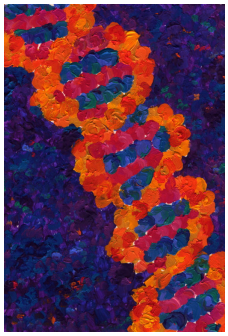
The Innovation Gap in Pharmaceutical Drug Discovery & New Models for R&D Success

Kellogg School of Management



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1 How Serious is the Innovation Gap Crisis in Pharma R&D?

To answer whether the pharmaceutical industry is undergoing a productivity crisis depends in part on how we define innovation productivity. If we adopt the pragmatic definition of the number of new drugs, defined by new molecular entities (NMEs), approved per year, then it appears that the industry is indeed in a midst of a major crisis. The number of NMEs and priority review drug approvals has remained relatively flat in the past decade [1] (see ***Figure 1***), despite a ballooning on the cost side. The amount of spending that pharmaceuticals poured into R&D has consistently increased year over year [2] (***Figure 2***), from ~15B in 1995 to approx 40B in 2005. This data is consistent with the DiMasi study[3] showing that the time discounted total cost of developing a single drug is $800M in 2002, increasing at an annual, inflation adjusted rate of 7.6% between 1991 and 2000. In short, between 1995 and 2005, the industry increased R&D spending by more than 2.5X in order to sustain its flat growth pipeline productivity.

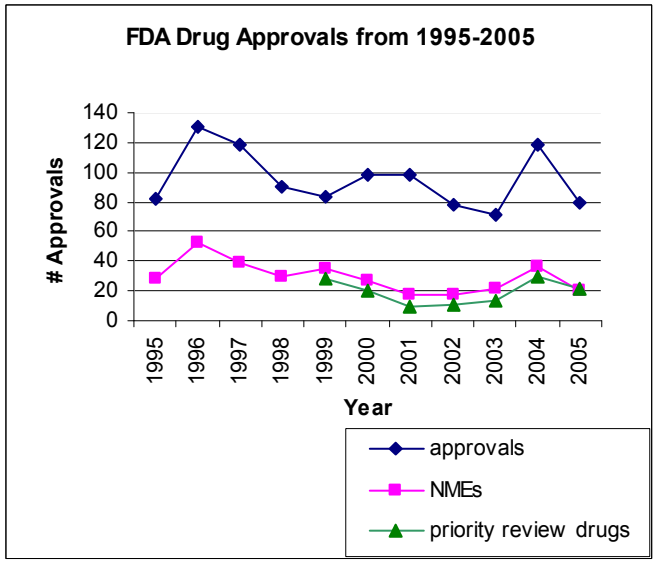


Figure 1 FDA drug approvals have remained flat

Moreover, the problem is exacerbated by the fact that the NME drugs that do make it to market seem to lack the market size/ revenue stream potential of their predecessors. During 1990-94, 11 new drugs had reached the "top 100 drugs" category in terms of global sales. From 1995-99, 10 new drugs approved made it into the "top 100 drugs" category. However, during the period from 2000-04, only 2 new approvals broke into the top 100 revenue generators[4].

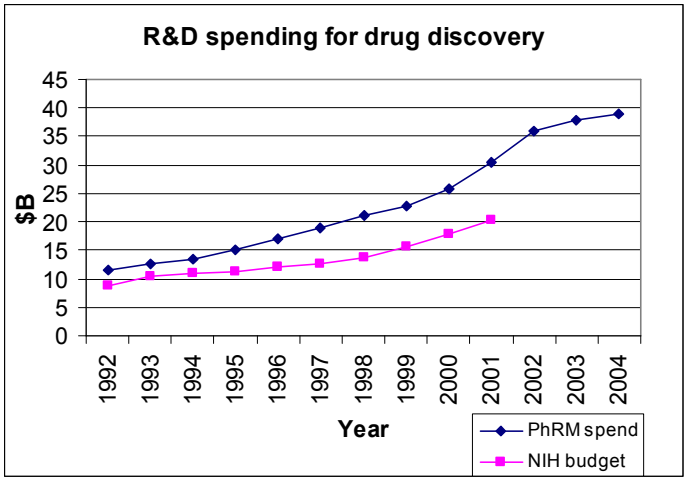


Figure 2 Pharma R&D spend from 1992-2004.

If these trends extrapolate into the future, the industry will not be able to tolerate the burden of this Red Queen Effect of continued cost escalation just to maintain the tepid innovation status quo.

In defense to the troubling trends, some studies report[5] that R&D innovation is showing a steady growth of 8% in new projects per year in the pre-clinical and phase 1-2 stages of the pipeline; however it is unclear if pharma can translate this to innovation productivity since:

i) unclear which of the early phase projects are truly new innovation products or simply second-in-class me-too products

ii) unclear if 8% growth in early phase will translate to material increase in approved products after going through the attrition, risk-laden clinical trials process

Others have suggested that this decade could be experiencing a lag between R&D spending and the extraction of value from that investment. During the 1960-70s, economists were also concerned about the simultaneous increase in annual R&D spending and the decrease in NMEs approved[6]. However the alarming piece of data is that the gap between the rate of R&D cost increase and the decline/flat growth of productivity is much wider now that it was in the 1960-70's[6].

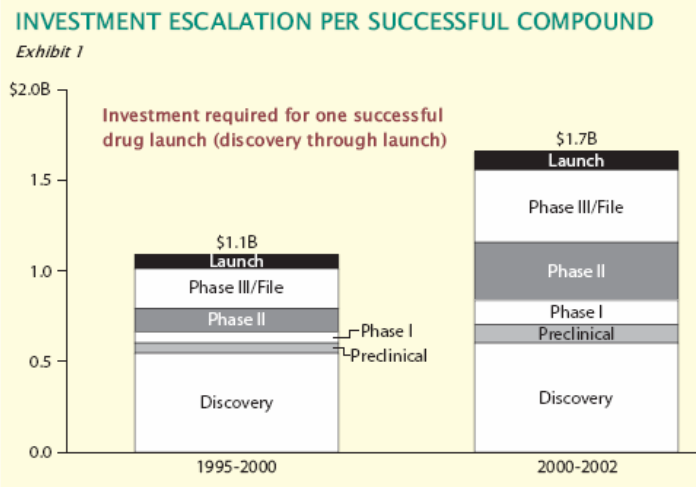


Figure 1 Comparison of R&D costs. Bain model 2003

In a Bain & Co analysis[7] (***Figure 3***), the total cost of doing pharmaceutical R&D has increased across the board between 2000-2002 compared to historical trends from 1995-2000; the rising costs was particularly pronounced in Phase II trials. A large part of the increase in costs is due to an increase in failure during clinical trials.

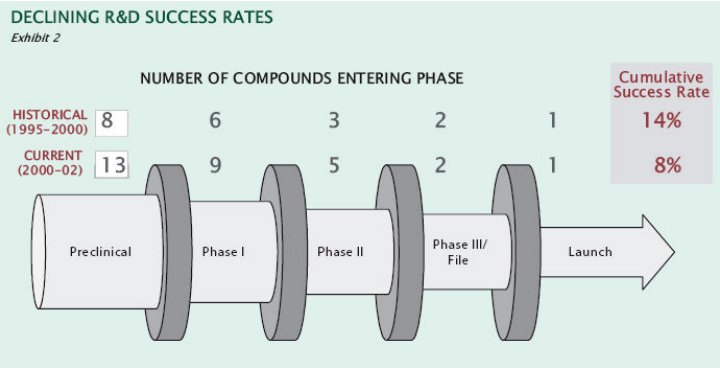


Figure 4 Failure rates in clinical trials have increased. Bain model 2003

According to the Bain study [7], during 2000-2002, it took 13 candidates coming out of pre-clinical trials to push 1 product to final launch whereas between 1995 and 2002, only 8 preclinical candidates were required on average to yield one successful drug (***Figure 4***). The cumulative success rate (probability) of making it successfully across the clinical trials have decreased from the historical 14% to 8% in 2000-2002. Moreover, since the analysis was

done on all drug projects, we can reasonably assume that the success rates are even lower for NME class drugs.

2 Root Causes of the Innovation Gap

"Most of the easy wins have already been made…Now we are into more indirect ways of treating diseases: stopping tumours from growing by preventing their ability to get blood supply … These are much more complicated. This is not to belittle the advances so far, but things are getting difficult."

Lars Rebien Sorenson, CEO of Norvo Nordisk, BusinessWorld 2004

1) Saturation of low hanging fruits: we are pushing the limits of our current scientific understanding of the major disease related biological pathways where solving the productivity challenge requires an increase in the rate of basic scientific discovery and biological understanding. Some posit this as being one of the major culprits of the productivity decline [8], others such as in a 2004 McKinsey study[9] downplay the low hanging fruit hypothesis, stating as an example that the "G-protein-coupled receptor" (GPCRs) are the target of 30% of all marketed products, but there are several hundred more GPCRs that are yet to be characterized. We find this argument inconclusive since it could very well be that out of the 30% of the marketed products targeting GPCRs, 25% are me-too, incremental follow-ups with sub-optimal revenue streams; this would diminish the attractiveness of going after the remaining uncharacterized GPCRs.

