

The Current State of Pharmaceutical Industry Research and Development

Prepared by

Frankel Group LLC
Advisory Board

December 2011

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Introduction

An innovation drought currently exists in the bio/pharmaceutical industry that is significantly affecting the cash flow of the current business model. While recent FDA initiatives have the potential to accelerate approvals, this may disproportionately impact selected therapeutic areas, leaving whole swaths of chronic disease states with continued unfavorable investment, risk and return profiles. This unsustainable situation appears to be due to a number of internal and external factors:

- Risk/Return Measurement: A sub-optimal approach to capital allocation across the development portfolio
- Operational Processes and Costs: Increased cost of drug research and development as both failure rates and trial requirements rise
- Late Stage Asset Scarcity: Increased focus on the acquisition of bid up mid to late stage assets to address pipeline gaps
- Early Stage Risk Sharing: Reduced focus on early-stage classic development transactions, except in selected therapeutic areas where early proof of concept (POC) and follow-on market position allows commercial success, and more structured transactions that share risk but also undercapitalize emerging pharma
- Pricing Constraints: Increased pressures on launched drug revenues from price constraints, payer prior authorization requirements, and the growing presence of generic medicines

The solutions can be seen from a range of stakeholder perspectives: (1) the industry executive who seeks to optimize risk and return, and (2) the investor/portfolio manager who may prefer wide alpha return ranges and beta risk management within his/her own portfolio. This paper will take the perspective of industry. Furthermore, within the industry the perspective changes between: (1) the commercial organization that through early development program assessment may drive early kills and a narrowing of projects, and (2) the development organization that naturally sees the process as having some serendipity and drives continued investment in riskier projects. This paper will try to address both internal perspectives.

From the industry perspective, this low level of innovation risks becoming structural, unless individual players take a series of internal analyses to map out what their current costs, productivity and risk/return profiles are; where the opportunities exist to improve this performance on a sustainable basis, and how their business model and organization/incentives must change to realize the benefits. Fortunately, initiatives can be experimented with to address these challenges:

- Deciding between innovation driven business models and a more commercially driven models ... and within an innovation driven model a fast, first to market approach in validated platforms vs. taking on more scientific risk with more novel targets.
- Improved approaches to capital allocation and portfolio planning, which consider elements such as covariate portfolio risks/opportunities, development focus both by therapeutic area and mechanism of action, and others.
- Increasing the participation in translational and early clinical development on a scientifically focused process through the use of structured deals and deployment of excess development assets in lieu of

capital. This must be coupled with improved, and at times radically altered, internal governance practices.

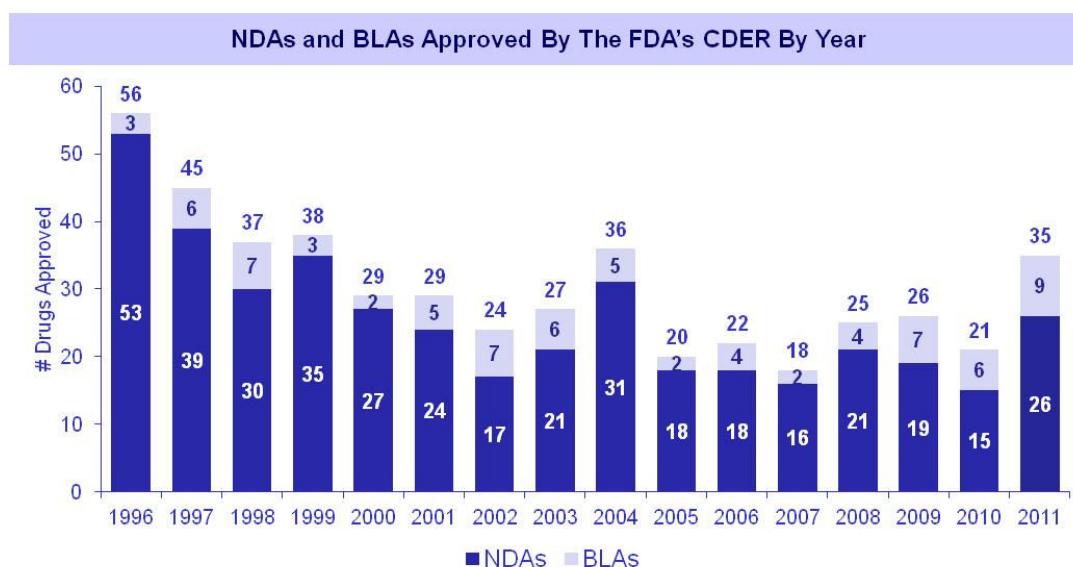
- Driving the business model to selected therapeutic opportunities where the use of biomarker driven development and commercialization, and potentially drug/diagnostic/device combinations exist.
- Integration of key bio/pharmaceutical stakeholders into novel external structures, including financial institutions, academia, and the government in new collaborative business models which promises to enhance industry access to capital and sources of innovation.

