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Commentary

Pharmaceutical companies, faced with growing pricing pressures, should look outside their products for new revenue opportunities

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For much of the history of the biotechnology industry, the practical question faced by therapeutics companies throughout the discovery and development process was, "Will we be able to get this approved?" That has changed. Though companies are no less concerned about their experimental products proving to be safe and efficacious, the overriding question for executives and investors evaluating a potential product's worth has become, "Can I get paid for this?"

Consider Sanofi and Regeneron Pharmaceuticals' experience with their new colorectal cancer drug Zaltrap, which won U.S. Food and Drug Administration approval in August 2012. Critics of Zaltrap say the drug provides the same survival benefit as Genentech's Avastin when either drug is added to standard chemotherapy. Like Zaltrap, Avastin is also used to inhibit angiogenesis in patients with colorectal cancer. But at launch, the average price for a month of treatment with Zaltrap was more than $11,000, compared with about $5,000 per month for Avastin. Concerned about the question of Zaltrap's value, Memorial Sloan-Kettering Cancer Center decided not to give the drug to its patients.

In an October 2012 op-ed article in *The New York Times*, three physicians at Sloan-Kettering (two of whom have served as paid consultants to Genentech) said the decision should have been a "no-brainer." The exclusion of Zaltrap from Sloan-Kettering's formulary, though, didn't come easy, according to the doctors. That's because, they said, the culture of medicine equates new with better. "Our refusal to adopt this remarkably expensive therapy," they wrote, "risks being labeled 'rationing,' not 'rational'". Following the editorial, Sanofi swiftly moved to cut the price of its drug in half, according to a report in *The Cancer Letter*.

Today's pressures on drugmakers reflect greater pressures throughout the entire healthcare ecosystem as payers, patients, and providers wrestle with the escalating cost of healthcare and push systems around the world away from a cost-based orientation toward a value-based one. For pharmaceutical companies, this reflects not only a growing pressure on pricing, but pressure from all quadrants of the healthcare world to demonstrate the value their products provide to justify their costs. This new reality is altering the life sciences landscape and changing business models, development strategies, and funding opportunities for companies.

Already drugmakers are facing these barriers to get drugs to market in countries such as Germany, where the legislation known as AMNOG put into place a pricing scheme that requires drugmakers to justify the pricing of their new products. The United Kingdom's National Institute of Clinical Excellence is working on introducing a new value-based pricing scheme as well, with expectations to introduce it by 2014.

In the United States, the industry is waiting to see what two institutions created by the Patient Protection and Affordable Care Act—the Patient-Centered Outcomes Research Institute and the Independent Payment Advisory Board—will mean for it. PCORI is explicitly

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charged with comparative effectiveness research while the IPAB has broad authority to meet its mandate to achieve specific savings to Medicare. And now a February 2013 report from the Institute of Medicine says the rising cost of healthcare remains a threat to the global competitiveness of the United States and that the time has come to evaluate not only the safety and efficacy of new cancer therapies, but their costs as well.

As pricing pressures continue to intensify for pharmaceutical companies, the opportunity for drug companies to capture value directly through the sale of their products will diminish. Smart companies should take a lesson from other industries to find ways to capture value outside of their products. High technology companies, retailers, and Internet companies have all provided examples of this.

Consider New York's Museum of Modern Art, which in fiscal 2011 generated $22.7 million through admissions and $15 million through membership fees. That sum was dwarfed by the $50.5 million in revenues—by far its largest single source of income—produced from what it calls "auxiliary activities." This includes sales from the Museum's stores (on and off-site), e-commerce, mail order, publishing, restaurant, and other operations.

Then there's the online retailer Amazon.com, which has moved beyond generating revenue just from online retail sales, but has also capitalized on the platform it created to build a major new business in cloud computing. Analysts have estimated that revenue from the cloud computing business may exceed $2.5 billion in 2014, according to *Computer Reseller News*.

Other examples abound. Grocery stores have learned to capitalize on the data they gather from customers to sell to marketers. Facebook now allows users of its social network to send gifts through major retailers, and the social networking giant generates its revenue not from users, but from advertisers, who put a premium on the highly targeted audiences Facebook delivers. Life sciences companies have also learned to capture value outside of their products.

The personal genomics company 23andMe, which helps individuals understand their own genetic information through DNA analysis and web-based interactive tools, derives its revenues from selling genomic analysis to individuals and providing information to help people understand its meaning. But 23andMe has also created a research program called 23andWe. It allows customers to participate in research projects and help discover new genetic associations with diseases.

Those efforts led in 2012 to 23andMe winning its first patent, which relates to indentifying a genetic mutation associated with Parkinson's disease. This could eventually lead to licensing revenue for the company. The company is also capitalizing on its customer base by helping drugmakers conduct studies that require a population of people with specific genetic make-ups. In March 2012, the company began helping Genentech recruit breast cancer patients to find genetic predictors of how well they would respond to the company's drug Avastin.

But if pharmaceutical companies, rather than thinking of themselves as being in the business of selling drugs, think of themselves as being in the business of preventing and treating illness, they will see new possibilities to provide services in conjunction with, or alongside, the products they sell. Already, several companies have waded into this area by offering a variety of services intended to improve patient compliance, prevent complications from disease, promote wellness, and help doctors find new treatment options. In some cases services may provide new revenue opportunities for companies, but they are also important in driving use of the companies' drugs by improving compliance, helping new patients access care, and building relationships with patients.

In July 2012, the German pharmaceutical company Boehringer Ingelheim announced a collaboration with U.S.-based Healthrageous, a company that provides a digital self-management program for patients with diabetes. Boehringer is concentrating on new business models, saying patients with certain conditions, such as chronic diseases, should be treated with more holistic approaches than just drugs alone. Bert Tjeenk-Willink, a member of Boehringer's board of managing directors, said the company is committed to a "beyond pill" approach in healthcare. "We have to pursue a new approach to see the patient with all his or her aspirations, but also limitations," he said.

