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Using Inside-Out Open Innovation to Recover Abandoned Pharmaceutical Compounds

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Abstract. Pharmaceutical drug development costs have risen rapidly over the past twenty years. However, the number of new molecular entities being approved has not increased. As pharmaceutical companies scale back their R&D in light of this deteriorating productivity, significant unmet medical needs remain unaddressed. Much of these rising costs can be traced to work on compounds that are abandoned before getting to market. There is a growing need to recover these abandoned compounds. The inside-out branch of open innovation provides a way to increase the performance of pharmaceutical firms, both in addressing unmet societal needs, and potentially in identifying new revenue sources and business models for a more distributed model of commercializing new drugs. This aspect of open innovation is not much discussed in the literature to date. The medical research community, in conjunction with a number of industry and nonprofit organizations, has started several projects to recover more abandoned compounds. These new initiatives are still at an early stage, and have not received much critical evaluation to date. Examining four of these initiatives, we find that they do extend the cognitive frames in the research phase, while doing less to extend those frames in the commercialization phase.

Keywords. R&D, Project Evaluation, False Negatives, Open Innovation, Pharmaceuticals.

1. Introduction

Pharmaceutical industry observers and participants have long noted the incredible challenges of drug development. The development costs per approved drug, including the cost of failures, have increased from approximately $140M in the 1970s to $320M in the 1980s, $800M in the 1990s, and $1.2B in the 2000s (PhRMA, 2012). The latest analysis from the Tufts Center for the Study of Drug Development pegs the figure at $1.3B (Tufts CSDD, 2011). Meanwhile, average drug development timelines of new compounds have remained steady at around 14 years from initial screening to approval (Abrantes-Metz et al., 2006; Bogdan & Villiger, 2010; Tufts CSDD, 2011). Despite the great promises of biotechnology, the industry as a whole has failed to create significant value in excess of its costs over its lifetime (Pisano, 2006).

Existing analyses of the crisis in pharmaceutical drug development readily note the skyrocketing costs, the declining productivity of R&D, and the cliff of drugs coming off patent (Pammolli et al., 2011). Less often noted, however, is the unstated assumption of the prevalent business model for pharmaceutical drug development - that of the blockbuster drug. The blockbuster model discards innovations that have expected revenues below large thresholds, typically $1 billion annually. A more distributed business model that divides the innovation work among multiple parties

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might enable more compounds with smaller market sizes to reach the market.

The emerging shift from a blockbuster to a distributed business model is being driven by two key factors. First, scientific and technological advances have enabled a deeper understanding of the biological underpinnings of disease. Genetic sequencing technologies are becoming ever cheaper, rapidly approaching a cost point that would make sequencing available for mainstream use. At the same time, drug targeting approaches are becoming ever more sophisticated. Technologies such as antibody drug conjugates and nanospheres allow scientists to address specific disease targets in a manner that was not previously possible.

The second key factor has been the rise of value-based reimbursement practices around the world. The combination of increasing healthcare costs and weakened state economies has forced governments and insurance companies to re-evaluate their approaches to paying for drugs. We've seen a shift from volume-based to value-based reimbursement. For example, the UK government struck a deal with Johnson & Johnson (J&J) to cover its drug Velcade, but only for those patients in which clinical benefit is seen. For the patients who do not respond to therapy, J&J will pay for the cost of their product. (Europharma Today, 2009). A similar risk-sharing reimbursement contract was established in Germany for the reimbursement of Roche's cancer drug Avastin.

Combined, these scientific and economic factors along with the research productivity challenges are fundamentally transforming the pharmaceutical industry. As the nature of their products moves away from one-size-fits-all towards personalized medicine, pharmaceutical companies will also be forced to change their business model. This will require more use of open innovation.

Open innovation is defined as the "use of purposive inflows and outflows of knowledge to accelerate internal innovation, and expand the markets for external use of innovation, respectively" (Chesbrough et al., 2006). The former part of the open innovation model, "to accelerate internal innovation," is referred to as the "outside-in" approach. The latter part of the open innovation model, to "expand the markets for external use of innovation," is referred to as the "inside-out" approach.