One potential cause of this saturation is that for the past decade, most of pharmaceutical research efforts have focused largely in four major disease areas: central nervous system, cancer, cardiovascular and infectious disease. Increasingly, it will have to search for products in poorly understood and more complex therapeutic areas such as autoimmune diseases and genitourinary conditions[10].

2) Pharma focusing on riskier, genomics based candidates rather than clinical validated drug targets. In the McKinsey study [9], Booth and Zemmel found that during 1999-2004, many companies have opted to go after novel targets discovered from the human genome project and computational analysis methods. Consequently the aggregate industry portfolio is much riskier than in the previous decade. They estimate that in 1990 a typical target in development had ~100 scientific citations while in 1999, an average drug candidate had only 8 scientific citations. Targets that lack clinical validation fail at significantly higher rates in trials.

The more interesting question is why collectively, all the pharmaceutical companies decided to shift their discovery portfolio to these riskier candidates. One rather extreme answer is due to sheer irrational exuberance; the science behind these novel candidates were so novel and exciting that pharma decided to abandon risk adjusted, systematic project development processes in favor of these riskier and more exciting alternatives. Another more rational explanation is that the pharma as an industry were already running out of promising, clinically validated candidates and thus had few options but to adopt the less validated, novel candidates to refill their pipelines in pursuit of NME, blockbuster drugs. This would support the hypothesis that the low hanging fruits have been picked.

3) Pharma too big to innovate: Another potential source for pharma's productivity woes is their size; some argue that pharmaceuticals have grown too large to maintain an entrepreneurial culture and business environment required for innovative R&D discoveries. The only alternative existing commercial based R&D model to benchmark against is the biotech industry. However it is unclear if biotech, although commanding a higher stock multiplier, indeed actually generates better productivity per dollar spent than pharma. In his article[11], HBS professor Gary Pisano argues that the biotech industry has fared no better than pharma in terms of cost vs productivity in trying to bring new drugs to market. Pisano argues that the small, fragmented and the entrepreneurial structure of the biotech sector with venture based funding focusing on short time horizon gains does not create an optimal "anatomy" or architecture for performing scientific discovery. In addition, studies conducted on the productivity of the pharmaceutical industry from the 1960s to the early 1990s between large and small pharma companies also show that larger firms enjoyed better productivity overall due to economies of scope[12].

3 Pharma's Existing Strategies for Improving R&D Productivity

The pharmaceutical industry in the past decade have responded to the innovation gap through a variety of tactics, from throwing money into internal R&D to horizontal industry consolidation to an increased dependence on in-licensing from biotechnology sector. If one traced the timeline of when these ideas were popular among the industry and were actively implemented, they more or less follow a serial sequence across the timeline; moreover each of the aforementioned "solutions" increases in implementation difficulty in terms of process coordination and managerial complexity. ***Figure 5*** is a graphical depiction of the above two observations. The pattern suggests one key take-away: none of these tactics have proven the panacea to pharma's R&D innovation woes and

pharmaceuticals are resorting to more risky and complex initiatives in an effort to curtail the Red Queen Effect of R&D stagnation.

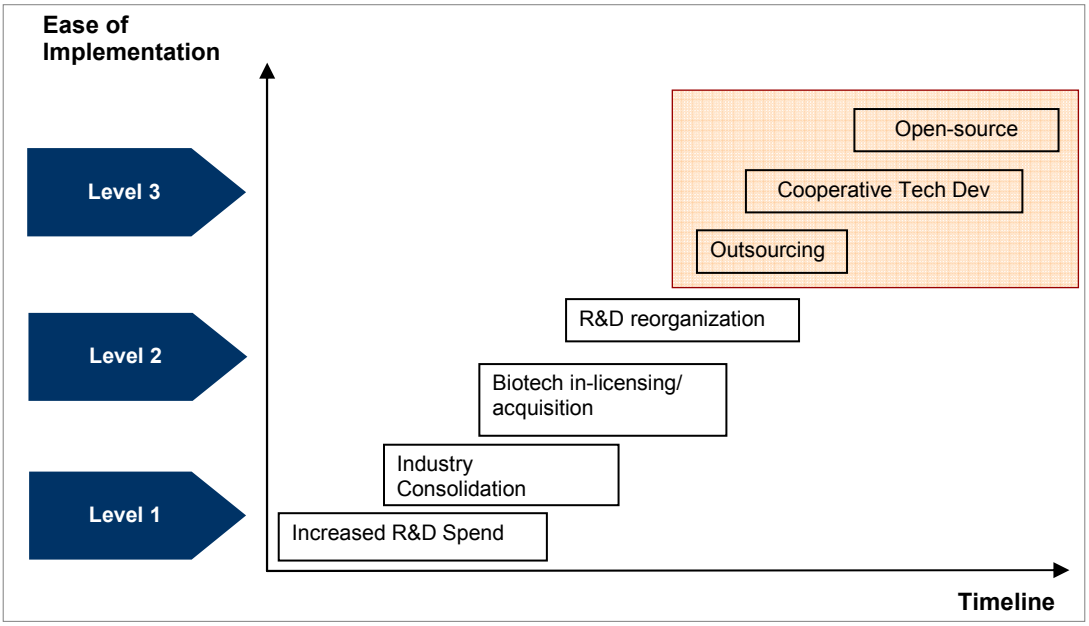


Figure 5 - Diagrammatic depiction of the different models of innovation; the three in the red box are emerging models at the horizon while the others have already been adopted by the industry.

Increased R&D Spending: This strategy was implicit in the increasing R&D costs associated with each drug brought to market, and the speed with which these figures are rising.

Horizontal Consolidation: The industry saw a wave of horizontal consolidations as drug companies sought to seek either i) economies of scale across the entire value chain, from R&D discovery to sales force or ii) short term growth engines in light of expiring patents and enervated pipelines. Often executives cite that synergies in R&D competencies and increased research productivity as key motivations for M&As. To date there is mixed evidence in the literature on the effects of scale on R&D productivity. Most evidence seems to indicate that there is no strong correlation between scale and improved productivity[13].

Biotech In-Licensing: Pharmaceuticals are increasingly relying on partnerships and in-licensing drug candidates from the biotechnology sector to supplement its pipeline (see ***appendix 1A***).
There are two potential problems of delegating the discovery task to the biotechnology sector:

i) There is no evidence that biotech can live up to the challenge. Although the pace and number of in-licensing deals and alliances have increased, the total number of NME approvals (both

small molecules and biologics) in the pharma as well as the biotech sectors have not increased to date or kept pace with the spending.

ii) Even if biotechnology firms can fill pharm's pipelines, this will shift the bargaining power and thus the value capture lever to the biotechnology sector[1], thereby reducing the profitability of the entire pharmaceutical industry. This trend is already evident in the rapid increase in prices for in-licensing biologics from biotech firms. For example, the average deal price for a pre-clinical product doubled between 2002 and 2004 to $72MM/deal, and the average price for a phase I deal jumped from $57MM in 2004 to $82MM in 2005[14].

See ***appendix 1B*** for a listing of the biggest pharma/biotech deals in 2005.

In the context of ***Figure 5***, the industry is currently somewhere between the "Biotech in-licensing" and "R&D Outsourcing" regimes in the evolution of its innovation model adoption. The rest of the paper will explore several new innovation models on the horizon, namely: *outsourcing*, *cooperative technology development* and *open sourcing*.

[1] Biotech will demand both more up-front payments as well as the % of profit as royalties upon successful product launch.

4 New Strategies & Models for Improving R&D Productivity

"That is why the business model is under threat: the ability to devise new molecules through R&D and bring them to market is not keeping up with what's being lost to generic manufacturers on the other end. This situation requires new thinking, new urgency, new capabilities."

Fred Hassan, CEO Schering-Plough

4.1 'R' follows 'D' in R&D Outsourcing

Definition of Drug Discovery Outsourcing

To begin, a clear definition of discovery outsourcing is warranted, as this term is often applied in different ways. For this discussion, a discovery outsourcing firm is defined as a vendor providing discovery services to the pharmaceutical or biotech industry. These companies are often referred to as Contract Research Organizations (CROs), although such companies may provide a range of services beyond drug discovery. And while our focus will be on CROs, other service providers, such as academic institutions or platform technology firms, may share some of these qualities.