In a separate agreement that same month, Merck said it is collaborating with the integrated health services organization Geisinger Health System in an effort designed to improve patient outcomes by facilitating shared decision making between patients and physicians and bettering adherence to treatment plans to improve clinical care. The first tool the partners are developing is an interactive web application designed to help primary care clinicians assess and engage patients at risk for cardiometabolic syndrome, a clustering of various risk factors that put an individual at risk of developing type 2 diabetes and cardiovascular disease.

And then there's Pfizer, which in 2010 launched a pharmacy-based service in the United Kingdom to provide health screenings to prevent heart attack and stroke. By running cardiovascular tests in community pharmacies and then referring patients who are at risk to primary care physicians, the company says it provides a more cost efficient approach to preventing heart attacks and strokes.

A world in which companies must evaluate their pipelines by asking whether a drug in development is something a payer would reimburse is fundamentally different from the world in which this industry has operated in the past. While companies today feel pressure to do more with less, improve their R&D productivity, and find ways to replace revenue lost to generic competition in the face of expiring patents, they also need to fundamentally reconceive themselves.

A focus on value is not a bad thing. It should be embraced. It will help impose discipline in corporate decision-making and prioritize true innovation. Creating value alone, though, is not enough. Companies will need to figure out how to capture value as well, and that is a greater challenge in a world where there is increasing cost consciousness, and where comparative effectiveness becomes a gatekeeper to the marketplace as patients are remade into healthcare consumers.

Commentary

Commercial Biotechnology in Mexico

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The year 2013 marks an important transition period for commercial biotechnology in Mexico. At the start of a new national administration, several public policy elements are already in place to enable the country's business and academic sectors to more fully pursue innovation opportunities in this area. Novel applications are being explored in human and animal healthcare, agricultural modernization, environmental protection, biofuels and other areas. The trends and directions of Mexico's market situation in biotechnology as it relates to research, commercialization and international business relations is both expanding and diversifying.

For commercial biotechnology development, Mexico offers an increasingly attractive business climate. It is part of one of the largest free trade agreement networks in the world, involving 12 trade agreements with 44 countries. Its geographical location, user-friendly regulatory and legal framework, skilled labor force and competitive costs continue to make Mexico home to highly-developed industry groups. The daily trade between US and Mexico is 1.3 billion dollars and Mexico is the first or second export destination for 21 U.S. states.

Evolving areas of application. Traditional industrial sectors are benefiting from modernization and innovation programs involving research institutions, private industry and selected government agencies. Of the more than 180 firms that develop and/or use modern biotechnology in Mexico, 31% are in the agricultural area, 23% in environmental applications, 18% in health care, 18% in food, and 10% in other areas. In health care, there is growing interest in protein-based therapies, vaccines, anti-venoms and related areas. The areas of environmental protection, remediation of contaminated sites, treatment and reuse of wastewater and solid waste management are all subject to process improvement through certain biotechnology approaches, as are the more commonly associated areas of renewable fuels and clean processes. Similarly, Mexico's marine resources and aquaculture represent a growing focus of selected biotechnology-based field studies.

Expanding research platform. Mexico's rich biological diversity is one of the most unique in the world. As the fifth richest region in biodiversity in the world, Mexico has a long tradition of research in the area of biological sciences.

Mexico offers great advantages and incentives to the research and development of the sector, thanks to its solid educational system. Every year, Mexico's leading public and private research centers train more than 110,000 engineers. The country has over 100 institutions dedicated to biotechnology research and more than 750 senior researchers working in biotechnology-related fields. Additionally, Mexico's institutions produce more than 400 graduates (master's and doctoral) per year.

Mexico has contributed a great deal to the advent of modern biotechnology. In the late 1970s, scientists such as Dr. Francisco Bolivar participated in the development of the first genetically engineered protein (human growth hormone). Although not commonly known, the oral contraceptive "pill" was developed in Mexico by Syntax. Additionally, some of the best known anti-venom serums and treatments are developed in Mexico by Laboratorios Silanes.

The National Institute of Genomic Medicine (INMEGEN), is a public entity dedicated to research in genomic medicine and related fields. Having just

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recently inaugurated is new state-of-the-art research laboratory facilities in Mexico City, INMEGEN works with national and international institutions in the public and private sectors to generate new products and health services for the benefit of the Mexican population.

In the agricultural area, the National Laboratory of Genomics for Biodiversity (LANGEBIO) in Guanajuato is one of the best centers of agro-biotechnology and plant biology research. Some its research focuses on natural insecticides, treatments for agricultural diseases through the use of spores, development of biological processes to produce nano-particles of silver, alteration of plants to act as bioreactors for vaccine production and other leading-edge efforts. The University Center for Biological Sciences and Agriculture in Jalisco has programs in neurobiology, molecular and cell biology, genetics, breeding and agricultural biotechnology.

It was recently announced that the Carlos Slim Foundation in cooperation with the Bill and Melinda Gates Foundation are providing a 25 million dollar grant to the International Center for Improvement of Corn and Wheat (CIMMYT) located in the State of Mexico. The investment will go to support work of maize and wheat research in an effort to address challenges resulting from food shortages in the world, climate change and rising population. The new research and training infrastructure at CIMMYT will include biotechnology laboratories and other facilities to enable world class research in plant genetics and related areas.

Legal and regulatory framework. Mexico's legal framework is now one of the world's most advanced in the area of biotechnology and it provides one of the highest levels of certainty regarding intellectual property protection. Patent data from the World Intellectual Property Organization estimates that the number of applications for patents in Mexico has grown at an annual average rate of 10% in the last fourteen years. From 1997 to 2011, 197,076 patent applications were recorded. Of these, about 25% are in biotechnology-related fields.

Mexico has signed the Nagoya Kuala Lumpur protocol, joining 46 other countries. The agreement includes its Supplementary Protocol on Liability and the Redress to the Cartagena Protocol on Biosafety. Since 2003, Mexico is part of the Cartagena Protocol on Biosafety. In 2005, law of biosafety of genetically modified organisms was published in the Official Journal of the Federation.