Most academic discussion of open innovation has focused on the outside-in half of the model, and indeed, many papers treat that half as the totality of the model (e.g., Boudreau & Lakhani, 2009). Overlooking the inside-out half of the open innovation model is more than an important oversight. It inhibits creative approaches to addressing business model restrictions that hold back innovation. We focus in this paper on the cognitive barriers to increasing inside-out innovation in drug development. We then consider how "inside-out" open innovation approaches can be overcome these improve the societal and financial performance of pharmaceutical firms.

2. The case for redeveloping abandoned compounds

It is well known that it takes $1 billion or more in investment to get an approved compound into the market (DiMasi et al., 2010). Much less well known, however, is that the actual cost of development per approved product, without adding in the cost of failures, is closer to $100 million (Abrantes-Metz et al., 2006; DiMasi et al., 2010). In other words, roughly $900 million of the investment companies make per successful drug development program has gone to failed compounds. Yet this waste in the system is generally accepted as a cost of doing business in the pharmaceutical industry.

Declining clinical approval success rates means that more and more compounds are

being abandoned in intermediate stages of development. Such compounds have taken years of research and investment to reach the clinic. In many cases, they have also already been proven to be safe in humans. One review of the reasons for abandonment of compounds after this clinical stage found that only 20% were due to safety while 34% were due to economics, and another 38% were due to weak efficacy for the intended disease (Bogdan et al., 2010). While safety issues may rightly foreclose further exploration, the other 80% of abandonments have as much or more to do with the lack of an identified market or an attractive business model.

This large percentage of non-safety related abandonments creates opportunities for recovery of some of these compounds for alternative uses and/or smaller markets. If more people had access to the relevant pre-clinical and clinical data, more thorough consideration of alternative diseases, markets or business models could ensue. For example, a small patient population for a particular drug may not deter patient groups from advancing a compound in concert with a foundation's funding support. Weak efficacy signals, in turn, might be greatly enhanced with more advanced diagnostics, which could sort potential patients via one or more markers, such that a subset of patients might receive significant therapeutic benefit. Unmet medical needs thus could be addressed in more economical ways, by utilizing extant knowledge more thoroughly.

False Negative Evaluation Errors in Drug Development

Drug development is highly complex, and organizational decisions about whether to continue or abandon a particular program are subject to evaluation errors of the Type 1 (false positive) or Type 2 (false negative) variety. On the one hand, false positive (Type 1) evaluation errors are largely eliminated due to rigorous review by regulatory bodies such as the FDA. Drug candidates that companies think will succeed based on early animal or human studies may only yield insignificant or negative clinical trial results in larger studies, and then be abandoned.

On the other hand, false negative (Type 2) errors often are not mitigated through any formal regulatory or internal R&D process (Chesbrough, 2003, chapter 4; Chesbrough et al, 2006, chapter 1). These are compounds that could have been valuable, had the organization found an appropriate market and business model to commercialize them. GlaxoSmithKline, for example, recently decided to abandon its entire neuroscience program that had been built over decades, with hundreds of compounds effectively cut off from any further consideration for subsequent development (Ruddick, 2010). This may be an appropriate decision for the company, but the abandonment of all these compounds, and the associated research data collected on them, is a loss for society, especially for patients suffering from unmet neurologic disorders.

This false-negative aspect of innovation is a latent source of performance improvement for firms. Allowing unused projects to go outside the firm lets others examine these projects from the perspective of new and different business models. While many projects will doubtless languish outside the firm, a few may reveal unforeseen social and financial benefits.

Recovering False Negative Drug Compounds

There are examples of drugs that were once abandoned, and then successfully recovered. These examples provide evidence that Type II errors in drug development can and do occur. The prototypical example is thalidomide, which was originally developed to treat morning sickness during pregnancy. After being linked to tragic birth defects, the drug was pulled from markets around the world in the 1970s. It was

precisely this calamity that led to substantially enhanced FDA oversight of drug development. After being reclaimed by a small biotech firm, Celgene, it was eventually approved for use under proper guidelines in cancer patients suffering from myeloma, a form of bone cancer (Bartlett, et al, 2004). So this once discredited drug is now a common therapy, albeit in a very different use. Another well-known example of repurposing is, of course, Viagra. In human trials to reduce hypertension, the drug was failing in clinical trials for efficacy, relative to the placebo. However, the drug evoked unusual side effects, and the drug's eventual use for erectile dysfunction was thus initially discovered.