What are the major areas in drug discovery that CROs are now active in? Four major market segments are: Chemistry, Biology, Screening, and Lead-optimization. The two areas growing fastest are Lead-optimization and Biology (over 20%/yr). Chemistry is growing 10%/year; Screening at 6%. The overall market for outsourced drug discovery in 2005 was $4.1 billion, and is projected to grow at a 15% rate to reach $7.2 billion in 2009. This remains a highly fragmented market. Even the top suppliers each have less than 1% of the contract drug discovery market. Major players include: Albany Molecular, ChemBridge, Evotec, MDS Pharma, Pharmacopeia. The following table shows R&D spending in the pharma industry over time. The data shows that spending is increasing for both discovery and development outsourcing, and that development outsourcing is leading the way.[2]

[2] Gardner, J. Outsourcing in Drug Discovery, 2nd edition, A Kalorama Market Intelligence Report, January 2006. p: 1-232.

Outsourced Drug Discovery and Development Expenditures by Type (Discovery vs. Clinical Trials) 1997, 2001, 2005, 2009

	Spending (in billions)			
Year	Discovery	Clinicals	Total	Percent Outsourced
1997	$0	$2	$2	10%
2001	$2	$5	$7	24%
2005	$4	$9	$13	33%
2009	$7	$17	$24	41%

Source: Kalorama reports

Research Follows Development Outsourcing: Moving Beyond In-house Capabilities

In this paper, innovation is defined as the ability to produce NMEs. Doing so requires finding a large number of high quality lead compounds, through innovations in the drug discovery phase. While drug development lies downstream from this process, interesting parallels can be drawn between the two to predict the evolution of the discovery outsourcing model. Drug development outsourcing is more mature than drug discovery outsourcing, so this model serves as a good predictor. A close analysis will show that drug discovery outsourcing can lead to innovation.

Originally, drug development was outsourced by big pharma because of limited resources. Large late-phase drug trials are highly labor intensive and the stream of such trials is inconsistent; therefore, growing in-house capabilities to cover such intermittent needs would be economically unfeasible. CROs were traditionally seen as a necessary evil: While in-house teams allowed better oversight and typically had more experience, outsourced teams were more cost efficient. Often, only the most labor intensive and highly standardized parts of the development process were outsourced (i.e. clinical monitoring and data management for large phase III trials).

Big-pharma was also looking at ways to cut costs in the drug discovery stage. Initially, only routine steps were outsourced. Innovation was left to the in-house scientists. Some companies

like Pfizer decided not to outsource any work in drug discovery. Concerns about loss of IP and a belief that core competencies must be developed in house, were major drivers for this strategy.

The emergence of biotechnology provided a big boost to the outsourcing model. Suddenly, biotech start ups with limited funding but a great idea needed to outsource nearly all aspects of both research and development. In extreme cases, these companies acted as virtual companies, with a core team of experts managing multiple vendors to complete all drug discovery, clinical trial monitoring, data management, and NDA submission work. Suddenly, demand grew for full-service CROs.

With time, the pharma industry discovered that outsourcing firms could not only do all steps in the development process, CROs could do it cheaper and faster. And quality was no longer an issue. Because CROs began to specialize in certain steps of the development process or specific therapeutic fields, they became the experts in those areas. They learned to reach patient recruitment goals faster, reviewed and cleaned data files more quickly, and found innovative ways of managing clinical sites.

A new reason to outsource also emerged. With growing pressure about vigilance and independent review the FDA began to look more favorably on CROs, as they did not have a direct stake in the success of drug trials. This aspect also helped to make CROs so profitable. Most contracts were set up as fee-for-service. Whether a drug succeeded or not was irrelevant. The CRO was paid for its services regardless.

While this historical perspective provides insights into the rise of CROs, the question remains whether CROs have helped or hindered the development of NMEs. While outsourcing development may have led to faster approvals and lower development costs, the clinical trial process only affects innovation indirectly. The key is to find more lead compounds with a greater likelihood of making it through the clinical trial flow.

Why the Need for Outsourcing is Greater Now than Ever

The current growth in the discovering outsourcing arena will increase. Section one of this paper provides an interesting look at the lack of innovation in the pharmaceutical arena. Closer investigation of some of these root causes is warranted in order to show how CROs can fill a very specific need.

High Risk and High Cost of New Technology

Pharmaceutical companies have been burned with several hyped platforms. It's unclear if any of these technologies will still pay off in the long run. Many argue that pharmaceutical companies invested too much money into these technologies too soon. The cost of these new technologies continues to grow. As technology becomes ever more advanced, with higher specificity and larger throughput, the investment required to fund a single technology can easily reach into the millions.

Lack of Efficient Learning

In the past ten years, many of the big pharma companies have merged to produce mega firms. These mergers were touted for their ability to benefit from synergies and complementary assets. The reality has been less rosy. Research centers that traditionally struggled to communicate internally were suddenly faced with the burden of coordinating their efforts with many more labs. Even if the two merged companies were involved in different therapeutic areas, many of their discovery capabilities were redundant. Researchers were expected to combine efforts across groups and research centers often located large distances from each other. Power struggles and cultural differences served as major roadblocks to innovation.

Another trend in the pharma industry has been the reorganization to therapeutically aligned business units. Larger pharmas with multiple research centers now place different therapeutic expertise in each location. Novartis reorganized to this model in 2001, and Roche announced

that it will change its structure to this model later in 2007[3]. The reason for this move is to promote communication along the development pipeline for each product. Pharma companies had learned that a huge amount of information was lost each time a product was handed off during successive steps in the R&D process. A negative side effect of this reorganization is that functional groups from different therapeutic areas are less closely linked. The shared learnings across a functional group are therefore diminished.

IP and Cultural Issues Associated with Expansion into Asia

The final point that should be considered in our outsourcing model, is the trend for pharma to enter Asia. While a steady increase in the standard of living in this area represents a market with huge growth potential, pharma's are looking eastward for other reasons. Cheap labor coupled with a well-educated workforce makes this a very attractive area for conducting R&D. However, IP concerns as well as cultural and communication barriers hinder this expansion.

CROs Can Help

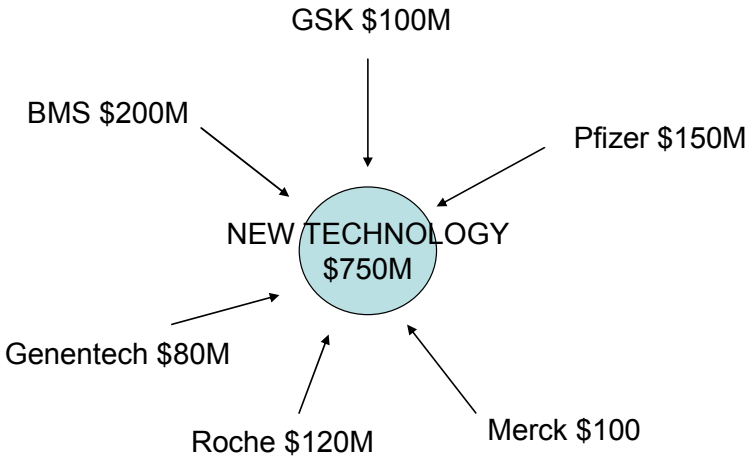
CROs can provide solutions to each of the issues noted above. Each point will be revisited from the standpoint of the CROs, and how such firms can create answers for the barriers to innovation.

Risk Sharing for New Technology

Risk sharing occurs when separate entities invest in a common, risky endeavor. In the case of technology, sharing risk can be a necessity. In the past, many pharma companies have invested in expensive technology, but then are unable to fund the endless experiments that are required in order to find a pay-off for this investment. If these companies could better pool such investments, the pay-off may look different. By contracting out the research to another firm (such as a CRO), each company pays only a fraction of the expected total. Universities have taken this approach. Investing in large equipment, they find that these machines are used much

[3] Ward, M, Strategy: Mini Roches, Biocentury, 2007. 15 (8), February 12, p:A8.

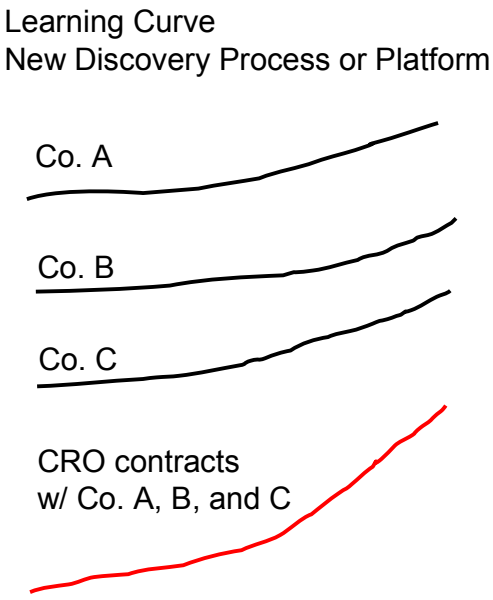
below their full capacity. As a way to generate more revenue, these university research centers contract out their equipment. The problem with this model is that these university centers are typically very small, and have large turn-over. Much of the research is conducted by graduate students who have limited experience, and thus the quality of the work can be unacceptable. More preferably, larger CROs can invest in these technologies and hire the top specialists in an area. If specialized CROs become the provider of choice for specific technologies, they can advance more quickly than the singular pharmaceutical company. They will run more experiments with more partners, and gain more learning as a result. The diagram below illustrates that separate contracts by different pharmaceutical companies can lead to cost savings for all players.