Regional bio-clusters. The major bio-clusters in Mexico are located in areas where the leading life science research centers are found. In addition to the well-known centers in Mexico City and Cuernavaca, there are growing bio-clusters in Monterrey, Guadalajara and Irapuato. Studies performed by the Council on Competitiveness and the University of California, San Diego describe the main advantages and opportunities that these Mexican bio-clusters offer. The larger ones are located in the States of Nuevo Leon, Queretaro, Jalisco and in Mexico City. Besides these clusters, Mexico has several world-class research institutions, including The Center of Applied Technology of the National Polytechnic Institute, the Biotechnology Institute of the UNAM in Cuernavaca; The Monterrey Institute of Technology and the University of Guadalajara. These institutions and others generate highly-qualified human resources.

The State of Nuevo Leon has created a park for research and technological innovation (PIIT) where as many as 30 R&D centers are located with various technology focuses, including nanotechnology and biotechnology. The State of Morelos has the largest number of members of the Mexican Society of Biochemistry. It is also the second state with largest number of researchers registered in the National System of Researchers (SNI). Morelos's 17 research centers provide a high concentration of specialized human capital.

Increased public and private investment. There has been a steady increase within the federal budget of Mexico to support small and medium sized companies; much of this funding has been earmarked for the high tech industry which includes agro-biotechnology and environmental technology. There are several programs dedicated to stimulating regional areas that offer competitive advantages, and federal initiatives that serve more than 1500 small and medium businesses.

The National Council of Science and Technology (CONACYT), is a federal institution that sets government policy and is in charge of the promotion of science and technology activities in the country. It works through an inter-ministerial department for the development of biosafety and biotechnology through a program that aims to support and strengthen the scientific research in this area. With regard to biotechnology, CONACYT supports projects in research development and innovation as well as training of specialized human resources. It works to strengthen of research groups and infrastructure of universities and public research centers, to solve specific productive needs of the country for the direct benefit of domestic producers.

The largest percentage of resources currently dedicated to biotechnological research are concentrated in the area of pharmaceutical development, with agriculture and energy applications also receiving significant attention. In the agricultural area, Mexico continues to explore the use of biotechnology-related tools such as marker-assisted breeding, bio-pesticides, seed certification and other agricultural applications. The Mexican Ministry of the Economy estimates the domestic market

for products of biotechnological origin to be approximately US$1 billion with strong potential for growth.

In Mexico today, there are close to 100 companies using biotechnology processes for productive purposes. The biotechnology community is clustered in active professional organizations like the Mexican Society of Biotechnology and Bioengineering (SMBB). Novel biotechnology products are being developed by innovative Mexican companies such as BioClon, ProBioMed and others.

In 2011, the well-known, biotechnology company AMGEN announced plans to invest more than 100 million dollars in Mexico over the next 5 years. Founded in Thousand Oaks, California in 1980, AMGEN is a leader in the development, manufacturing and sale of biotechnological medicines. AMGEN has had a presence in Mexico since 2006. The company will establish strategic alliances with research centers, hospital, universities and national institutes specializing in the battle against serious illnesses like cancer, chronic kidney damage, autoimmune thrombocytopenic purpura and osteoporosis among others. The five-year plan projects investments in highly specialized human resources and technology transfer in order to sell biotechnology products. During this period more than 150 direct jobs and 300 indirect jobs will be created.

International networks. As Mexico's public institutions, private companies and academic research centers advance in their ongoing efforts to stimulate innovation in traditional industrial sectors, we will see an increasing number of opportunities for commercial biotechnology applications. The growth areas will certainly include human and animal healthcare, agriculture and food science, environmental protection, new materials and others. Mexico's diverse international networks will continue to play an important role in this development, providing an increased number of opportunities for advancing commercial biotechnology in the country.

Commentary

Defining valuable information in a shifting industry

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Every decision in a high risk market relies heavily on accurate and intelligent information. Yet often times, the markets with the highest risk are those with limited data, few established trends, and little actionable intelligence. This experience is common in the biotechnology industry, where innovation provides new opportunity, and the inherent challenges associated with exploration.

The union of biotechnology and pharmaceutical drug development is an example where high risk has been rewarded. Biology based therapies can address medical concerns in ways chemically synthesized products cannot, and many have been very successful in doing so, as multiple biologic drugs have received blockbuster status with worldwide dose sales exceeding over $1 billion annually. The trend is expected to continue too, with eight of the top ten world's biggest-selling drugs in 2014 to be biologics.[1]

Due to high cost and limited patient access associated with biologic products, regulations have been implemented in most major markets to permit competition. The EU approved its first subsequent entry biologic (SEB) in 2006 and has since been a leader in product approval. Currently 13 SEBs are approved through the EUs abbreviated pathway, and more are expected in the next year. In the United States, enactment of biosimilar legislation didn't come until 2010, and the market is still void of any approvals.

This is not the first time regulations have created competition in the pharmaceutical industry. The Drug Price Competition and Patent Term Restoration Act established the generic drug market in the United States through an abbreviated drug approval process. Almost 30 years later, the generic drug industry has indeed provided cost savings in the US where in 2011 alone generics saved $193 billion.[2] The hope is that biosimilar competition will result in the same.

But while the generic and biosimilar markets are both fueled by the same desired outcomes of increased patient access, innovation and cost savings, they do not share many of the same characteristics. Small molecule products have a lower molecular weight and a well defined structure which can be completely characterized. Conversely, biologic products have a more complex structure and can be highly sensitive to peripheral conditions. As more is learned about the specific attributes of products, relevant policy and regulation will shape accordingly.

Since the US passed regulations permitting biosimilars, further interest in biosimilar competition has been generated. Due to the surge of interest, and the high risk associated with entering the biosimilars market, companies are again looking to make informed decisions based on limited knowledge. For information providers hoping to provide insight to these companies, it is important to understand that the information of value to biosimilar competitors is always not the same as what generic companies consider of value.