These approaches will be explored in future Frankel Group Advisory Board white papers. This paper will establish the environmental foundation and summarize the processes individual industry players should consider to address their research and development productivity challenges.

Industry research and development productivity has been in a state of decline

Even a cursory review of the global state of health shows considerable unmet medical need, perhaps more focused in the developed world on chronic diseases while the developing world seeks cost effective access to the most basic care. Yet, across all regions, governments and private payers simply cannot afford to fund unrestricted access to all pharmaceutical discoveries. Yes, new innovative solutions are required. But, today all solutions must also show a health economic benefit versus current standards of care. Is the pharmaceutical innovation engine up to the task?

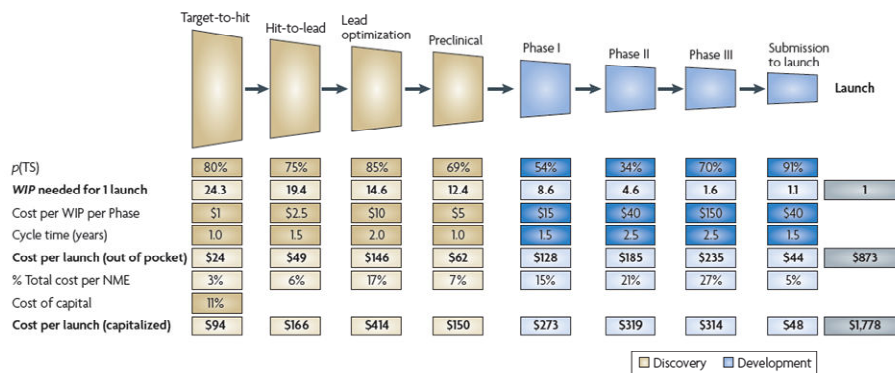
A great deal has been written about the unprecedented challenges facing the bio/pharmaceutical industry's historic R&D model, which is less than half as productive today as it was 15 years ago as measured by new product launches. While 2011 approvals have witnessed a spike, it is not clear how sustainable this trend is.



Source: FDA, *Nat Rev Drug Disc* 10:82-85 (2011)

And, the chart above only accounts for approval rates, not the rising costs to get each approval and the diminishing commercial returns from each approval. The industry is spending significantly more for each approval. In 1991, it was estimated that the cost of a successful drug approval was \$318M but by 2003 that estimate had grown 2.5 fold to \$802M (*J Hlth Econ* 10:107-142 (1991), *J Hlth Econ* 22:151-185 (2003)). This trend shows no sign of abating with more recent estimates coming in at \$1 billion or higher (*Health Econ.* 19: 130–141 (2010)).

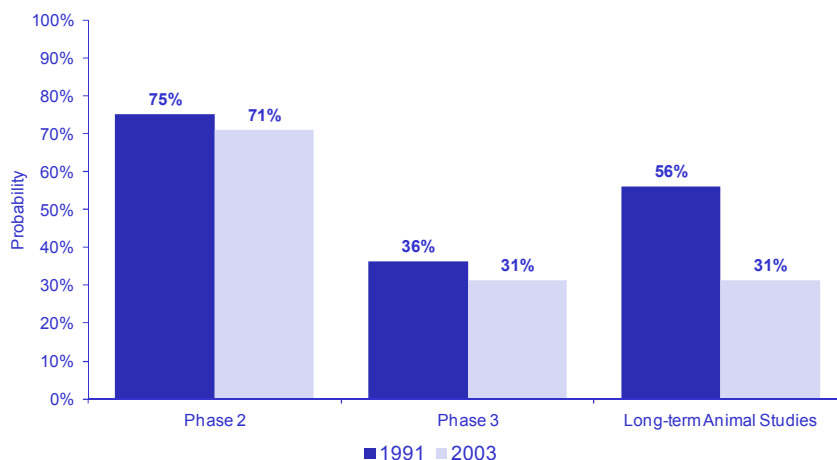
Current Industry R&D Model



Source: Nat. Rev. Drug Disc. 90:39-45 (2010)

While some of this can be attributed to increasing regulatory requirements, the bulk appears to be representing the fact that more development risk is present as illustrated by increasing failure rates. This may be due to more challenging targets, less well understood mechanisms of action, or the need to beat the standard of care for approval and certainly reimbursement ... a combination of scientific risk and commercial risk. But, clearly the picture is of an industry dependent on innovation slowly losing the ability to innovate sufficiently for commercial success.