Shared Learning through the CRO

Learning often occurs through incremental improvements in processes. Through collaborations, process learning can be made more efficient; all parties within the collaboration learn from each other and the rate of learning is thereby improved (see learning curve figure, below). While some processes in the pharmaceutical or biotech industry are patented many more that could be improved incrementally, are not. Suitable vehicles for this sharing often do not exist. Consortiums have this same goal in mind, but the economic benefit is not centralized sufficiently to maximize the learning. CROs are in a better position, and are accustomed to learning from

their environment: they are constantly updating their standard operating procedures and lab protocols. Improvements in processes can lead to greater quality and higher efficiency, which both are drivers for innovation.[4]



Bridge Cultural and Communication Barriers and Limit Risk in Asia

Experts are still skeptical about the ability to gain an innovative advantage by expanding into Asia, but most agree that the environment is improving. China and India have joined the WTO, and understand that it's in their best interest to protect IP of overseas clients. Communication links have also improved. Managers and scientists at outsourcing companies are getting better at speaking the languages of their clients. Cultural differences between countries can still be a barrier. Interpersonal relationships require time to cultivate. Business and social practices may work differently in different countries. Questions of trust, honesty, and transparency may still remain.

Pharma companies are increasing their stake in Asia. Novartis announced their plan to invest $80 million in a new research center in China. Roche already has operations there. A prime reason to open research centers in these countries is to gain access to the untapped intellectual

[4] Powell, W. Learning from Collaboration: Knowledge and Networks in the Biotechnology and Pharmaceutical Industries, California Management Review, 1998, 40(3), p:228-240.

property. Some big pharma companies have recognized that local CROs can help to bridge bridge cultural barriers. These CROs have connections with the local governments and universities, are staffed by the local work force, and understand the environment in which they operate. At the same time, the western companies are helping these local CROs to get up to FDA standards. Bridge Pharmaceuticals, a Stanford Institute spin-off, is doing exactly that. This western company has moved their in-house capabilities into China, partnering with Chinese labs, and helping them get up to FDA standards. Long term, Bridge will create all the elements of drug discovery and development by internal development or acquisition.[5]

Examples of Discovery CRO Partnerships

Different pharmaceutical companies have varying strategies for outsourcing drug discovery. The following examples best illustrate different options.

Amgen

Amgen relies on a sole-source vendor model, with a focus on maximizing communication. Quality, cost, speed are their main considerations. Amgen previously partnered with ten CROs for their discovery work. More recently Amgen has shifted their strategy to outsource to only one provider. Amgen has found that they are better able to manage this relationship and get better results. The CRO has a predictable income from Amgen and can better invest in new technologies.

GlaxoSmithKline

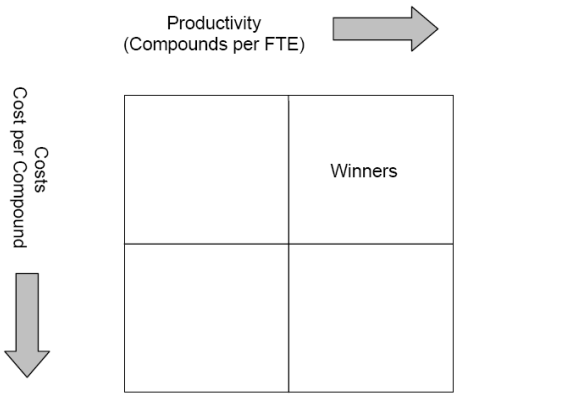
GlaxoSmithKline uses many suppliers mainly for building blocks and chemistry. They use a cost vs. productivity matrix to evaluate partnerships. The number of building block suppliers has grown exponentially. A decade ago there were only 20 building block suppliers, now there are

[5] Gardner, J. Outsourcing in Drug Discovery, 2nd edition, A Kalorama Market Intelligence Report, January 2006. p: 82.

over 200. GlaxoSmithKline partners with vendors in the US, Europe, China, India, and Eastern Europe.

Figure 4-1

GlaxoSmithKline Productivity/Cost Supplier Evaluation Matrix



Merck

Merck seeks to diversify research through relationships with new technology suppliers. Merck has been fully committed to outsourcing for some time. They see it as a way to access novel technologies, pursue parallel approaches, and leverage their scientific expertise. Merck sees partnering as an integral, essential part of their business strategy. In fact, 35% of Merck's sales come from licensed products. To succeed, benefits must accrue to both partners. Merck has experience doing deals in basic research, platform technologies, preclinical development, and delivery technologies.

Merck

At one time, Pfizer only considered outsourcing clinical trials work. But they have found that outsourcing is an excellent way to supplement their internal chemistry capacity and extend their resources. It is also a very good way to access new technologies without having to develop them internally.

TargeGen

TargeGen is an Asian outsourcing success, proving that outsourcing works for small pharma. TargeGen is a start-up pharma, founded in 2002 with $40 million of VC funding. They discover and develop their own drug candidates through both in-vivo and in-vitro screening . TargeGen created a wealth of candidates and their pipeline grew too quickly. TargeGen currently has four drug candidates, each with different routes of administration that treat different diseases in different stages of development. Their solution was to outsource selected parts of their research program.

Innovation Through Pathway Development

As a final note, an interesting change in the discovery approach is underway. Porter and Fischman of the Novartis Insitutes of BioMedical Research describe a current shift from a focus on organ pathology to the elucidation of complex signaling pathways.[6] Successful players in this new era of discovery will best be able to harness information from the various resources available to them. Following the arguments provided above, it is likely that CROs can help to elucidate these pathways more efficiently. The IP no longer lies only in the rights to the best molecules or the newest technologies, but in being the first to understand these pathways.

Discovery Services Provided by CROs

Biology Services

- Protein Expression & Purification
- Protein Structural Analysis
- Determining Protein-Protein Interactions
- Functional Genomics
- Bioinformatics

Chemistry Services

- Providing Building Blocks
- Compound Synthesis & Purification

[6] Porter, J. and M. Fishman, A New Grammar for Drug Discovery, Nature 2005, 437, p: 491-493.

- Process Research
- Library Design

Screening Services

- Assay Development
- Secondary Screening

Lead Optimization Services

- Early Absorption Distribution Metabolism Excretion (ADME)/Toxicity
- Compound Analogues and Structure Activity Relationships (SAR)

Source: Kalorama Reports

4.2 Cooperative Platform Technology Development

"First you have to have the tools that will help you discover those drugs more quickly"
JP Garnier, CEO of GlaxoSmithKline

Advances in technology can improve R&D productivity and efficiency, in particular in early stage discovery work. New technologies can significantly enhance or speed up an existing experimental procedure and discovery process, allowing for not only quicker and cheaper hypothesis generation and validation but potentially unlocking new scientific insights leading to new therapeutic pathways. We fill focus our discussion on platform based technologies that enhance or enable better R&D productivity rather than therapeutic product based technologies aimed at end patients.

To date, only a handful of new and disruptive technologies have crossed the market adoption chasm from odd lab curiosities to powerful tools used en-mass to truly improve industry-wide productivity. Two such examples are PCR and microarray/gene-chip. Read ***Appendix 2*** for a background of the two technologies and their impact on biomedical R&D.

PCR revolutionized the entire field of molecular biology, speeding up the fundamental experimental process of DNA replication by over a thousand fold. PCR saw quick and widespread adoption because of three principal factors:

i) It had a clear value proposition and application of use for scientists.

ii) Although the first generation PCR products had certain limitations, it was inexpensive to make incremental improvements to the technology. This enabled PCR to reach ***dominant design form*** quickly. We define dominant design as a stage of technology maturity where

both the fundamental architecture/science behind the technology is established and where the major incremental improvements required for the technology to deliver a compelling value proposition to the "mass" users is achieved.

iii) PCR also possessed what economist call ***low complementary asset requirements*** (the technology does not require or depend on other significant technologies/processes, such as deep user expertise, complex ancillary equipment, etc.