Certain information considered to be valuable in the generics industry would provide little to no insight to biosimilar competitors, such as knowing the availability of active substances in merchant markets or identifying which ANDA filers have filed for paragraph IV certification. Equally, biosimilar competitors must be aware of clinical trial information in more regulated markets, as well as marketing considerations in regions that do not allow automatic substitution, two knowledge areas generic companies often ignore. Valuable information in the biosimilar market stands apart from the established competitive intelligence of the generics industry,

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and the challenges associated with providing information to a young market with limited data and distinct characteristics are met with innovation. New searching techniques, analytics, data collection methods, and forecasting models that focus on the uniqueness of the biosimilars market but also take into account shared attributes with the generics market can guide decision makers and mitigate risk.

As the biosimilars market continues to establish itself in the United States and matures globally, it may become as complex as the monoclonal antibodies products that will drive it. Already, issues with language have created communication challenges and uncertainty. An inconsistency in terminology has made it difficult to ensure biosimilar references do not refer to non-approved follow-on biologic product, or even a generic drug. Information providers can help facilitate the growth of the biosimilars market by offering well-informed intelligence to decision makers, and being ready to adapt to the further changes ahead.

ENDNOTES

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Perspective

Technology transfer: Bridging academic research and society — a communicative approach

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ABSTRACT

To make basic research transcend the domain of a university for the benefit of the society, technology transfer processes such as patenting, market analysis, and economic assessment are essential. Therefore small dedicated units, called technology transfer offices, have emerged during the last four decades. The emergence is a manifestation of a general political intention to make basic research have direct impact on society — to focus on application *and* publication, and not just the latter. The process is, however, not straightforward and different universities have different way of doing it.

The University of Southern Denmark has recently implemented a highly extroverted and progressive science-based communicative strategy providing an adequate framework for a "grass-roots moving" among researchers. By working on four frontlines we aim to ensure high degree of transparency in the technology transfer activities, to demythologize pseudo-idealistic and inadequate perceptions on the role of e.g. patents, to scout early-stage business opportunities, to map the competence landscape of the university and to ensure a three-faceted political alignment.

We here present the *SDU-model* of doing technology transfer anno 2012. Despite the short timeline in which it has been implemented we have already harvested the early fruits, which encourage us hereby to present the model, its underlying strategy, its rationale, and its perspectives. Briefly, the number of invention disclosures at the University of Southern Denmark increased 2.3-fold one year after the SDU-model was implemented. We believe that the model represent a coherent and rational innovation strategy with respect to the *holistic* four-frontline focus, addresses some of the major challenges of academic technology transfer and we are confident that universities worldwide could benefit from it or a context-dependent modified versions hereof.

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INTRODUCTION

Technology transfer in academia essentially involves patenting, licensing, and creating spin-out companies based on research results and inventions. In this way research results would potentially be able to transcend the walls of the university and the archetypical stage of disclosure within often highly narrow (though not limited to) scientific environments. In order to achieve a competitive advantage on science, technology and innovation, countries dependent on a knowledge-based economy have experienced that during the last five decades political focus has been significantly intensified on this technology transfer discipline resulting in the introduction of so-called Technology Transfer Offices (TTO) at universities.

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Technology transfer activities involve analysis of research results from a business perspective in the light of what society (i.e. the market) actually needs. A solution to a non-existing problem, or one that is not compelling or highly differentiated, is in this perspective not interesting and will not result in economic gain, unless — of course — the society finds out it has a problem to solve that they did not realize they had before (e.g. Apple is really good at presenting new needs and business models to serve those needs before customers or users realize that such needs exist). The analysis includes investigation of novelty and patentability (typically done by external patent attorneys), market research (understanding customer need, mapping the landscape of competitors, stakeholders, etc.) and competitive intelligence, i.e. assessing emerging technologies/alternative solutions that might compete with those being pursued in the university, among others. If patentability investigation turns out positive, patent writing is initiated and the TTO is responsible for the management of intellectual properties hereafter.

TTO activities also include interaction with the local, national and global industry as well as investors, which is essential for maturation of the research results into real-life products, i.e. accessing the innovation ecosystem network. This interaction implies a great deal of caution to avoid inadequate technology transfer, another word would be "technology theft", since early technology presented is highly vulnerable to theft and/or reverse-engineering. To deal with this issue, non-disclosure agreements are often signed before technology transfer meetings and prior to any presentation of the technology. It is, however, even better if the invention is protected by a patent, which is the strongest protection that intellectual properties can have (much stronger than e.g. copyright or trademark protection). Additionally, when trying to convince investors to provide funding, patents are essential and required, since the very high risk of immature inventions with significant uncertainty needs to be compensated by patent protection, i.e. protection from technology theft. It is estimated that for each medical drug that reach the market the development cost will be in the order of one billion USD[1]. Obviously such an investment points out the pivotal role for patent protection. Patent protection therefore functions as an important incentive for investment in, or licensing of, early-stage technologies and to eliminate business-eroding competition that would ultimately result in a situation, where a drug will not arrive to market (even though it has several benefits — see discussion on this topic later). However, we are aware that patents are seldom approved prior to licensing, but filing a patent application early to provide the safest possible intellectual property right protection remains essential if academic research is to be translated into business solutions sold or licensed to private companies via a lump-sum or royalty payment for the academic institution. Moreover, freedom to operate analysis is obviously a continuous process since it needs to be adjusted to ever-changing patent landscapes, especially in the field of medical research and biotechnology, Thus freedom to operate analysis is required even after patents are issued.

The patenting process is a "must-do" for technology transfer (for natural science, not for social sciences necessarily). However, researchers are rarely trained in patenting, market analysis, business development etc. — because this is not *their* job. This points toward a pivotal role for TTO units that are dedicated to facilitate and manage the process of making academic research have direct impact on society. The process of technology transfer obviously requires that TTO and researchers act in concert, are committed, are well aligned on the process and strategy (milestones, deadlines etc.) and that both parts are familiar with the gross elements of the process. To ensure this, transparency is essential: The researchers must know what TTO is and is not, what TTO does and does not. And the TTO unit must get a real-time updated picture of the pool of competences that exist on the university in order to select the best projects for technology transfer, facilitate synergies among non-connected researchers as well as understand the researchers *perception* of technology transfer which determine his or her world-view on technology transfer. Therefore it is essential to be able to talk in two synergy-facilitating languages: The language of science and the language of business development — and to communicate continuously.