Probability Of Entering Phase



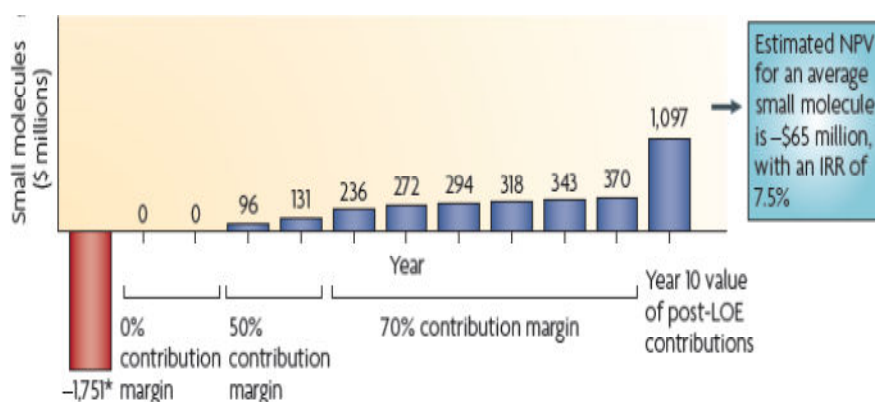
Source: J Hlth Econ 10:107-142 (1991), J Hlth Econ 22:151-185 (2003)

This combination of escalating costs and declining productivity has placed the industry in position of being unable to provide sufficient new product launches to sustain its growth. (Kola & Landis, 2004, Nat. Rev. Drug Disc. 3:711-715; Paul et al., 2010, Nat. Rev. Drug Disc. 90:39-45). The most recently published analysis

of overall R&D productivity strongly suggests that without a dramatic increase in R&D productivity, today’s pharmaceutical industry cannot effectively replace the impending loss of revenues from patent expirations nor the threat of pricing pressures from budget constrained governments and payers. The historic focus on a scale driven, blockbuster development model is gradually turning towards more niche oriented products where early proof of concept and follow-on market position allows commercial success (i.e.: oncology, rare diseases). But, the sheer volume of smaller new product approvals necessary to fill the product gap is staggering and the equally sheer lack of sufficient opportunities in the niche opportunities calls for a new approach. The pharmaceutical industry simply cannot find sufficient innovation driven opportunities across the players if the increased development risk profile in large chronic disease states (i.e.: diabetes, cardiovascular) is not addressed. Otherwise, breaking up the larger pharma, accepting a high company failure rate in innovation models, and re-valuing commercial models will continue to emerge.

Industry development returns appear to be below the cost of capital

Overall R&D returns have been falling over time with the IRR on small molecule R&D currently estimated at 7.5%, which is certainly below the industry’s cost of capital. While selected sectors such as biologics and vaccines have historically had somewhat more positive returns due to expedited approvals (biologics) and less pricing erosion post-patent (biologics and vaccines), it is not clear that this will be the case in the future given increasing levels of competition which will include biosimilar entrants. While one can debate the calculation of IRR, the conclusion that the industry is not investing development capital effectively is clear.

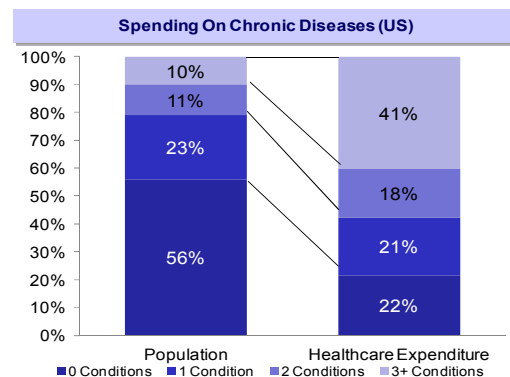
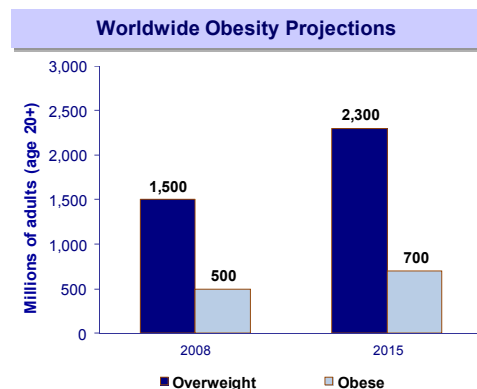


Source: Nature Reviews – Drug Discovery 8:609-610 (August 2009)

Environmental factors will place continued pressure on returns

Pressures on bio/pharmaceutical industry returns are only likely to increase in the future due to a variety of external factors. Specifically, there is likely to be increased pressure to control healthcare spending across the globe given the burden placed on governmental budgets. In the United States, healthcare is expected to consume almost 20% of GDP by the end of the decade with government spending alone projected to

double from ~\$810 billion in 2010 to ~\$1.6 trillion in 2020 (CMS, CBO Budget Projections (January 2011)). This increase will be driven in part by over-utilization of healthcare services, but will be compounded by demographic trends. The general global rise in obesity is just one example, which creates a need to manage a series of co-morbid, chronic diseases; e.g. hypertension, hyperlipidemia (JAMA. 299:23:2789-2791(2008), CBO Report: "Technological Change And The Growth of Healthcare Spending"(January 2008)).