Gene-chip is one of the success stories in biomedical research in the past decade. The gene-chip enabled biological scientists to interrogate the expression level of thousands of RNA expression simultaneously rather than in manual, serial fashion. It changed the rules of the game for conducting gene expression experiments. Despite its importance, gene-chips took three times as long to achieve mass adoption as did PCR. Originally invented in the late 1980s by Steven Fodor at the startup firm Affymetrix, gene-chips did not achieve wide usage until 1999-2001. ***Figure 5*** on the left tracks Affymetrix's revenue and profit trend since its inception; we can roughly use the revenue growth as proxy for its intensity of use in the industry. It took six years, from 1990-1996, for the early adopters at the leading R&D labs to establish the complementary assets required to fully leverage the technology, namely:

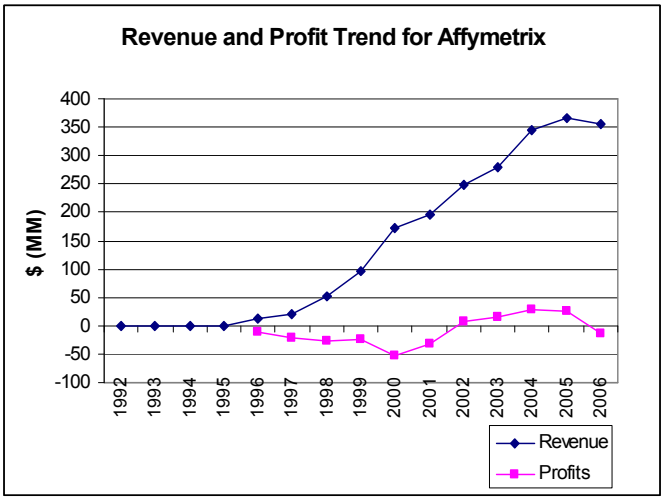


Figure 6

- The development of sophisticated noise reduction algorithms by the statistics & computer science community. This improved the raw data quality into a dependable signal that biologists can interpret.
- The accumulation and development of genomic annotation databases, which allowed scientists to easily cross-reference their gene-chip expression data with gene function.

After its early adoption by a segment of the R&D community, it took another four years, from 1996-2000 for a dominant design to establish. At first, there were numerous vendors with different technology platforms/architectures (e.g. Affymetrix, Agilent and Motorla to name a few). Before the emergence of a dominant platform, adoption of a particular technology was hindered since scientists

were seeking referencing and validation from their peers. Only around 1999-2001 when the Affymetrix chip and its complementary software emerged as the "standard" did its level of use take off.

The PCR and gene-chip examples show that even if a technology has, in concept, a clear value proposition to scientists, its wide spread adoption depend on both its ease in achieving a dominant design form and its complementary asset requirements. ***Figure 7*** on the left depicts some existing platform technologies and their positioning along the dominant design and complementary asset axis. Complex and emerging technologies with an unclear dominant design form AND/OR require high amounts of complementary assets will face higher challenges in achieving commercial viability and wide usage.

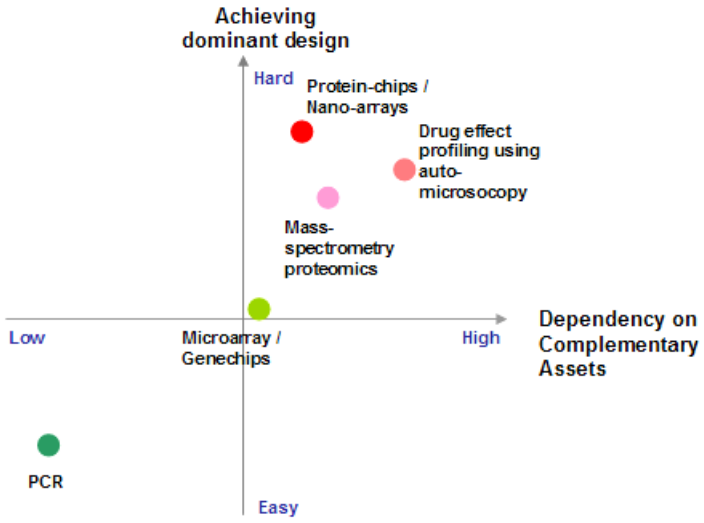


Figure 7

Historically, most of the breakthrough technologies have spawned out of biotechnology startups or from academia research.

Shortcomings with technology development in academia: The biggest issue with academia-based innovation is ironically also the source of its strengths, namely its incentive and cultural structure. The currency of academia is publications in top-tier journals where revolutionary concepts and breakthroughs are rewarded rather than application utility. Thus, platform technologies coming out of academia tend to be revolutionary rather than evolutionary, with potentially high value but low dominant design form. Moreover, these technologies often have a high complementary asset hurdle (deep expertise to operate and to interpret, ancillary complex technologies, etc.). Another added tension is that interdisciplinary R&D in academia is still challenging. In biological/biomedical research, it is pivotal for scientists to attain the first or last author position in journal publications since the "authorship position" is a principle metric of scientific merit. This necessarily encourages small group collaborations and/or projects with limited breadth of scope since the reward system is

built to recognize individual performance rather than team based progress. As such, academia initiatives are biased toward:

i) Developing emerging technologies that are hard to achieve dominant design form and possess high complementary asset hurdles. In addition, academia does not have the incentive structure or resources to take these high potential prototypes into the commercialization stage.

ii) Developing technologies in small personnel groups, not spanning more than 1 or 2 disciplines. This impedes the development of either crucial complementary assets or the core of interdisciplinary technologies.

Moreover, academia initiatives are not focused on evolutionary technologies (i.e. those in the SW quadrant in ***Figure 7***), that can nevertheless deliver large economic value.

Are biotechnology startups the answer?: At first glance, the biotechnology sector seems ideal for new technology development. The combination of its small size and entrepreneurial culture combined with VC backed money should encourage the commercialization of application based technology. The biotech industry structure presents two critical challenges:

First, the industry structure creates a tension for technology development. On one hand, most biotech startups are funded by VC money and are under a definite time pressure to create a viable exit strategy such as an acquisition by big pharma. This fundamentally limits biotechs' pursuits to the relative short term (<10 year horizon) window. On the other hand, due to its close ties to academia, biotech mostly work on technological endeavors with a long path to a dominant design form and require a high complementary asset hurdle; these technologies are risky, costly and often require a long time horizon to perfect into a commercially viable form. In addition, the biotech industry is fragmented, characterized by intense competition, lack of data/knowledge sharing and repeated failures and reinventing the wheel inside closed walls. This further exacerbates the time horizon required for commercialization.

Second, biotech's industry structure does not create a high profitability opportunity for platform technology development[15]. Value creation does not imply value capture. The industry is fragmented whereas the downstream consumers (i.e. the handful of big pharmas and research institutes) are consolidated and thus have bargaining power advantage. The industry fragmentation persists in part due to the relative ease of entry; armed with a cool academia prototype and a few million venture dollars, someone can enter and compete in the biotech platform technology sector. In ***Figure 5*** we

see that even for Affymetrix, a successful platform technology that has both reached industry-wide adoption and produced documented breakthroughs in how scientists perform discovery work related to gene expression analysis, it has yet to realize a net NPV positive scenario for its investors.

Big pharma can address the untapped innovation space: Big pharma can fill the void in the technology innovation space not covered by academia and biotech, namely:

- Developing evolutionary technology that improve the speed and/or accuracy of an existing process or activity in R&D (e.g. automating certain mundane experimental tasks, developing software for better information exchange within a large R&D facility, etc.)
- Developing revolutionary technology with high complexity in achieving dominant design form AND/OR requiring significant complementary assets (e.g. protein expression chips); these technologies often take 10+ years to perfect.
- Developing large team based, interdisciplinary technology requiring talented personnel and a new incentive structure for rewarding team-based results rather than personal achievement (e.g. developing a microscopy system for automatic profiling of drug effects on cells require expertise from physicists, computer scientists, biologists and pharmacologists)

Specifically, big pharma can achieve these objectives through a cooperation model such as a ***technology innovation consortium***. The consortium should have autonomy, long term funding and focus on platform based technologies that will benefit all the participants rather than specific product classes (i.e. a positive sum rather than a zero sum game). The specific challenges include:

- Managing the ownership of intellectual properties and valuating the resulting intangible assets
- Prioritizing research projects and attributing future payoffs commensurate with the participants level of resource contribution while ensuring that the fidelity of the consortium's mission of advancing productivity enhancing platform technologies and not product specific endeavors.
- Establishing an incentive system and culture that encourages team-based, multi-disciplinary progress.

Some of the above challenges such as the last bullet-point are starting to be addressed by forward looking foundation initiatives. For example, the Howard Hughes Medical Institute in 2005 devoted $1B in funding to establish *Janelia Farm,* an autonomous research institute to focus on cutting edge, interdisciplinary R&D on neuroscience as well as the relevant imaging technologies[16]. The premise of Janelia Farm is to create an incentive structure and culture amenable for team based, multi-disciplinary research lacking in academia.

The key benefits of a pharma based consortium for platform technology development are:

- Risk pooling so that no one firm bears all the idiosyncratic risk of failure.
- Aggregation of resources and talent.
- Cooperation to expand the size of the pie (developing basic tools that will enhance everyone's productivity) rather than closed door competition which increases overall cost/spending.
- Minimize stalling on progress due to inability to come together on issues of data and technology standards.