For this we at University of Southern Denmark (SDU) implemented an "interfacial" concept of Business Scouting subsequent to a political formulation of an overall strategy of technology transfer based on mutual dialogue and science-based communication. We would like to point out that we believe that one should be careful about defining and comparing best practices regarding technology transfer at universities since every university is unique and there are many ways to support and facilitate applied research and technology transfer. However, we do believe that the best long-term result from technology transfer will be realized by meeting the researchers in their own environments and from there facilitate the process of technology transfer as a partnership with TTO, management of the university and the external partners in society. Focus on communication of possibilities and relevant case stories are essential.

1 Drug development cost estimates hard to swallow. *R. Collier.* CMAJ. 2009 February 3; 180(3): 279–280.

THE EMERGENCE OF SDU-MODEL: SCIENCE-BASED COMMUNICATION

To dedicate researchers to the process of technology transfer, it is critical that TTO activity is visible, transparent and is adjusted to their scientific environment. In this way myths and inadequate perceptions that act as barriers to technology transfer are overcome. Perception *is* reality (for the percipient) and by adequate (with respect to timing, context, rationality and respect) communication, reality *as such* can be transformed by modification of perceptions. This is indeed an ongoing process — pivotal and essential for success. The SDU-model defined and implemented a communicative four-fronted strategy, each being described below.

Frequent information meetings — ensuring transparency and modifying perceptions

To enhance visibility of the persons and activities of the TTO unit we participate in a diversity of meetings and seminars for institute managers, group leaders, natural science PhD students, natural science graduate students, innovation course participants and the academic staff. We make a presentation of who we are, what we can offer, how TTO-related laws are at the university, how the outline of the patenting process looks and what models of academic technology transfer exist. Additionally, we have asked researchers engaged in technology transfer to talk about their personal experiences when working with the TTO unit including pros and cons by doing translational research. Thereafter we invite researchers for a dialogue to discuss (in plenum) issues they might think of and to describe their present perception of technology transfer. Frequently the burning point is patenting, since there is a common feeling that patenting and basic research cannot co-exist: "Research relies on open-source, full-sharing and nothing-to-hide mentality and patenting is essentially the opposite due to the protective nature of patents". This perception is *a priori* wrong. Patents are disclosures of inventions (i.e. full sharing of knowledge) with the reward to the inventor that he or she can exploit the *commercial* potential him/herself for a given period of time — i.e. *everyone* can use the invention *as long* as it is for non-commercial purposes. Similarly, rewards for scientific publications are impact factors (essentially as point-system) and immaterial acknowledgements. In summary: Patents are 1) *full-sharing* of knowledge, 2) freely usable to everyone for non-commercial purposes and 3) implies society's reward to the inventor (and his institution)..

Frequently researchers think that patents are unethical for the reason that patents might hinder superior inventions, e.g. patent protection and monopoly could block critical cancer drugs from entering the market. It is unethical to hinder the benefit to people from drugs that can treat patients suffering from cancer, they state. In essence patents seems to be perceived as incompatible with the idealism that drives basic research. This view seriously suffers from bypassing *reality*, and while thriving to glorify one's own apparent ethics and idealism, the opposite of the goal of wide and open dissemination most often occurs. This view actually directly implies that the seriously ill cancer patient will never benefit from one's patented drug! It might seem paradoxical — but the explanation is remarkably straightforward: If a researcher invents a drug against cancer and publishes it so that *everyone* (in principle) can use it and see how great the drug is, this drug will almost certainly never be used for treating cancer patients. Why? Because the drug must be validated, be toxicologically tested, must "survive" clinical phases, must be formulated for everyday-use, and it might cost > 1 billion USD before the drug will be on the market where patients can benefit from it. And for anyone (private persons or companies) one will obviously need to protect this huge economic investment, which can *only* be via a very strong patent! Publication prior to patenting means that the drug will never be developed because of the extremely high risk/reward ratio, so that is will *never* benefit suffering patient because it won't exist in a form that they can use. Patenting prior to publication means that the patient might have a chance (at least) to benefit from it![2,3]

We advocate understanding both science and business principles that are required to bring innovations to the marketplace. It is an illustration of how misunderstood idealism and perception actually negatively interferes with an otherwise noble intention. Publications may get researchers citations — something to add for his/her curriculum and maybe the next grant — but without patents patients are unlikely to benefit from the research.

2 Due to the so-called "Grace period" in USA one can patent an invention up to one year after publication so *in theory* publication of a wonder drug followed by a patent within one year should not be a problem. However *in practice* an investor will very rarely invest 1 billion USD on a drug, which can only be protected in one or few countries. Such investment generally requires protection worldwide of the drug.

3 We are *fully* aware that this "wonder drug-scenario" does not apply to all types of science and inventions, e.g. not research on basic mechanisms in nature. However for many "product inventions" the drug *metaphor* applies "within a scaling factor".

This is misunderstood idealism driven by an inadequate perception fueled by lack of appropriate knowledge. Indeed it is of the essence of TTO-work to demythologize the common close-to-immortal myths on "research *versus* patents" in academia.

This story also illustrates a perception, which is ingrained in academia, which can only be changed by dialogue and transparency. Metaphorically (here we choose a drug for cancer for pedagogic purposes) it is these kinds of perceptions we strive to change via communication. Modifying these perceptions changes reality of the percipients, which is essential if researchers should engage in technology transfer, which is the fuel that drives TTO units and technology transfer. Therefore frequent meetings, participation in seminars and face-to-face communication in the scientific environments are important. In this context real-world examples would be very useful illustrations of how products are brought to market successfully to provide value to patients (or customers).