Sources: WHO, Chronic Conditions Making The Case For Ongoing Care (December 2002), Burrill & Company (Biotech 2008: A 20/20 Vision To 2020)

Despite the fact that pharmaceutical intervention is often more cost effective than other interventions, the visibility of pharmaceutical spend allows scrutiny by payers on the health economics (HECON) of different therapeutic options. This will only increase. In order to meet these requirements, the bio/pharmaceutical industry has generated increasing amounts of data. A recent Frankel Group literature review showing ~150% more cost utility articles published in 2009 than in 1999 is just one proxy showing this increased cost justification burden. In the future, some of this data generation will reside with government-sponsored entities such as the US Patient-Centered Outcomes Research Institute, and even pharmacy benefit managers, causing a potential asymmetry in information with the industry. But, in almost any scenario, pricing/access pressure will continue to increase requiring drugs to generate significant improvements over the standard of care in order to be a commercial success. Getting an approvable drug is not necessarily a success commercially (www.prcori.org, Medco press release 8/18/2008).

Additionally, scrutiny on safety by regulatory agencies has grown steadily throughout the last decade and shows little sign of abating. This scrutiny has resulted in high-profile product withdrawals, including Vioxx globally and Avandia in the EU, as well as a 50%+ increase in the number of drug recalls conducted in 2009 compared to the average of the previous 3 years (CNN, August 16, 2010). To address these concerns, future drug applications will likely need to rely on larger and more costly clinical development programs to demonstrate safety and increasingly invest not only in Risk Evaluation and Mitigation Strategy (REMS) programs post-launch, but also in large Phase III trials that have placed a chill on the commercial viability of whole therapeutic areas (i.e.: diabetes, obesity). This will in turn have the effect of furthering lowering the probability of success on new drugs and the profitability of drugs that are successful.

Internal processes and incentives are not structured to drive efficient nor effective development

Internal drug development organization processes and incentives often create unintended consequences on multiple levels. And, without a fundamental understanding of how incentives are driving decision making, and a willingness to discard old metrics and even a reliance on best practices that may limit new ideas, most strategic initiatives may be doomed to failure.

The perspective of commercial vs. development organizations may be in opposition. The involvement of commercial organizations, that place Target Therapeutic Profile (TPP) hurdles in the development pathway, often can result in early kills. This is good for an efficient allocation of capital perhaps, but can an organization accurately assess an early stage program's ability to hit that TPP? Yes, on the extreme perhaps. But how accurately within the middle of the bell curve of potential performance? Conversely, the perspective of the traditional research and development team may be diametrically opposed in its view that, to some extent, discovery and development has a serendipitous aspect that can best be addressed by a wider early to mid stage development effort. How can an industry under financial pressure find the capital to keep programs moving beyond early kill points? The organizational incentives certainly have the potential to be out of synch.

Many large bio/pharmaceutical companies have created incentive structures across the organization that are either short term focused or are too mired in historic best practices. Many organizations seek, or need, short term success to such a degree that longer term performance may be virtually doomed. These organizations seek to maximize short-term performance by tying compensation to the number of assets that advance to Phase I, II or III. This can ensure that poor assets advance compounding the capital allocation problem. Additionally, it has been hypothesized that the decision-making process in large pharmaceutical companies overly focuses on research methods that have proven successful and overlooks innovative ideas (*Nature Reviews: Drug Discovery 9: 867-882 (Nov 2010)*). This can manifest in a focus on best practices rather than novel practices. Or even a reluctance to adopt novel processes and incentives optimized for a particular operation and its strategy due to the perceived risk of larger organization disruption. It has been posited that improved decision making, tied to restructured incentive programs, could increase small molecule IRR by as much as 2%. (*Nature Reviews: Drug Discovery 8: 609-610 (August 2009)*). The organizational incentives risk unintended, negative outcomes.

On a more macro basis, the move of larger pharma towards a therapeutic area focus in validated targets may limit visibility towards novel mechanistic approaches that emerging pharma is structured to do. The majority of large firms have chosen to organize themselves according to therapeutic areas in order to create sales and marketing synergies. And, to a significant extent, larger pharma has chosen a validated target focus to address risk. However, this approach may fail to appropriately identify promising early stage assets from academia that a more novel mechanistic or target focused approach might surface. Secondly, this validated target approach must assume a fast, first to market orientation to address the risk that the product profile at launch will be insufficient to displace existing therapies in the same class. Is large pharma sufficiently nimble? Other firms, usually smaller in nature, have chosen to organize around

potentially more novel mechanisms of action allowing for effective management of development risk and creation of a scientifically synergistic portfolio. Commercial synergies are not as visible for these firms. But, these emerging pharma is also structured for speed and first to market processes. It may be that the ideal approach combines elements of both methods to maximize return/reduce overall risk ... be it scientific or commercial. This will require significant change including earlier and more comprehensive portfolio prioritization, exploration of mechanisms that may originate outside of a therapeutic area, out-licensing of assets/indications not within a company's strategic focus, and more open innovation models (to be explored later in this paper). In other words, a radical change in some organization structures, processes and incentives.