Platform technologies can bring orders of magnitude improvement in the speed or scope of certain discovery processes. Although the current commercialization environment of academia and VC funded biotechnology play important roles in developing & commercializing new platform technologies, their inherent industry structural factors leave certain regions in the "innovation space" untapped. Big pharmaceuticals can create a cooperative consortium marketplace to tap into those innovation opportunities to advance and commercialize technologies for increasing R&D productivity.

4.3 Open Source Innovation

I. Overview of Open-source and Pharma

Open-source is a way of collaborating in the research and development of some end product, most famously software such as Linux starting in the 1990s. The chief founder of open-source was Linus Torvalds, who brought together programmers on the early Internet to add features to his operating system and incrementally improve the code. From Linux, the software industry expanded to include thousands of development efforts, many of which are gathered on public forums for open-source projects such as SourceForge. Developers collaborate, publish the software under a public license, then offer it at no cost to the public. As interest is increased, others join the project and add features and submit their ideas to the open-source home page. If the new feature is good enough, it becomes part of the standard release of the software.

The key attributes of open-source are sharing of information in an incremental, cumulative fashion across companies, institutions, areas of expertise, and platforms of research. Individuals contribute

their efforts for free, with the understanding that it will be published under a public domain license for non-profit use by all.

As the pharmaceutical industry has become increasingly focused on harnessing IT systems and developing computational approaches to finding new solutions, the possibility for applying open-source in pharma has become a topic of interest. Open-source approaches have already emerged in biotechnology. An example is the international effort to sequence the human genome. All resulting data is in the public domain.

We will explore open-source to gain understanding of the following:

> Benefits: What is the impetus behind open-source and how might it benefit pharma R&D?
>
> Barriers and Potential Solutions: Given the enormously complex and costly nature of pharma R&D, what specific problems might arise and how could they be addressed?
>
> Potential for Applying in Today's Environment: Has anything resembling open-source been achieved in pharma R&D today? Can the barriers be overcome or will the applicability remain limited?

II. Benefits of Open-source

Creativity

One of the main benefits of open-source is to improve creativity by putting together the best minds on one problem, regardless of organizational affiliation. Research on biomedical innovation has shown that innovation increases when scientists from diverse backgrounds interact on a regular basis, without formal hierarchy. [7] Open-source would leverage the best scientists from around the world to tackle enormously difficult diseases. A problem today with pharma R&D is that failure can occur at numerous stages, and researchers in the pharma company may not have the solution. However, outsiders might be able to see the problem from a different view and break the impasse. Open-source would involve a larger population compared to the research staff of an individual pharma.

[7] Hollingsworth, J. R. in Creating a Tradition of Biomedical Research (ed. Stapleton, D.) 17–63 (Rockefeller Univ. Press, New York, 2004).

Karim Lakhani of Harvard Business School conducted research on the "The Value of Openness in Scientific Problem Solving." 166 scientific problems from 26 firms were addressed over four years. The research found that outsiders were most likely to find answers to a scientific problem when the issue was "broadcast" for public solutions. 8 Of course there were basic requirements for participation, such as minimal levels of expertise. And as we will see later, not all outside participants would have access to the equipment or funding needed to perform tests. But both overall results and anecdotal evidence from the Harvard experiment showed the impressive success of outsiders. One major biotech firm sent its problem related to rapid detection of DNA sequences, after reaching stalemate internally following months of work. They offered prize money and broadcast the problem to outsiders, and after 4 weeks of participation by 574 scientists, they received 42 proposals. The winning proposal was from a scientist in Finland who worked in a different field, but was able to use a common methodology to achieve an elegant solution.[8]

Another potential creativity benefit is that publishing results of unrelated experiments might allow scientists to tap core component parts for use in their work. This could promote specific research areas. The idea is to create a "core signature," or "connectivity map" of an experiment related to any given set of compounds or conditions, and then put it into a database for future searching. [9]

Speed

A second area of improvement would potentially be speed of innovation. This revolves largely around the issue of intellectual property. A key motivator for IP rights is the creation of incentives for investment. However, due to the current patent system, it is possible to patent broad areas (such as targets or pathways) that might prevent other firms from innovating in that area. This is called "strategic patenting." The problem is that researchers might have to negotiate expensive licenses, or may be denied access. This creates a transaction cost, and could delay cumulative research efforts. Studies focusing on the net benefit or loss to society associated with strategic patenting haven't shown that is obviously a bad policy. However, they have shown that this patenting may cause researchers to pursue other areas of work rather than cumulative research. Such an implication would

[8] Lakhani, Karim; Lagace, Martha. Open Source Science: A New Model for Innovation. Harvard Business School Working Knowledge. November 20, 2006.
[9] Friend, Stephen; Dai, Hongyue. Accelerating drug discovery: Open source cancer cell biology? Cancer Cell, Nov. 2006. 349-351.

potentially represent one reason why pharma R&D began to focus on so many novel targets during the late 1990's.

One case study of the problems with licensing is found in CellPro, a former Seattle, Washington cancer biotech. CellPro had created a novel cell separation device, but was challenged by Johns Hopkins University, which had a broad patent related to the antibody area. CellPro was unable to license the technology because JHU had already licensed it to two competing biotech firms. Even though CellPro's technology was only loosely related, the firm ultimately went bankrupt due to the patent battle. Open-source would allow for community property rights for such basic upstream patents. Speed would also benefit from fewer committees, compared to internal development in large pharma firms. [10]

Risk sharing

A third potential benefit is risk sharing. Scientists could collaborate on the early, most risky stages of research such as qualifying targets, finding biomarkers, or understanding basic cell characteristics. There has recently been a debate regarding the sharing of negative results. Advocates, such as Merrill Goozner of the Washington, DC's Center for Science in the Public Interest, believe that sharing Phase 1 failures would reduce dead-end research. [11] Currently many companies share results of Phase 2 through 3 trials in the ClinicalTrials.gov database. As of March 2007, ClinicalTrials.gov currently contains more than 36,100 clinical studies sponsored by the National Institutes of Health, other federal agencies, and private industry. However, the industry group Pharmaceutical Researchers and Manufacturers of America (PhRMA) believes that because Phase 1 trials are exploratory, sharing them would be unproductive and would stifle innovation by releasing sensitive competitive information. [12]

A novel approach to sharing data would be required to allow firms to truly pool risk from early stage research. This will be discussed later in the "Potential Models" section under "Voluntary Publication of Fundamental Knowledge."

[10] Munos, Bernard. Can open-source R&D reinvigorate drug research? Nature Reviews Drug Discovery. August 18, 2006.
[11] Bouchie, Aaron. Clinical Trial Data: To Disclose or Not to Disclose? Nature Biotechnology, Volume 24 Number 9, Sept. 2006. 1058-1061.
[12] Niman, Neil; Kench, Brian. Open Source and the Future of the Pharmaceutical Industry. DRUID Summer Conference 2004.

Impact

A fourth benefit is the ability to harness scientists from less developed areas of the world who have close contact with some of the diseases under research. These researchers may not have similar capabilities to the pharma firms, but through open-source they could benefit from knowledge sharing and help impact the treatment of neglected diseases in their home country. Public-Private Partnerships (PPP's), discussed later, provide this type of unification towards research in areas such as malaria and tropical diseases. [13]

Also, the impact of research would benefit from fewer distracting motives. The goal of an open-source development would be therapeutic value solely, as opposed to other motives such as brand differentiation or patent potential. In essence then, it would discourage the creation of me-too drugs and shift medical resources towards novel therapeutic areas. Beyond anecdotal evidence in the market, studies have shown that competitors are often patenting similar therapies with slight differences. 12 Follow-on, cumulative research could prove more beneficial to society.

Agility

In open-source, projects can be easily discontinued if the results do not look promising. In traditional pharma firms, molecules in the late stages of development may be harder to kill because careers are tied to their outcome. This will depend on the incentive and reward structure as well as company culture. According to Bryce Carmine, President Global Brand Development of Eli Lilly, any organization will deal with internal politics to some extent, and projects might not always be halted at the optimal point for the company due to internal coordination delays.

Affordability

One potential attribute of open-source is the donation of resources by people and organizations towards common goals. If there is capital equipment (such as computational time on corporate mainframes) that is being sub-optimally used, open-source could more efficiently utilize society's resources across organizations. Small organizations could also gain access to equipment and research talent typically only afforded by the largest firms or institutes. Unused capacity also impacts speed, if there are issues with queuing in the laboratory.

[13] http://www.tropicaldisease.org

III. Barriers and Potential Solutions

If it were easy to implement a model with such great benefits, presumably it would already have been done. There are very difficult problems that must be addressed before open-source can function in pharma, such as economic incentives and management of the effort. William Dempsey, President of Abbott Laboratories, commented that Abbott has been trying to engage in more partnerships but coordination alone is a huge challenge. He said it is often difficult to decide who gets to make key decisions during each stage, and what the goals should be.