Other, more general evidence for the presence of false negative evaluation errors comes from the very large number of drugs prescribed by clinicians to their patients for off-label use. This means that the drug was not approved by regulators for the treatment prescribed, but the physician nonetheless believes that the drug may provide therapeutic benefit to the patient (often based on limited clinical data and the physician's personal experience, without the benefit of a double-blind, controlled study). These off label uses can be quite beneficial to patients who are nonresponsive to approved medicines. Off-label prescriptions of drugs are quite common, and in some disease categories like central nervous system (CNS) disorders, the bulk of sales of certain drugs come from off-label usage. Off-label usage of a drug effectively is a repurposing of that compound, albeit in a limited and informal way for a small number of physicians and their patients.

The Improved Economics of Recovering Abandoned Compounds

None of the foregoing analysis is meant to imply that all abandoned drugs should be redeveloped; some may not be of sufficient medical or economic value to warrant continuation under any business model. Rather, our hypothesis is that at least some compounds that do not make economic sense under a blockbuster model may become medically useful and economically viable if pursued under a more distributed business model. Enabling this shift will require new, more inside-out open innovation practices with regard to unutilized compounds in R&D.

One of the strongest arguments in favor of redeveloping abandoned compounds is not just that untapped potential opportunities exist but that there is potentially an abbreviated development path to capturing those opportunities. Compounds that were abandoned after positive clinical trial results were achieved in Phase I have proven drug formulations and have been shown to be safe for human use within a certain dosage range. Past this stage, research can focus entirely on finding unmet medical needs that the compound could address. Building on the years of prior research experience with the compounds, further development could start at a much later point than for a new compound, with a potentially shorter path to market.

The other very strong argument for redeveloping abandoned compounds is their potential ability to address otherwise unmet patient needs. For example, there has been an alarming exodus of pharmaceutical companies from studying neurologic diseases in recent years due to poor return on investment in the therapeutic area (e.g., GlaxoSmithKline discussed above). Yet patients suffering from central nervous system disorders, such as epilepsy, suffer from a significant amount of unmet medical need. It is estimated that fully one-third of the epilepsy patient population is refractory (meaning that these patients do not obtain any meaningful therapeutic benefit) to all existing therapies on the market. Another one-third of the population obtains therapeutic benefit at the expense of incurring moderate to severe side-effects (including cognitive impairment) from the medicines taken (Devinsky, 2007). While there may not be another blockbuster drug available in the pipeline for treating epilepsy, there may be a range of drugs that provide significant benefit to different

sub-sets of these patients. If the development costs decline sufficiently and if the probability of success increases as well, some of these new drugs may well come from the pool of previously abandoned compounds.

However, if this is really the case, then why hasn't a market mechanism developed to take advantage of this scenario? Why are the recoveries of compounds like Viagra and Thalidomide the exception, and not the rule? We explore these questions in the next section.

3. Cognitive barriers to inside-out open innovation in drug development

To better understand the barriers to greater inside-out open innovation, we conducted interviews with pharmaceutical executives and managers. Our interview respondents were primarily in the R&D or business development organization in the company (different companies organized the management of unused compounds differently). Table 1 lists the titles, headquarters location and type of company we interviewed. Each respondent was promised anonymity, along with a copy of the paper upon its completion. We deliberately sampled companies of different sizes and locations, to get a range of industry perspectives.

Table 1. List of pharmaceutical industry interviews conducted.

Title	Company type	Company HQ location	Interview date
Sr Vice President, R&D	Pharma	Europe	04/28/2011
Sr Director, Business Development	Biotech	US West Coast	05/06/2011
Sr Manager, Business Development	Biotech	US West Coast	06/22/2011
Director, Business Development	Pharma	US Midwest	08/25/2011
Associate Director, Alliance Management	Biotech	US West Coast	09/02/2011
Associate Director, Strategy	Pharma	Europe	09/30/2011
Director, Business Development	Biotech	US West Coast	10/7/2011
Vice President, Medical	Pharma	US East Coast	10/19/2011
Head of Intellectual Property	Biotech	US West Coast	01/23/2012
Senior Director, Corporate Development	Biotech	US West Coast	01/18/2012
CEO	Biotech	US West Coast	01/26/2012
Director, Marketing	Pharma	US East Coast	03/07/2012
Vice President, Corporate Development	Biotech	US West Coast	04/17/2012
Corporate IP Counsel	Biotech	US West Coast	12/18/2012
Partner, Technology & IP Litigation	Law Firm	US West Coast	01/02/2013
Vice President, Business Development	Pharma	US East Coast	7/22/2013
Attorney	Academic Research Institute	US East Coast	7/26/2013