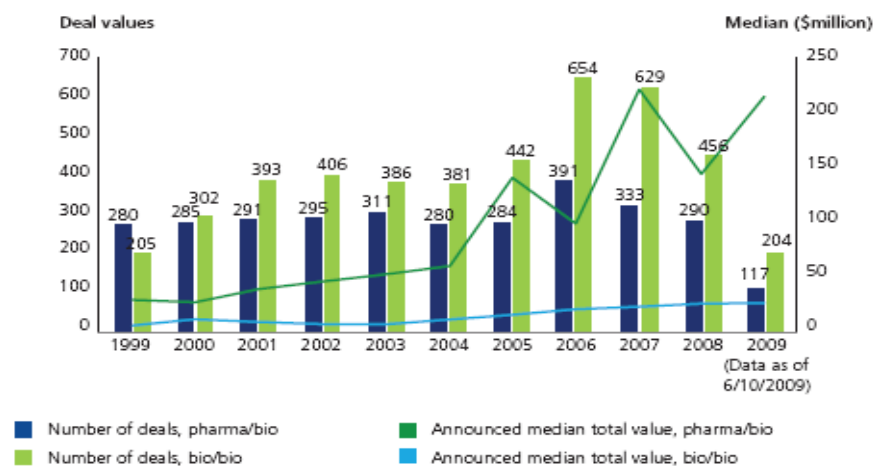
Finally, industry mergers strongly incent efficiencies, perhaps at the expense of effectiveness. The raft of mega mergers may have only provided short term cost efficiencies to date. The ability of scale to drive research and development success has yet to be validated, and may in fact be a hindrance. Certainly, the need to divert resources to rationalize combined development organizations can tax an already slimmed down organization. But, more threateningly, rationalization of early stage programs on limited data can too quickly narrow options and deplete the pipeline of potential wins.

External asset purchases are concentrating in limited platforms, and deal structures are shifting to structured deals with more risk/less oversight

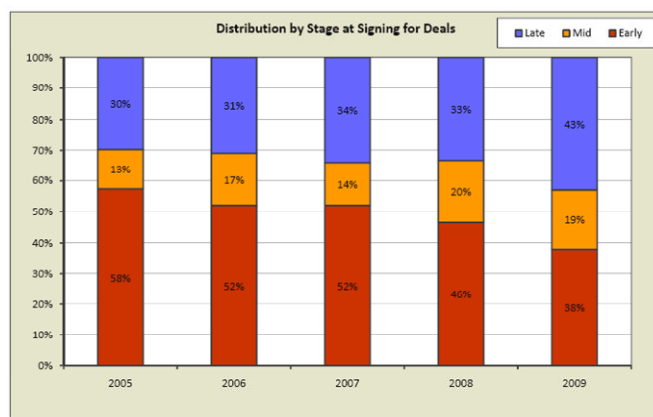
One natural response across the industry has been for the larger players to use their current cash flows to fill pipelines with asset purchases. But, a herd effect has led to a highly competitive in-licensing environment in terms of deal volume and average deal values. This has created not only a rush to later stage assets that can fill the near term pipeline gap, but threateningly a rush to a limited number of targets and mechanisms in earlier stage platform deals. For example, Cowen's December 2011 Pharmaceutical Industry Overview Report notes that there are 1,151 products in development, of which oncology and CNS disorders are the clear leads in terms of investment (over 40% of compounds in development are in these two therapeutic categories). Similar trends were seen in an analysis by New Leaf Venture Partners regarding venture backed biotechs. Of cumulative deals done in the past 4 years, about 40% are in oncology or CNS markets. In this environment, the external pipeline expansion that is essential for growth carries with it increasing cost, no change in development risk, rising commercial risk, and therefore continued pressure on ROI.

A key challenge is to bring additional resources to bear in addition to corporate capital, in such a way as to expand the external research and development portfolio at superior returns or lower risks levels when compared to historic internal development programs ... a tall order to fill.