Business scouting — integrating the language of science and business

Our university found it pivotal that TTO should meet researchers in their "natural environment" speaking the language of science to facilitate a dialogue based on a mutual understanding of the context of the research. The implementation of this strategy was personified in a position we call a "Business Scouting Officer" (BSO) who in our case has a PhD in natural science, who has participated in a significant number of and business/innovation courses in parallel to the scientific education and who is in parallel enrolled on an MBA education. Essentially we aim to operate like a business development group in a biotech/pharmaceutical company. The scientific background combined with insight in central business/innovation-related matters provides a framework for mutual understanding of the scientific topics, facilitating a motivated and equal dialogue his or her research as such. In terms of organizational design the BSO is a part of the TTO-staff and refer directly to the Head of TTO. Importantly, the BSO was a young researcher who came directly from his finalized PhD study and thus came directly from the scientific environment and had therefore many direct contacts to researchers present at the university. We found it particularly important for the SDU-model to work that a business scouting officer needs to be credible technically as well as business wise. This is a corner stone in the concrete implementation of the SDU-model. An additional benefit is that the young PhD is not and will not be viewed as a scientific/commercial competitor to the researchers, which could easily be the case if the BSO was a senior researcher aiming for academic progression as an assistant professor or professor with experience in business development.

During sessions of talking with researchers on their particular topics and projects that motivate them, the BSO have the unique chance to frame the talk about TTO activities and processes into a relevant specific context directly related to his/her research project: Does the specific research have perspectives in terms of patentability, should one consider this at a more mature stage or is a pre-mature stage "enough", are there possibilities for proof-of-concept funding etc.? Contextualization of TTO processes indeed seems to have a profound positive effect of understanding and transparency of what TTO activities are all about.

The huge benefit from this progressive strategy is that TTO will no longer have to wait for researchers to "come to TTO", since the TTO is actually coming to the researchers to see if there are inventions that they researchers did not think of as inventions themselves (maybe because the focus was on the next grant or publication). And since the inventions caught in this way are often early-stage technologies a more tailored and rational plan that crosslink the further research and coming TTO-activities can be made, which dramatically minimizes e.g. the risk of prior-to-patent publishing of scientific results that would compromise commercialization. Likewise the researchers can benefit from having TTO review their research from a business perspective to come up with ideas they did not think of themselves.

To systemize the business leads discovered via the scouting process (which is highly important) a description of the personal meetings are journalized into a traditional costumer relation management system (CRM) accessible for all TTO-officers. The CRM system facilitates sharing and accessibility of real-time information of current potential business possibilities as well as research projects currently ongoing so TTOs can be up-to-date on scouting activities. In the CRM system all relevant mail correspondence, documents, market reports, competitor analysis etc. are included for inspection of all TTOs.

As a curiosum to the BSO-role we also implemented so-called scouting seminars where external life-science consultants made presentations of selected areas of research institute-wise. By selecting a few specific cases, market analysis, competitor analysis, different ways to crystallize the technology into real-life applications, assessment of economic gain of the invention, patentability of the research results etc. were presented. Inviting external experts to make concrete business presentations of the researcher's results had a significant high motivation to the researchers and provided a frame

for important discussions and for providing concrete and specific information of technology transfer issues.

Mapping of academic competences

In our TTO unit we decided to implement a progressive strategy that implies we need to have not only a real-time picture of possible business cases at immature or mature stages, we also decided to make a detailed catalogue/database of scientific competences present at the different faculties. Hence the BSO should in parallel to the business scouting perform a survey of each and every researcher at the faculty of science, in our case 170 researchers. The survey includes reading abstracts from related publications from 2005-2012, reading of selected publications, collecting data from PubMed, Web of Knowledge, USPTO (U.S. Patent and Trademark Office), EPO (European Patent Office) and BiomedExperts databases as well as using the Google search engine to retrieve otherwise "hidden" data on the researcher of interest (from newspapers etc.). Information from these sources was combined and three major parts of sub-information were journalized into the CRM system: 1) competences, 2) special instrumentation and 3) potential applications.

The comprehensive competence landscape provides a powerful strategic tool the scouting process as well as for the matching of external academic and/or industrial parties who could be potential collaborators in research projects and/or commercial activities. The CRM system directly provides a physical framework for doing fast matching based on detailed inquires on 1-3 mentioned above.

Such comprehensive analysis of the competence/instrumentation landscape is to our knowledge rarely performed (we do not know of an example hereof) at this level of details and accuracy on universities worldwide where the analysis is based on manual inspection and cross-source correlations performed by scientific personal. Based on our experiences we strongly advice other universities to make such a repository of information to facilitate TTO activities. Additionally, this can also be used by key-decision makers at the university with respect to strategic decisions on research perspectives, focal areas to support financially etc. The repository should ideally be updated once a year to ensure alignment along the line of time progression. Finally we would like to stress that the CRM system described herein could also be very useful if it was supplemented with an external database of commercial needs that could be aligned with the internal assets — i.e. link asset to need to optimize licensing opportunities. We have not yet implemented this systematically in the CRM but this particular feature is part of the TTO strategy for SDU in 2013. Briefly we have developed a system where customer needs (submitted by public institutions and private companies) are aligned with the in-house confidential CRM database described above.

Political alignment

Technology transfer is a process that involves tight alignment to not just researchers but also importantly political decision-makers, without whose support TTO activities are severely compromised. Essentially three political 'units' should be balanced and aligned: 1) The President, 2) the Dean of the faculty and 3) the institute heads. These three political units are three distinct constituents all of whom may have agendas and need to be aligned — and each unit exerts its own delegated power on the TTO-activity. At least this applies to the organizational design of Danish universities. The President is highly important for the overall TTO-strategy and determines the intensity of the TTO work, partly via economic and political impact. The Deans have a huge influence on economic impact as well as determining to what extent the institute heads should focus on TTO activity. Moreover the institute heads have direct contact to the academic staff and can promote translational research activities via meetings with and personal talks to the researchers. All three political constituents are highly important to be aligned to due to the diversity of political roles that have direct impact on the TTO framework, and they are all equally important with respect to direct personal support to the TTO activities which is unfortunately often be viewed as secondary or even tertiary activities to the overall university mission and vision. Alignment is ensured via frequent information, update and follow-up meetings between the Head of TTO and key decision makers as well as presentation of quantified and timely key performance indicators to the various parties. Without political support and mutual alignment on two-sided expectations, TTO activities are very likely to fail.