Each interview was conducted with a semi-structured instrument of questions regarding the respondent's experience with the management of unused compounds. Where geographically possible, these interviews were conducted in face-to-face discussions. Where geographic distance was large, we relied on phone interviews. Each interview ranged from 30 minutes to over an hour in length.

In multiple interviews, we heard about compounds abandoned due to insufficient market size or lack of definitive clinical signals. Both reasons explain why a firm would not pursue a compound internally, but do not explain why other parties would not be given the chance to consider licensing that compound for their own pursuit.

We also heard about lack of organizational resources severely limiting any potential outlicensing activity. For example, one leading pharmaceutical manufacturer in Europe has just two executives tasked with licensing out the company's compounds. This same company has 7,700 people in R&D positions. One of the two outlicensing executives reported that one outlicensing transaction had been completed in the past year, while the company was working on thousands of internal R&D compounds. We also heard from both R&D and business development executives that while they don't like to admit it, they were sometimes happy when a program would fail because they already had more work than they could handle.

But these are merely symptoms that beg a deeper analysis. Why do companies lack the motivation or resources to pursue recovery of abandoned compounds? We posit that the underlying reason is that the cognitive frames of pharmaceutical executives reflect interpretations arising from previously successful responses to the environment (Weick, 1995; Prahalad and Bettis, 1986) – in other words, they are dominated by the blockbuster business model. As a result, the organizational structures and managerial incentives of today's pharmaceutical companies have been developed to optimize that blockbuster model, which does not attribute significant value to recovery of abandoned compounds. .

Cognitive limits can be particularly relevant when the underlying business model that commercializes technological developments is itself in transition. Tripsas and Gavetti (2000) document the challenges that Polaroid faced in trying to adapt its "razor and razor blade" business model of instant photography to the challenges posed to that business model by digital technologies. Chesbrough and Rosenbloom (2002) detail the difficulties Xerox had in utilizing the technologies developed at its PARC laboratory in the nascent computer industry, given its copier and printer business model. Furr, Cavarretta and Garg (2012) report similar challenges for various firms in photovoltaic manufacturing.

We argue that a similar fundamental challenge faces the pharmaceutical industry as both scientific and economic pressures are forcing a change in its business model. In order to make a successful transition, managers will need to move beyond their existing cognitive frames. Here is precisely where inside-out open innovation can play a role. Open innovation can engage new and different actors in the innovation process, and explore alternative commercialization approaches beyond the blockbuster business model.

Based on these issues, we now turn to four different initiatives focused on recovery of abandoned compounds in public-private partnerships. We highlight the differences in each approach. None of the initiatives are designed to fully redevelop and commercialize abandoned compounds on their own. Rather, the goal of these initiatives appears to be an effort to enable a compound to advance one step further in

its clinical development. The greater impact, we would argue, is the potential for these initiatives to collectively show the value of unlocking abandoned compounds in a more distributed business model. Therefore, we try to understand how well each initiative might fare in successfully shifting cognitive biases and eventually drive organizational adaptation to a more open, distributed business model in pharmaceutical companies.

4. Evaluation of initiatives to recover abandoned compounds

A number of initiatives have recently emerged with the intention of addressing the problem of recovering abandoned compounds. We chose four initiatives to focus on based on their salience, as well as variation in the types of participants and the models used in recovering abandoned compounds. Specifically, the initiatives vary in the number of companies contributing their abandoned compounds and the number of potential research partner organizations (see Figure 1). Each of the initiatives is detailed in Table 2 and described briefly below.