Trends in Biotech Out-licensing Deal Values



Source: Deloitte “Acquisitions vs. product development: An emerging trend in life sciences” (2009), Deloitte Recap “Recap Roundup: First Quarter 2010” (May 2010)



Source: Deloitte Recap “Looking Back At 2009: Trends in Licensing and Partnership” (Jan 2010)

When looking at how leading bio/pharmaceutical players have chosen to secure earlier-stage assets, there has been an important trend to mitigate risk via structured deal terms. These structures have evolved from straight licensing agreements toward: (i) “back-loaded” structures with smaller upfront fees and greater emphasis on milestone payments; and (ii) deals that secure access by paying a relatively small upfront option fee, with exercise of a payment contingent upon future milestones (*Datamonitor, 2010, “Pharmaceutical Licensing Overview”*). Structured deals by the top 20 pharmas increased ~65% in 2009 vs. 2008 (Papp & Walton, 2010, *Nature Rev. Drug Disc. 9:422*). While these approaches offer a potentially attractive means of leveraging available capital, they also increase asymmetry of information, where the seller possesses considerably more information than the buyer, and reduce oversight of the partner’s development efforts. In aggregate, these factors may create greater overall execution risk. In addition, these back loaded deals may not provide sufficient capital to the emerging bio/pharmaceutical companies to sustain sufficient early stage research and development.

The problem, therefore, appears to lie in a combination of internal organizational barriers and business models coupled with a lack of ready risk capital. While it is likely that no single silver bullet will solve all of the ailments faced by the industry, several strategic options do appear to exist which will be explored in greater detail in future Frankel Group Advisory Board whitepapers.

Strategic Option 1: Deciding on the fundamental business model ... innovation or commercial

Perhaps the first fundamental decision involves a choice between business models appropriate for the asset, competency and investor base of each company, and will cleave the industry further between innovation driven business models and more commercially driven models ... and within an innovation driven model a fast, first to market approach in validated platforms vs. taking on more scientific risk with more novel targets.

This paper focuses on the innovation business models, and believes that there is room for both a validated platform, fast to market approach as well as a more novel target approach. However, the issue facing most players today is that those companies focused on the former approach, one that requires nimbleness of response, may be the largest scale players to a large degree and least capable of achieving first to market success. This, as mentioned, just compounds the return pressures from commercial barriers to what is seen as modestly improved offerings. Significant organizational and process change is likely necessary to follow this model. Concurrently, those companies that focus on the latter approach, one that requires significant risk capital to sustain failure rates, have seen traditional sources of capital dry up. This may be an even more threatening issue across the industry as insufficient early stage pipeline moves forward. In this case, new investment structures and players are likely necessary to follow this model.

Strategic Option 2: Improve approaches to capital allocation and portfolio planning

Clearly, meticulous strategic planning and portfolio decision making is increasingly required to allocate the capital that is available to the most promising assets. But are the relative research and development stage assets, particularly early stage assets, being viewed through the same set of prisms and attendant incentives? As mentioned, the commercial organization perspective may be driving towards early, perhaps premature kills. The research and development organization perspective may be equally driving towards later, perhaps delayed kills. And, are early stage assets capable of being accurately measured?

Bio/pharmaceutical firms are currently experimenting with changes aimed at optimizing capital allocation in drug discovery and early development. Given the level of uncertainty at these stages, it is no surprise that the capital allocation problem may suffer from imprecision present in asset valuation. While individual project eNPV is the primary means at asset selection, eNPV valuation methods may have an embedded erroneous assumption of distributed returns. More robust approaches such as decision theoretic methods (decision trees), real options valuation, and Monte Carlo simulation models can also be considered. Additionally, an argument exists that correlation analysis across interdependent opportunities can identify assets that increase the eNPV of the portfolio, even if the eNPV of the just added compound individually is negative. And, finally, are investors seeking industry to reduce beta risk or would they rather see larger alpha extremes and use portfolio diversification to manage risk? How can this perspective alter measurement endpoints and the metrics to get there?

Strategic Option 3: Increasing the participation in translational research and early development with structural changes to the business model

The current focus on mid to late stage assets to fill the impending pipeline gap perhaps should be modified to allow for expanded early-stage investments. This could increase the chances of success, satisfy the biases of the classic research and development professional, and perhaps satisfy investors. However, a number of barriers exist to achieving this:

- An organizational desire and incentive to invest only in validated mechanisms in a given class or disease
- A herd effect among larger pharma in these validated mechanisms and therapeutic areas
- Insufficient capital across the industry to capitalize on the early stage opportunities