CONCLUSION: IMPLEMENTATION AND EARLY RESULTS

The SDU-model described here has been successfully implemented at University of Southern Denmark with the aim to accelerate science-based innovation and bridging between academia and society. As a starting point we have hired one business scouting officer per faculty (Faculty of Science, Faculty of Medicine and Faculty of Technical Sciences) each having 100-200 principal

investigators (PI). The cost of the initial implementation of the business scouting concept has been approx. EUR 250.000 per year for 3 business scouts and additionally increased central TTO costs associated with the business scouting initiative (external consultants, patent agent fee, promotion etc.) of approx. EUR 150.000. Moreover EUR 400.000 are allocated to Faculty grant programs for maturing and validation of disclosed technology concepts.

A measurable key performance indicator for the implemented SDU-model is the number of invention disclosure and the percent-wise increase after the implementation. I the period 2009-2011 approx. 20 invention disclosures were yearly produced at the three mentioned faculties. After implementation of the SDU-model in November 2011 the Technology Transfer Office received and facilitated the production of not less than 66 invention disclosures in the year of 2012, i.e. more than three times as many invention disclosures were produced in 2012 as compared to each year that previous three years. We are confident that this dramatic incensement of more than 200% can only be explained by the implementation of the SDU-model and the timing hereof. Clearly there are synergies that we have observed but which are not directly quantifiable. For instance success stories tend to spread mouth-to-mouth leading to new success stories and willingness of principal investigators to interact with the Technology Transfer Office.

One such success story originates from the Faculty of Science where an invention has been disclosed which is a piece of software. Initially, the business scouting officer identified a motivated principal investigator to file his first invention disclosure together with a skilled and innovative Master-student who had not considered to hand-in an invention disclosure despite the fact that many people could benefit from his scientific work. University of Southern Denmark then acquired ownership of the intellectual properties rights, filed a patent application, secured proof-of-concept funding of EUR 100.000 and has recently employed the graduated Master-student. The funding which was a direct consequence of the IPR acquisition by the Technology Transfer Office is an important cornerstone in the forthcoming process of making it possible to further develop and mature the patent applied technology. Without the initial informal meeting between the business scout and the principal investigators the patentable software would not have been disclosed as an invention and a business solution with enormous potential could have been lost.

The SDU-model is essentially a bottom-up model where we try to sow seed in the academic research environment by information, mutual scientific understanding, dialogue and respect for the researchers "natural environment". The strategy aims to deliver a framework for grass-roots movement among research towards translational research by demythologizing myths on patenting and business development in relation to basic research. Additionally, it provides maximal transparency in TTO-activities via information meetings and informal business scouting meetings face-to-face. By means of the described progressive science communication-based approach to technology transfer we try to address current challenges and try to create synergies across disciplines facilitating science and business to collapse into solutions to existing problems in the society.

We are fully aware that the SDU-model does not provide all answers to the complex discipline of doing technology transfer (which is not our intention either). However, we do think that the model provides a powerful holistic, integrated and self-coherent framework for facilitation of research to transcend the academic domain into the society where people with everyday-challenges can benefit from the great fruits of academic research.

Competing interests statement

The authors declare that they have no competing interests.

Original Article

The financial ecosystem available to early-stage biotechnology firms and its misalignment with interests of these firms, of the biotechnology industry and with global disease burden

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ABSTRACT

The development and commercialization of new therapeutics have had immense impact on the quality and length of human life. Nevertheless, the biotechnology and the pharmaceutical industry have evolved to be driven mostly by a profit oriented market system, in which distinct stakeholders interact with different motivations to make the development and commercialization of therapeutics a reality. This study discusses the financial ecosystem available for early-stage biotechnology companies and its influence on the their strategic business objectives and on the biotechnology industry. On the basis of this, distinct paradoxes in the funding ecosystem are uncovered, which suggest that the present ecosystem is not well aligned with the interests of these biotechnology firms, the biotechnology industry, and it neglects strategic disease burden needs. To address these, it is recommended that increase in funding and improvement of current financing approaches for early-stage biotechnology companies by more government and big pharmaceutical company participation should take place, because the cost of capital for these two organizations is substantially lower compared to private corporate investors such as venture capitalist. Even partial resolution of these paradoxes will enable further growth in the industry and lead to more innovative therapies for untreatable diseases with large social and economic burdens.

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INTRODUCTION

The development of novel therapeutics for any disease has been a great challenge throughout the history of mankind and it still remains to be an enormous task today. Several life-threating diseases remain yet to have a disease-modifying cure such as cancer and neurodegenerative diseases. Disappointingly, innovative technological advances have not lead to a significant increase in the number of novel therapeutics, while the cost of developing them and their development periods have escalated substantially. This should be a concern to all of us since new therapeutics have vital consequences for the quality and length of our life and for our social well-being.

It is well known that the road from exciting basic research results to a novel drug is challenging, long and expensive. In fact, there is not a straightforward path today in which innovative scientific findings can be translated into drugs. What we actually have is an

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ecosystem, in which distinct players, such as biotechnology and pharmaceutical companies, business angels and venture capitalists, governmental, academic and philanthropic organizations, with different motivations interact together to make the development and commercialization of therapeutics a reality. This system is inefficient and mostly driven by profits.