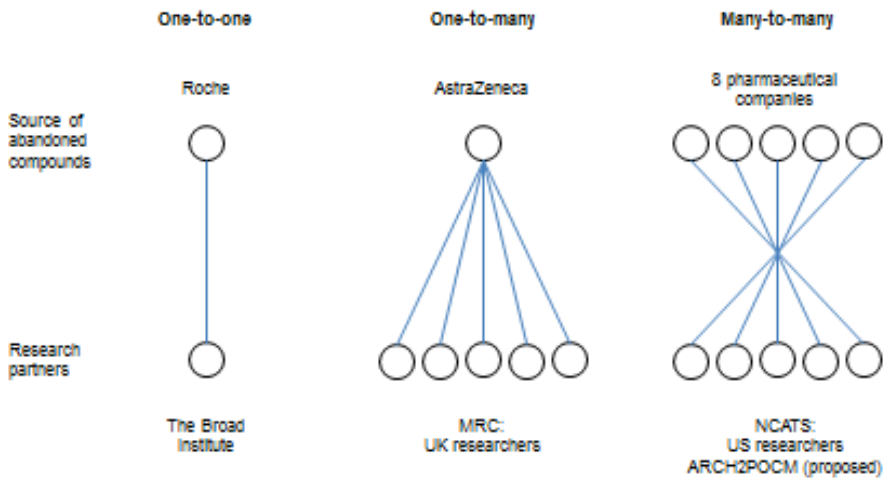

Fig. 1. Alternate structures of initiatives to recover abandoned compounds

Table 2. Description of recent initiatives to recover abandoned compounds.

	AZ-MRC	**NIH NCATS**	**Roche-Broad**	**ARCHZPOCM**
Model	One-to-many	Many-to-many	One-to-one	Open science
Governance	Public-private partnership with MRC as administrator	Public-private partnership with NCATS as administrator	Private partnership	Not-for-profit consortium
Country of origin	UK	US	US	US

Scale	22 compounds	58 compounds (8 companies)	300+ compoun ds	To be determined by participants
Types of compounds	Preclinical and clinical stage	Clinical stage that have completed Ph1 safety testing	Clinical stage that failed Ph2 or halted for strategic reasons	Preclinical and clinical stage
Operating model	Companies provide 1 page summary on each compound and in-kind contributions: drug supply, data, expertise; Researchers provide novel idea, define experiments, collect the data; Final MRC proposals written collaboratively by MRC and AZ	Roche providing compound library; Broad using novel screening technologies to find new applications	Pharma companie s have been reluctant to participat e to date	
IP rules	Contributors maintain original IP; Researchers own new IP; Researchers have right to publish with companies given 30 days to review	Undisclosed	Open Science approach	
Announceme nt date	Dec 2011	May 2012	Nov 2012	Planning stages
Funding	$15 million Funded 15 projects; 7 clinical, 8 preclinical	$20 million Funded 9 projects	Undisclos ed	To be determined by participants

The first initiative is a government supported public-private partnership between the UK's Medical Research Council (MRC) and AstraZeneca. Launched in December 2011, the "Mechanisms of Disease" program will provide up to $15 million of funding to UK academic researchers to study 22 of AstraZeneca's abandoned compounds. Both government and industry participants are hoping that crowdsourcing new ideas from a broad range of academics will lead to recovery of

the abandoned compounds (Mullard, 2012).

The second recently initiated pilot, led by the National Institutes of Health (NIH), has perhaps received the most attention. The "Discovering New Therapeutics for Existing Molecules" program, administered by the National Center for Advancing Translational Sciences (NCATS), was launched in May 2012 (Mullard, 2011). Eight large pharmaceutical companies have combined to make 58 abandoned compounds, which have already undergone safety testing in humans, available to the program. NCATS will then match novel scientific ideas proposed by academic researchers with the existing compounds, providing up to $20 million in funding for approximately nine research grants aiming to show new proof-of-concept data (Mullard, 2012). These academic researchers, in turn, will own the IP to whatever subsequent discoveries they make, while the contributors continue to hold their original IP on the compounds.

A third initiative, announced in late 2012, pairs the Broad Institute and over 300 compounds from the Roche Repurposing Compound Collection (RRCC) in search of new applications. Under this collaboration, the Broad Institute will screen all of the compounds in Roche's collection, leveraging its advanced biological assays and disease expertise. The RRCC includes drug candidates from the past 20 years that did not make it to market, which have been compiled into an annotated set (Roche press release November 28, 2012). The IP arrangements under this agreement have not been made public, but we assume Roche retains all IP rights needed to commercialize any hits.