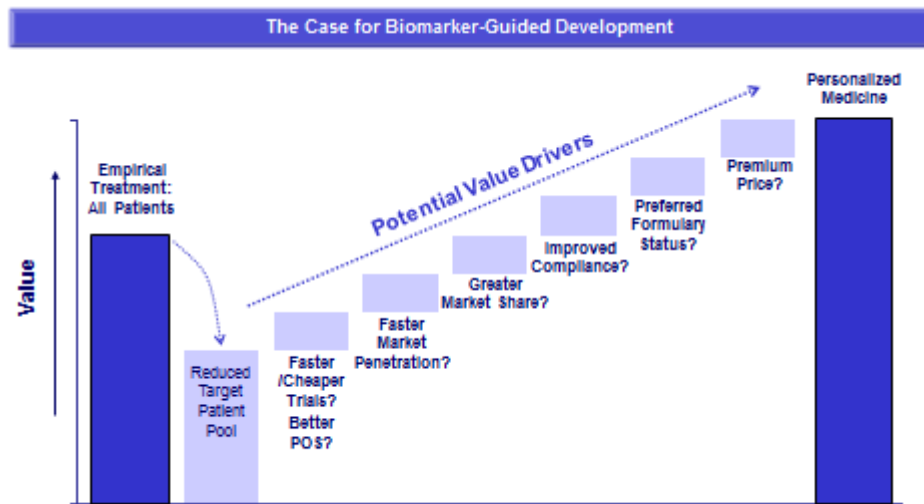
In many areas, such as liver fibrosis and diabetic nephropathy, while possessing a significant number of assets in the pipeline, no leading mechanism/pathway has emerged from research. As little opportunity exists to de-risk assets in this situation, a different investment approach that cost effectively creates portfolio diversification may be possible. One option is the creation of internal option-funds through which companies are able to place multiple bets on promising mechanisms, bringing them in-house if and when the science advances. A second option is one in which firms use their own pipeline as currency to create asset pools with other companies who have a similar therapeutic focus, with option rights to or participation rights in successful development projects ... as is the case in the BMS/Pfizer collaboration in

HIV and Astra Zeneca/Merck collaboration in oncology (and has long been the model in venture capital). A third option is the use of excess research and development assets, now being discarded as companies retrench, in lieu of capital to gain access, on a non-exclusive but early information basis, with a range of emerging academic and corporate research programs.

Looking most broadly, it is also possible that possession of a fully integrated value chain is no longer a competitive advantage and instead ties up capital that could be otherwise deployed more effectively. The future role of large bio/pharmaceutical companies may be as an “information broker” leveraging historic strengths in regulatory affairs, medical affairs and market access. Capabilities would still be retained in basic science to drive partnerships with external collaborators, but restructured to drive “open-collaboration” (discussed in Strategic Option 5). This approach could allow large bio/pharmaceutical firms to maintain control of the overall strategy of an asset, while transitioning costs from fixed to variable and potentially reducing these costs at more efficient out-sourcing providers.

Strategic Option 4: Driving the business model to therapeutic opportunities where diagnostics can affect development and commercial risk/return equations

Historically, drug development has been pursued from a “one size fits all” perspective, but increased understanding of key drug targets and associated biochemical pathways, coupled with advances in biomarker discovery and novel diagnostic, has enabled an alternative approach. Development programs can at times target patient sub-populations based on molecular characterization of disease. Examples of this approach have come largely from oncology to date, but biomarker programs increasingly accompany development efforts in other therapeutic areas, including autoimmune/inflammatory disease, central nervous system (CNS) disorders, cardiovascular and metabolic diseases. While molecular-based market segmentation in theory makes for a smaller target market, value can be gained through higher efficacy rates leading to improved probability of success, more cost-effective clinical trials, and the potential opportunity to utilize a number of commercial levers. And, it is in these therapeutic categories that have witnessed the largest risk shift in development requirements, namely metabolic and cardiovascular, that a biomarker approach may begin to help address, and in which the industry must re-learn how to participate in if it is to have markets sufficiently attractive to continue an innovation model.



Source: Frankel Group

This approach is requiring bio/pharmaceutical companies to become increasingly familiar with the diagnostics space, especially since recent FDA guidance on companion diagnostics has suggested that lack of an FDA-cleared IVD product may hold up drug approval in the future. Importantly, given stark differences in the business and operational models of bio/pharmaceutical vs. diagnostic companies, creative approaches to commercialization of companion diagnostics are required to ensure the broad test utilization that is a prerequisite for uptake of the associated drug.

Strategic Option 5: Integration of key stakeholders into novel open innovation structures

Traditionally, the industry has been built on a hub and spoke ecosystem, with large bio/pharmaceutical companies at the center and connections to external stakeholders including academia, government, and external sources of capital, but only used episodically on an as needed basis. It is possible that a new, continuous business model can unlock significant value for all parties. In other words, an open innovation system with more structured economic and governance relationships between the pharmaceutical industry and academia, government and capital markets.

Many of the leading bio/pharmaceutical firms have chosen to focus on a self-funding approach to R&D and have made relatively modest use of external sources of capital. Given that R&D budgets are expected to continue to contract, new sources of capital from external financial stakeholders may be required.

- For clinical stage assets, partnering with asset funds may be able to increase the size of the drug development pipeline while sharing development risk (albeit at the expense of giving up some ownership in the asset). Alternatively, capital markets might provide new solutions which could include a pooling of IP assets that can be sold as a security on the secondary market to provide additional R&D capital, similar to the film industry (*Milken Institute: Financial Innovations Lab Report (Oct 2006)*). Finally, an insurance product, similar to a catastrophic bond, may help mitigate

the risk associated with the late stage failure of a drug and attract capital.