Economic Barriers

Economic incentives are a significant barrier. The pharma industry is able to invest in drug development costing over $800 million because of the expectation of monopoly profits during the patent exclusivity period. Open-source software development requires only a computer and internet connection. Clinical trials require enormous resources to plan and execute.

Potential Solutions: Some have proposed that the government should fund open-source initiatives through universities as a coordinating mechanism. (Discussed in detail in "Potential Models: Medical Innovation Prize Fund.") This already occurs to some extent. The approach would be to charge a yearly membership fee to a database of open-source knowledge. The fee would be structured in a multiple-tiered tariff system to account for the level of usage of the data and appropriately charge members for their benefit from the knowledge.

Critical Analysis: However, who would decide which projects receive funding? Currently the National Institutes of Health have some funds and ability to decide upon projects. Open-source committees could theoretically apply to some part of the government for funding. But if society is staking a large % of its GDP on funding open-source, there would need to be a broader, more reliable decision process. Today, capital markets decide which companies are funded, and relying upon government to regulate the industry would be very questionable.

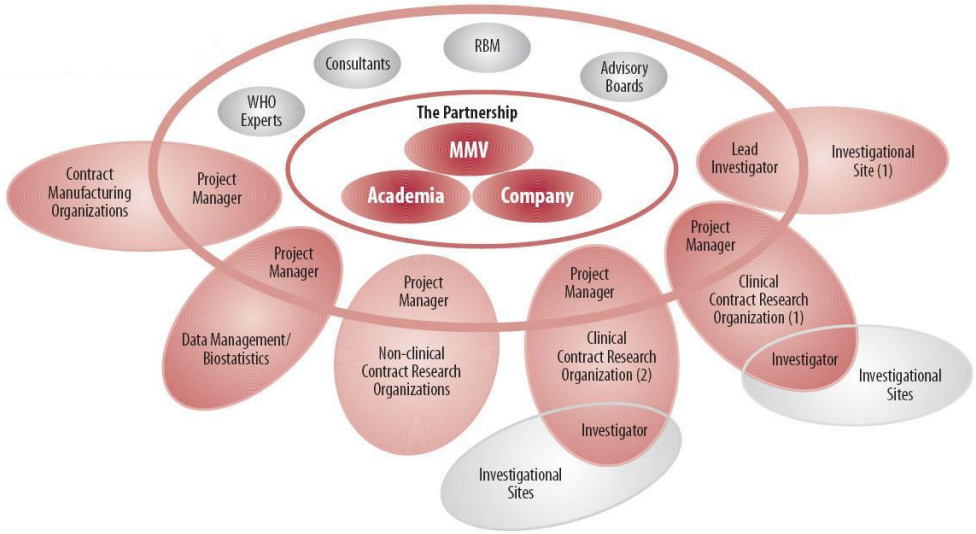
Coordination and Leadership Barriers

A second issue with open-source is the problem of coordination. Project management expertise exists in major pharmas today. While researchers might be able to devote a fraction of their free time to

open-source, gaining the full services of a senior leader might be difficult given that they have signed NDAs and vested their career (through personal relationships and financial commitments such as stock options) in a particular corporation.

In contrast to software development, which primarily requires programming expertise, pharma research cuts across multiple disciplines and is highly complex. Significant coordination is needed because problem-solving is not as modular and it would be impossible for one person to keep track of the information needed. Biomedical knowledge is complex and expands at 1,000 publications per day, all requiring peer review.

Potential Solutions: PPPs provide possibly the best example of coordination. Virtual R&D is conducted through contracts, relationships, and coordinating bodies. For an illustration of this dynamic. Another possible idea would be to harness entrepreneurs as coordinating leaders. If projects are public, entrepreneurs can gather information on promising investments and fund coordination teams that provide leadership.



Critical Analysis: In pharma, if one misstep is made, such as a wrong target or improper toxicology report, a late-stage effort can fail. This makes the process of accepting new approaches slower than software, where a change can be accepted into the project with little fanfare. Testing is vastly different, because while software undergoes “debugging” and user testing, the cost is hugely lower

than clinical trials and does not require FDA oversight. Solutions such as PPPs have limited applicability to diseases such as malaria because scientists are willing to devote time to developing nations. It would be nearly impossible to transition more of pharma development to this model, because coordination for more complex entities such as cancer would not be viable in a PPP model.

Regulation and Intellectual Property

Due to safety and health concerns, pharma research is highly regulated in contrast to software. The software industry's intellectual property system does not rely solely upon patents, because code is protected by copyright as it is written. In contast, drug patents must meet stricter standards of innovation and are expensive to submit. Quality control will be critical for a project with numerous diverse contributors.

Potential Solutions: This problem comes back to funding and coordination. Clinical trials must be run with adequate resources and strict processes. There is no solution except adequate funding and good management teams for this problem.

Critical Analysis: This issue is looming in the nascent Public Private Partnerships around Tropical Disease, many of which have not reached late stage. It may be necessary to relegate later stage development to traditional pharma, leaving early discovery to open-source.

Motivation and Availability of Talent

In software, projects can exist based on the work of only a few contributors. New versions of Linux may be the work of a team of six people. Pharma requires huge teams of researchers. Why would these people devote their time for free? In the Harvard study, the contributing researchers were divided between those who wanted the prize money and those who wanted a challenge to satisfy their idealism or curiosity. Even if they wanted to devote their time, would they be allowed? NDAs are a significant issue to participation. Also, because research contributions are voluntary, there is the issue of sustainability, with talent potentially coming in and out of the project according to their willingness to participate.

Potential Solutions: Pharma firms could generate goodwill by allowing scientists to devote a portion of their week to public-benefit open-source projects.

Critical Analysis: Some have speculated that the upcoming retirement of baby boomer scientists could create a pool of researchers willing to devote time to worthy initiatives. However, this is not realistic given the amount of human work required, so it would be necessary for broader groups of scientists to donate time. This is possible for small projects, but for larger efforts it would seem quite difficult to expect enough labor to volunteer.

IV. Potential for Application in Today's Environment

Pharma has yet to create a truly open-source initiative that has resulted in a finished product similar to a blockbuster drug, but some newly developed organizations have similarities to such a model.

Bioinformatics Initiatives

Efforts resembling open-source first occurred in initiatives such as the Human Genome Project. Various programs such as Biojava, BioPerl, BioPython, Bio-SPICE, BioRuby and Simple Molecular Mechanics for Proteins[14] shared results in a way similar to open-source, though not everyone could participate. More recent organizations include the SNP Consortium, the Alliance for Cellular Signaling, BioForge, GMOD and Massachusetts Institute of Technology's BioBricks.[15]

Public-Private Partnerships

Starting six years ago, new organizations began to form to address neglected diseases. These organizations, Public-Private Partnerships, use aspects of open-source and outsourcing models. One such group is the Medicines for Malaria Venture (MMV). This was created in 1999 to develop antimalarial drugs that are more affordable for developing countries. The MMV group has 19 projects, a staff of 13, a scientific advisory committee, and project managers who manage the development. 300 scientists at 40 organizations (ranging from academia to pharma) contribute their time. Projects are received through "open calls," allowing for anyone to submit an idea for review by the advisory board.

According to the Initiative on PPPs, there are approximately 24 PPPs working on drugs and vaccines. They typically work on neglected diseases and have projects in discovery through Phase 3 trials.

[14] Eisenmenger, F., Hansmann, U. H. E., Hayryan, S. & Hu, C. An enhanced version of SMMP — open-source software package for simulation of proteins. Computer Phys. Comm. 174, 422–429 (2006).
[15] DeLano, W. L., The case for open-source software in drug discovery. Drug Discov. Today10, 213–217 (2005).

Because R&D is outsourced to contributors who devote their time, each project is small, with lean budgets rarely greater than $50 million. [16] This makes PPPs a good way to fund projects large pharma would not be interested in running, but unlikely to fund large efforts similar to many of traditional pharma's projects.