The Archipelago to Proof of Concept in Medicine (ARCH2POCM), organized by the Structural Genetics Consortium and Sage Bionetworks, is the fourth initiative included in our analysis. Another public-private partnership, ARCH2POCM embraces an open source approach to early-stage R&D. The goal is to create a globally distributed pre-competitive collaboration to share data, reduce duplication of effort, and ultimately find more clinically validated targets (through Phase IIa). While the initiative hopes to advance many novel compounds to proof-of-concept, it will also include existing compounds not currently under active development.

Cognitive Implications of Each Initiative

One of the first observations to make regarding the four different initiatives is that each involves a private company collaborating with a nonprofit or public entity. This immediately broadens the cognitive frame at the research phase. The expectation is that academic medical researchers may have unique insights into possible ways to advance these compounds beyond those available within the large pharmaceutical firms. These researchers are not constrained by the managerial or psychological frames of the pharmaceutical firms. As NCATS director Christopher Austin recently stated, while the compounds being explored may not have made "the best business case…these [new] indications may be fantastic for patients and public health." (Nature News Blog, 18 June 2013)

This diversity of approaches is appropriate at such an early stage of exploration to increase variance in search (March, 1991) for recovering abandoned compounds. They invite more people from outside the originating organization to scrutinize the therapeutic potential of compounds. In addition, they employ different tools and processes beyond those used in the originating company. As one respondent told us, "…lots of companies are going after the [recovery] space, it only takes 2 or 3 successful compounds to make it worthwhile. Right now, I would posit that they probably don't have the right tools yet though, such as novel, high throughput screening profiling technologies."

The question then becomes, who will actually bring those products to market? The

Roche-Broad and MRC collaborations appear to keep all product commercialization rights with the participating pharmaceutical company. So any exploitation of new knowledge resulting from these initiatives will still encounter the extant managerial frame of that pharmaceutical company. The potential pitfall in this scenario is that even if some compounds are shown to be effective in new indications, the pharmaceutical company may still decide that the business case does not warrant additional investment, due to the cognitive limits imposed by its business model. The NIH/NCATS and ARCH2POCM initiatives, by contrast, offer the potential for another organization to exploit new knowledge gained from this research.

This new entrant, perhaps a start-up company or a patient advocacy group, may not be cognitively constrained by the blockbuster business model. That could lead to more novel targeted medicines reaching the market and encourage others, including large pharmaceutical companies, to reconsider the benefits of employing a more distributed business model.

5. Conclusions

In the past twenty years, pharmaceutical drug development has moved from a largely closed model of innovation to a far more open model. However, the implementation of a more open model of drug development within the pharmaceutical business model has been partial, and largely focused upon "outside in" innovation sources. At the same time, the vast majority of potential drug candidates fail during the development process. "Inside out" open innovation mechanisms could spur the recovery, and/or redeployment of these abandoned compounds to address unmet medical needs.

Rather than stockpiling potential products that are no longer being pursued, pharmaceutical companies and society as a whole would benefit from expanding their cognitive frames. The concept of false negative evaluation errors in drug development, the example of recovered compounds such as Thalidomide and Viagra, and the extensive use of off-label drugs to treat patients, all demonstrate the potential of these more creative approaches.

A number of early initiatives have recently emerged to address these issues. Though none in our judgment has fully resolved the cognitive issues we discuss, collectively we hope they will have a positive impact. Company collaborations with public and nonprofit entities to find new uses for their existing IP extend the efforts by pharmaceutical companies to pursue inside-out open innovation. The academic freedom of these research partners can help companies explore beyond not only their current scientific knowledge, but also beyond their extant cognitive biases and dominant business model.

6. References

Abrantes-Metz, R., Adams, C., & Metz, A. (2006). Pharmaceutical development phases: A duration analysis. *Journal of Pharmaceutical Finance, Economics, & Policy 14*, 19–41.

Bartlett, J. B., Dredgel, K. & Dalgleish, A. G. (2004). The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nature Reviews Cancer 4*, 314-322.