- For translational research, the academic institution may be able to secure funding to advance research programs in return for future asset rights. Matching capital and risk more effectively is critical, as ~30% of all scientifically novel drugs come from academia (*Nature Reviews: Drug Discovery* 9:867-882 (Nov 2010)). However, taking advantage of this opportunity will likely require the industry to develop new internal processes to manage open collaborations, and academia will likely need to enhance existing skill-sets in their out-licensing groups. Fortunately, several successful case studies exist.

The role of government in the bio/pharmaceutical industry could also evolve as a key translational funding source. Historically, government entities, such as the National Institute of Health, have provided research grants to fund early stage, largely academic programs. An expanded opportunity for governments may exist in providing capital towards specific drug assets approaching the clinic, in conjunction with financial investors and industry stakeholders. By inserting a third capital entity into the mix ... specifically a low cost government capital source that may not require market based returns ... the return for the other equity investors improves. Government participation can yield several other benefits, including increased employment and tax receipts and advancement of drugs that serve a public health mission. But, with this participation may also come increased oversight, including potential control over pricing of the approved drug as a means to reduce future healthcare costs.

A process to move from current low productivity levels to higher productivity levels

Many organizations have considered the range of options laid out in this paper, from capital allocation models to expanded open innovation models in translational stage development to refocusing on new growth sectors such as niche markets to novel alliances with governments, academia and capital sources. The questions may not only include “what is our development situation” and “what are our options to improve it”? But, most fundamentally, “is our business model innovation or commercialization asset based”, and within innovation business models “is it fast, first to market approach in validated platforms or is it taking on more scientific risk with more novel targets”, and in turn “are we structured internally for this model” and “do are we considering novel capital participation structures to fund it”. And, for all, a basic question should include “what is a structured yet straightforward approach we can take to get from our current situation to testable short, mid and longer term solutions”?

Any such approach should include the following steps:

1. Initially, what is our business model based on our assets, competencies, competitive stance and investor profile between innovation and commercialization? And, within innovation:
 - a. Do we focus on validated platforms that will require a nimbleness in our organization to be first to market?
 - b. Do we focus on more novel targets that will require adoption of and management of increased scientific risk and access to capital?

2. Assuming an innovation model approach, what are the visible opportunities? With a thorough review of the opportunity vs. risk vs. investment profile of our current development portfolio, where are the pivot points for improvement and where may the ultimate solutions lie?
 - a. How much more participation in R&D programs do we need to close the gap between development output and revenue requirements? What segments of the research and development process offer quick improvement potential to either lower costs or raise success, and are these present in technologies, organizational structures and incentives that are visible today?
 - b. Are we focused on those sectors that promise to leverage our core capabilities for optimal risk vs. return? Should we alter our focus in terms of niche opportunities and, if so, are the capabilities required present and the competitive opening still visible?
 - c. Are we even measuring the risk/return of our potential assets correctly? Do we even understand how our capabilities stack up against best in class?
 - d. Digging deeper into the first question, should we ground our development decisions in validated therapeutic areas, more novel mechanisms of action or some blend?
3. With selected end game options identified, what “reverse engineered” short to long term milestone achievements are possible?
 - a. What actions can be successfully completed via organizational change, including process, communication and incentive structures?
 - b. What actions require accessing new technologies or capabilities, and can these be captured via contracting, partnering or, because of the strategic value of scarcity, acquisition?
 - c. What actions more fundamentally require a business model change, such as deploying an open innovation model with academia, or more broadly a four legged alliance structure with academia, government, capital sources and our organization?
4. Finally, how can we design a milestone investment and feedback mechanism that gates and adapts our investments? And, how can we deploy this feedback mechanism to revisit the initial business model decision?



Summary

The bio/pharmaceutical industry has been a key contributor in improving overall healthcare in the last century and has been responsible for the eradication of debilitating diseases such as polio and smallpox from the developed world. However, as summarized in this paper, an innovation drought currently exists that threatens continued progress in core disease areas. This is due to a number of internal and external factors and appears to run the risk of becoming structural:

- Risk/Return Measurement: A sub-optimal approach to capital allocation across the development portfolio
- Operational Processes and Costs: Increased cost of drug research and development as both failure rates and trial requirements rise
- Late Stage Asset Scarcity: Increased focus on the acquisition of bid up mid to late stage assets to address pipeline gaps
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Fortunately, several initiatives can be experimented with to address these challenges, and will be explored in more detail in future Frankel Group whitepapers. These include:

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- Increasing the participation in translational and early clinical development on a scientifically focused process through the use of structured deals and deployment of excess development assets in lieu of capital. This must be coupled with improved, and at times radically altered, internal governance practices.
- Driving the business model to selected therapeutic opportunities where the use of biomarker driven development and commercialization, and potentially drug/diagnostic/device combinations, exist.
- Integration of key bio/pharmaceutical stakeholders into novel external structures, including financial institutions, academia, and the government in new collaborative business models which promises to enhance industry access to capital and sources of innovation.