Capital we maintain longstanding relationships with the pharmaceutical industry independent of specific companies or investments-- making these relationships two-way roads. We continue to have a strong focus on true innovation, but analyze downstream clinical development and market needs earlier.

Q: What are a few tactics a biotech company might consider when shifting to a more cost effective therapeutics development strategy?

HB: One product strategies, option deals and early partnering to be cash efficient.
JWE: Understanding the real needs of the buy-side and early dialogue with potential partners.

Q: What is the most common characteristic of a VAD company?

JWE: Bottom line is cost efficiency because no internal infrastructure needs to be financed and one explicit goal is a higher chance to kill projects if critical milestones are not met.
In other words, pushing attrition where it is deserved with tightly managed processes is saving money overall and leads to better quality clinical candidates. Of course this works best with a portfolio approach and a dedicated pool of experienced people.

Pharmaceutical Partnerships

Q: The Proteon Therapeutics option deal clearly details all possible exit opportunities. Have you found that this incentivizes all interested parties to accomplish the most lucrative exit option?

HB: It creates a balance between all stakeholder interests particularly for management and company founders who definitely know how they will be compensated at each possible exit option.

Q: Will corporate pharmaceutical option funds replace traditional venture funds? Why, or why not?

HB: Option funds are a child of today's difficult financing environment – I am convinced that they will have more challenges when alternative financing options re-emerge.
JWE: Option funds are simply one expression of more creative deal-making environment that allows sharing risk and rewards on both sides as well as collaborative relationships early on in the game.

Q: Are there still promising opportunities for out-licensing large pharmaceutical products?

JWE: The age of the blockbuster drugs based on fairly broad and unspecific mechanisms of action is coming to an end. These rather blunt therapeutic agents will be replaced by more sophisticated approaches combining biomarkers and specific therapeutics with much better clinical outcomes which in turn will justify premium pricing.

Exits

Q: The lack of IPO opportunities has created a substantial backlog of late stage biotechnology companies in venture portfolios. For companies (and their venture supporters) in this position, is a shift to an acquisition exit reasonable/possible? If so, what terms should one expect?

HB: Absolutely, it is the preferred exit. My guess is that 2-3x multiples are the most likely outcome given that the backlog has created companies that have already reached a funding peak.

JWE: M&A as an exit is not really anything new-- it is simply more common since the total closure of the IPO market. Since the 1999/2000 bubble more exits have been achieved through M&A than through IPOs. In fact, most IPOs in post-bubble times have been financing events not exits. In that sense there is no significant shift – biotech and life science companies have survived and profited through M&A for quite some time and this will not change in the near future.

Dr. Hubert Birner joined TVM Capital in 2000, and is a General Partner in the Munich office. He currently serves as Chairman of the Board of Argos Therapeutics Inc. (Durham, North Carolina) and is a member of the Board of Directors of Evotec AG (Hamburg, Germany), BioXell SA (Milan, Italy), Spepharm Holding BV (Amsterdam, Netherlands), Proteon Therapeutics, Inc (Kansas City, Missouri), Transmolecular Inc.(Boston, Massachusetts) and Nitec Pharma SA (Basel, Switzerland). Over many years, he was the Chairman/Vice Chairman of Direvo Biotech AG (Cologne, Germany) and Jerini AG (Berlin, Germany) which were acquired in 2008 by Bayer HealthCare AG and Shire Ltd. Dr. Birner also represents the interests of TVM Capital with Ardana Bioscience plc (Edinburgh, Scotland).

Dr. Jens W. Eckstein joined TVM Capital in 2004, and is a General Partner in Boston where he focuses on earlier-stage investments. He is a member of the Board of Directors of CoNCERT Pharmaceuticals, Inc., Enanta Pharmaceuticals, SelectX, Inc., Ascent Therapeutics and Rapid Micro Biosystems. He also served as an Advisor to Sirtris Pharmaceuticals.

For more information on the contributors to this TVM Capital Life Sciences Spotlight: Drs. Birner, Eckstein, Polack, DeBaey, Neubeck and Melnikova please visit:
http://www.tvm-capital.com/pages/lifesciences.php

TVM Capital Life Sciences

With 820 million Euros under management, the TVM Capital Life Sciences Practice is one of the largest global venture and growth investors in biotechnology and pharmaceuticals. The Life Sciences team builds on the expertise, experience, international approach and demonstrated success of more than 110 previous investments resulting in many successful trade sales and numerous IPOs. The team combines long-standing international investment experience and operating track records with extensive networks, and knowledge regarding science, product discovery and development, manufacturing, marketing and distribution, international commercialization and finance. Twenty years of successful investing and value creation, through three major industry cycles makes the TVM Capital Life Science Practice a unique partner for the needs of the life science industry. Founded in 1983, TVM Capital is headquartered in Munich and has offices in Boston and Dubai with a growing presence in Asia.

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