Bogdan, B., & Villiger, R. (2010). *Valuation in Life Sciences: A Practical Guide*. Springer, 3rd Edition. 370 p.

Boudreau, K. J., & Lakhani, K. R. (2009). How to manage outside innovation: Competitive markets or collaborative communities? *MIT Sloan Management Review 50*(4), 69-75.

Chesbrough, H. (2003). *Open Innovation: The New Imperative for Creating and Profiting from Technology*. Boston: Harvard Business School Press.

Chesbrough, H. (2006). *Open Business Models: How to Thrive in the New Innovation Landscape*. Boston: Harvard Business School Press.

Chesbrough, H., Vanhaverbeke, W., & West, J., (Eds.) (2006). *Open Innovation: Researching a New Paradigm*. Oxford: Oxford University Press

Chesbrough, H. & Rosenbloom, R. S. (2002). The role of the business model in capturing value from innovation: evidence from Xerox Corporation's technology spin-off companies. *Industrial and Corporate Change, (11)*3, 529-555

Chesbrough, H., & Chen, E. (2013). Recovering Abandoned Compounds Through Expanded External IP Licensing. *California Management Review,(55)*4, 1-19

Cook-Deegan, R. (2007). The science commons in health research: Structure, function, and value. *Journal of Technology Transfer 32*(3), 133-156.

DeMonaco, H., Ayfer, A., & von Hippel, E. (2006). The major role of clinicians in the discovery of off-label drug therapies. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 26*(3), 323–332.

Devinsky, O. (2007). *Epilepsy: Patient and Family Guide*, Demos Health, 3rd Edition.

DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics 22*, 151-185.

DiMasi, J. A., Feldman, L., Seckler, A., & Wilson, A. (2010). Trends in risks associated with new drug development: Success rates for investigational drugs. *Clinical Pharmacology & Therapeutics 87*, 272-277.

Europharma Today (2009). More Velcade-Style Risk-Sharing in the UK. www.europharmatoday.com/2009/01/more-velcadestyle-risksharing-in-the-uk.html Retrieved August 13, 2013.

Furr, N. R., Cavarretta, F. & Garg, S. (2012), Who Changes Course? The Role of Domain Knowledge and Novel Framing in Making Technology Changes. *Strategic Entrepreneurship Journal, (6)*3, 236–256.

Hunter, J. (2010). Is open innovation the way forward for big pharma? *Nature Reviews Drug Discovery, (9)*2, 87-88.

March, J. G. (1991). Exploration and exploitation in organizational learning. *Organization Science, (2)*1, 71–87.

Mullard, A. (2011). Could pharma open its drug freezers? *Nature Reviews Drug Discovery, (10)*6, 399-400.

Mullard, A. (2012). Drug repurposing programmes get lift off. *Nature Reviews Drug Discovery (11)*1, 1-2.

Nature blog 2013 (Nature News Blog, 18 Jun 2013)

Pammolli, F., Magazzini, L., & Riccaboni, M. (2011). The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery, (10)*6, 428-438.

Pharmaceutical Research and Manufacturers of America (PhRMA) (2012). Key Industry and PhRMA Facts.

Pisano, G. (2006). Profiting from innovation and the intellectual property revolution. *Research Policy, (35)*8, 1122-1130.

Prahalad, C. K., & Bettis, R. A. (1986). The dominant logic: A new linkage between diversity and performance. *Strategic Management Journal, (7)*6, 485-501.

Ruddick, G. (2010). GSK seeks to abandon 'white pill and Western markets strategy', The Telegraph, February 5, 2010.

Sagebase (2012). Arch2POCM: A fundamental systems change for drug discovery. http://sagebase.org/info/NewsInfoDownloads/SendaiFriend2.pdf (Retrieved July 19, 2012)

Tripsas, M., & Gavetti, G. (2000). Capabilities, cognition, and inertia: Evidence from digital imaging. *Strategic Management Journal, 21*(10-11), 1147-1161.

Tufts Center for the Study of Drug Development Reports (2011).

Weick, K. E. (1995) *Sensemaking in Organizations*, Sage

Winslow, R. (2013). Gene Breakthroughs Spark A Revolution in Cancer Treatment, Wall Street Journal, August 13, US edition: p.1.