Voluntary Publication of Fundamental Knowledge by Pharmaceuticals

Novartis made a move towards greater data sharing by publishing the genes likely to be associated with diabetes. In partnership with Lund University in Sweden and the Broad Institute in Cambridge, Massachusetts, the cooperative ran a study with 3,000 people to compare and locate the genes. By publishing a database library containing results of the research, other firms can avoid investing in fundamental research of 20,000 genes and begin to work on applied cures. [17]

Informal Clinical Trials through Field Discovery

In a recent study, it was shown that 59% of drug therapy were discovered by practicing clinicians via field discovery. This idea is supported by Dr. von Hippel at MIT, who advocates decentralizing the process for obtaining data on off-label use by collaborating with volunteer doctors and patients. This off-label trial and error practice cannot be endorsed and supported by pharma firms directly, but represents a fast and inexpensive way to trial drugs such as cancer treatments in different types of applications. [18]

Prize Funds: Medical Innovation Prize Fund

To address the barrier of economic incentive, some have proposed a prize fund created by the public. One such proposal was the Medical Innovation Price Act of 2005, which was a bill that would have created a fund to reward innovative research and support areas such as neglected diseases. Instead of granting patent rights and using a system of pricing to reimburse innovation, the fund would price drugs at generic levels immediately. Firms or projects creating a successful product would receive prize payouts for 10 years, based upon the novel therapy benefit and success of the product in the

[16] Gardner, C. & Garner, C. Technology Licensing to nontraditional partners: non-profit health product development organizations for better global health. Industry Higher Education 19, 241–247 (2005).
[17] Herper, Matthew. Biology Goes Open Source. Forbes Magazine. Feburary 12, 2007.
[18] DeMonaco, H. J., Ali, A. & Von Hippel, E. The major role of clinicians in the discovery of off-label drug therapies. MIT Sloan Working Paper 4552-05 (2005).

market. The fund was intended to have $60 billion, or .5% of the U.S. GDP. [19] Prize payouts for drugs with similarity to existing therapies would receive less prize money, perhaps reducing "me-too" drugs.

The bill, proposed by Rep. Sanders of Vermont, received little support and died in the Intellectual Property Subcommittee. A similar initiative was started by the World Health Organization, proposing that a percentage of GDP from every member country be committed towards a fund. The Medical Development and Innovation Treaty was referred to a task force in May 2006 and has seen little further development.[20] Clearly radical solutions such as this are not possible yet, and any open-source efforts will need to start with hybrid, small steps.

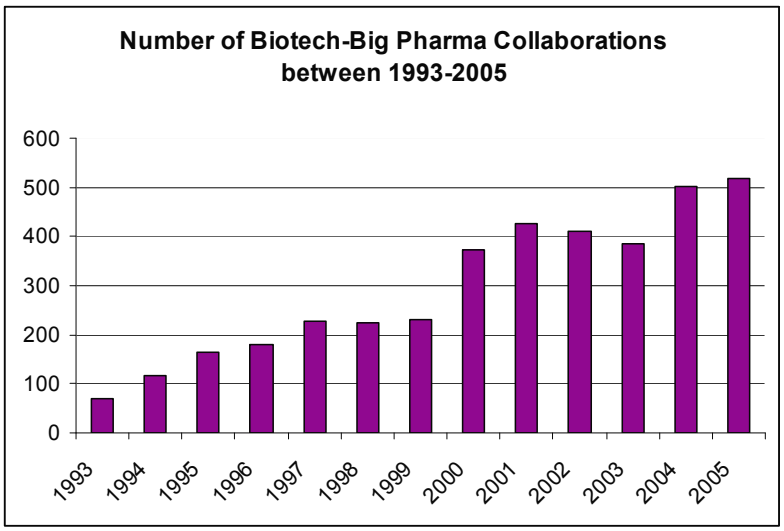
V. Open-source's Potential for the Future

While open-source is a novel idea with some advantages, in today's environment there would seem to be limited applicability. Certain areas such as tropical diseases have benefited from open-source initiatives, but to apply the model more broadly would require substantial changes to how healthcare is funded and perceived. It is not clear that open-source would be substantially better than the innovation produced by traditional pharma, and working outside of IP protection would do little to motivate investment in the projects. Still, making small steps towards sharing of information such as targets could be helpful to increasing speed and creativity among firms who are facing innovation trouble. The impetus will have to come from within pharma, rather than government regulators. If the innovation troubles continue within pharma pipelines, we may see an increased willingness to join alliances and share information in ways that resemble open-source models, but it is unlikely that we will see anything as full-fledged as in the software industry.

[19] Lyles, Alan. Creating Alternative Incentives for Pharmaceutical Innovation. Clinical Therapeutics, Volume 28, Number 1, 2006.
[20] Love, James. A new initiative at the WHO: Prizes rather than prices. Column in Le Monde Diplomatique. May 31, 2006.

Appendices

Appendix 1A – The number of deals/partnerships between Pharma & Biotech has increased dramatically in the past decade



Appendix 1B – Selected Pharma/Biotech Partnering Deals in 2005

Biogen/Protein Design Labs	$800M
Alnylam/Novartis	$700M
Medarex/BMS	$530M
Pfizer/Coley	$505M
Shire/New River	$500M
Plexxikon/Wyeth	$372M
Nastech/Merck	$341M
Avanir/Astra Zeneca	$340M
Cilag/Basilea Pharma	$308M
Pharmasset/Roche	$300M
CancerVax/Serono	$278M
Astex/AstraZeneca	$275M
GSK/Theravance	$252M
Sirna/Allergan	$250M
GenMab/Serono	$215M
Sucampo/Takeda	$210M
Novartis/Avanir	$210M

Sources: Adapted from Burrill & Company Presentiation, Bio 2006

Appendix 2: PCR and GeneChip Microarray

Adoption and impact of PCR: Discovered in 1983, Polymerase Chain Reaction is a technique that enables the large scale replication of DNA without the use of a living organism. In essence, PCR is a factory that achieves astronomical scale economy improvements for making copies of DNA segments. The workhorse of that factory is an enzyme called DNA polymerase, a molecule found in cells whose function is to replicate/copy DNA during cell division. Although scientists knew of DNA polymerase, extracting it into a stable, heat resistant form out of its natural cellular context had been a show-stopping challenge. In 1983 a scientist named Kary Mullis made a groundbreaking discovery of *Thermus aquaticus*, an organism that lived and flourished in environments of extreme temperature of up 230˚F (e.g. geysers and geological vents). These organisms evolved to survive extreme temperatures and thus Dr Mullis reasoned their cells and components in their cells should also be resistant to heat, in particular the DNA polymerase enzyme. In 1993, only ten years after his discovery, Dr Mullis was awarded the Nobel Prize for PCR and its impact on accelerating the pace of scientific discoveries.

Adoption and impact of Microarrays: Originally invented in the late 1980s by Steven Fodor at the startup firm Affymetrix, the micro-array is a glass based technology that allows the parallel interrogation of the RNA level of tens of thousands of 32-mer gene sequence probes. This is essentially a massive parallel scaling of the traditional "Southern method" for gene expression analysis. Due to its complex requirements on complementary assets such as sophisticated statistical noise analysis software, as well as heated competition among vendors such as Affymetrix, Agilent and Illumina to establish their architectural design as the industry standard, the adoption of microarray took much longer than PCR to diffuse across the biopharma industry. Nevertheless, the microarray technology has significantly increased the speed, scope and power of RNA based expression studies that have led to fresh insights into basic science as well as new clinical applications. For example, microarrays have paved new avenues for detecting alternative gene splice forms[21], predicting cancer treatment outcome and disease states at the molecular level[22], and in identifying new targets for therapeutic drugs[23].

[21] Johnson JM, et. al., *"Genome wide survey of human alternative pre-mRNA splicing with exon junction microarrays"*, Science, 2003 Dec 19
[22] Laura Van't Veer & Daphne De Jong, *"The Microarray way to tailored cancer treatment"*, Nature Medicine,2002
[23] Shawn E Levy, *"Microarray analysis in drug discovery: an uplifting view of depression"*, Science 2003 Oct 2003

References

1 FDA's CDER annual reports and author's analysis

2 Adopted from: *R&D in the Pharmaceutical Industry*, A Congress of the US Budget Office Study, Oct 2006

3 DiMasi M, et. al., *The Price of Innovation: new estimates of drug development costs*, J of Health Econ. (22)2003

4 Med Ad News, April Issue, various years

5 McKinnon R, et. al., *Crisis? What Crisis? A fresh diagnosis of pharma's R&D productivity crunch.,* Marakon Associates Report, 2004

6 Grabowski H, *Are the Economics of Pharmaceutical R&D Changing*?, PharmacoEconomics (22) Suppl 2, 2004

7 Gilbert J, Henske P, Singh A, *Rebuilding Big Pharma's Business Model*, In Vivo – The Business & Medicine Report, Nov 2003

8 Ed. Burns LR, *Chapter 2*, The Business of Healthcare Innovation, Cambridge University Press 2005

9 Booth B and Zemmel R, *Prospects for productivity*, Nature Reviews Drug Discovery, Vol 3, May 2004

10 *The Drug Drought*, Pharmaceutical Executive, Nov 1, 2002

11 Pisano G, *Can Science Be A Business*?, Harvard Business Review, Oct 2006

12 Henderson R and Cockbrun I, "S*cale and Scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research*", Journal of Health Economics (20), 2001.

13 Ed. Burns LR, *Chapter 5*, The Business of Healthcare Innovation, Cambridge University Press 2005

14 Biotechnology Annual Conference 2006, Burrill & Company Presentation

15 *Sustaining Platforms*, Chpt 4 in Kellogg on Biotechnology, Northwestern University Press, 2005

16 The philosophy behind HMMI's Janelia Farm Institute, http://www.hhmi.org/janelia/philosophy.html