Given the significant impact of novel therapeutics, it is perhaps surprising that the biotechnology and the pharmaceutical industry evolved to be driven by mostly a profit oriented market system. In general, governments have been funding basic research, which have led to innovative discoveries that are translated by biotechnology and pharmaceutical companies into drugs. Financing of the translational stage is critical, because it bridges the gap between basic findings and commercialization. Main funding contributors to this translational stage are 1) angel and venture capital (VC) investors, 2) pharmaceutical companies, and 3) state, federal and philanthropic funds and grant programs. Although, a variety of organizations fund this translational stage, there is still a *funding gap*, moreover, in the current economic climate the lack of capital in the market place for innovative, early-stage, high-risk biotechnology firms is growing. For example, while the annual research and development budget of the National Institutes of Health in the US and top biotechnology and pharmaceutical companies globally have significantly increased between 2000 and 2010 [$17.8 to $31.2 billion[1] and $26.0 to $49.4 billion (Pharmaceutical Research and Manufacturers of America member companies),[2] respectively], total funding by VC to biotechnology firms have barely increased in the same period ($3.9 to $4.5 billion).[3] Worryingly, VC funding of early-stage firms has dropped substantially in the last 5 years by about 230% calculated from the number of deals done; only ten start-up VC financing deals were reported in 2011.[3]

This study discusses the financial ecosystem available for early-stage biotechnology companies and its impact on the evolution of biotechnology firms with respect to their business objectives and the biotechnology industry. On the basis of this, an increasing funding gap is highlighted between basic research findings and commercialization, and several paradoxes in the ecosystem are uncovered, which suggest that the present ecosystem is not well aligned with the interests of early-stage biotechnology firms and strategic disease burden needs. To address these paradoxes, and to improve the funding ecosystem this study recommends the increase of funding and improvement of current financing approaches for early-stage biotechnology companies by more government and big pharmaceutical company (pharma) participation, because the cost of capital for these organizations is substantially lower compared to private corporate investors such as VC.

THE COST OF CAPITAL FOR BIOTECHNOLOGY AND PHARMACEUTICAL COMPANIES

An economically efficient investment requires undertaking projects, such as research, development and commercialization of a novel drug, with positive net present value (NPV). Most biotechnology businesses take 11 years to reach positive cash flow after the date of their IPO, while some firms have taken over 20 years. The cost of capital in drug development and commercialization projects can be defined by various factors including technical, commercial and financing risks. Technical risk is associated mostly with a high rate of failure of drug candidates.[4] Financial risk is associated with the ability to secure continuous funding.[5] Specifically, when a project requires multiple stages of cumulative investments, it is the risk that current investors take to rely on future investors to fund the project so that they can realize the benefits of their investment. It was estimated that the cost of drug development was $1.32 billion in 2006 by Pharmaceutical Research and Manufacturers of America,[6] while a more conservative publication[7] estimates this to be lower around $200 million in 2000. Furthermore, drug product development cycles are lengthy: research and development times for an FDA approved new drug [new molecular entity (NME)] in general is long and have been on the rise from 12.4 years in 2001 to 14.8 years in 2010.[8] Financing risk is an important factor, because only a few firms are able to raise such large amounts of capital for such long periods to support their drug development efforts.

A case of this is when investors forecast limited availability of funding at the next milestone stage, for example due to "cold market conditions." The lack of future funding, could impact the firm today, because it leads to increased financing risk, which results in less willingness in investors to fund new risky ventures. The opposite is the case in "hot market conditions."[5] Financial risk can have a significant impact on the sustainability of early-stage biotechnology companies, while its less likely to effect cash rich pharmaceutical companies.

Any early-stage biotechnology investor will need to take considerable risks and to hold illiquid investments for a long time. Therefore VCs target internal rates of return (IRR) as high as 50-75% on their investment requiring even larger equity stakes from early stage biotechnology companies. Two recent studies estimated the cost of equity capital for publicly traded firms in the pharmaceutical and biotechnology sectors using data for firms with publicly-traded stock on U.S. exchanges

during 2001-2005, 2006-2008 and 2009 using the capital asset pricing model (CAPM). One study estimated the cost of capital using CAPM to be 9.8% and 14.2%,[9] while the second study found it to be 11.4% and 11.7%,[10] for biotechnology and pharmaceutical firms, respectively. The cost of capital for preclinical stage was estimated to be 17.7%, for clinical stage between 13.3-13.6%, while for marketed drugs 8.7%.[10] Because the cost of capital rises with the increase of risk, the cost of capital for early stage high-risk biotechnology companies are even higher, 21.5% or higher,[11] compared to these estimates.

PROFITABILITY OF PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRY

Historically, the pharmaceutical industry is one of the most profitability industries. According to M. Porter, the ROIC (earnings before interest and taxes divided by invested capital less excess cash) for pharmaceuticals was one of the highest among all industries, about 32% between 1992 and 2006.[12] Moreover, according to CNNMoney, historically and also recently (see for 2007–2008[13,14]), the pharmaceutical industry was one of the leaders in profitability among all industries as derived from Fortune 500 companies, on the basis of return on revenues, return on assets, return on shareholders equity. Although, the pharmaceutical industry has been doing well lately as it has managed to keep profits high, it is struggling to keep growing and to maintain its historically high profitability.

Conversely to the high profitability of pharmaceutical companies, the profitability of the biotechnology industry has been significantly lower. G. P. Pisano performed a comprehensive analysis of the financial performance of publicly held biopharmaceutical companies in existence between 1975 and 2004 to show that while revenues grew exponentially between 1990 and 2004, total operating income stayed close to zero (page 115, Figure 6-2).[15] The economic success has come from a relatively few firms such as Amgen, Genentech, Genzyme, Gilead and Biogen etc. (page 116, Figure 6-3).[15] Most biotechnology businesses take 11 years for positive cash flow after the date of their IPO, while some firms have taken over 20 years. Such long lag times for positive cash flow is an important structural feature of the biotechnology industry. This makes the valuation of early stage biotechnology companies particularly difficult compared to entrepreneurial business in other industries where revenues can be generated much earlier.

On the basis of the above, one could presume that the biotechnology industry has been a failure because it has not generated profits comparable to the pharmaceutical industry. The opposite of this is argued here. Biotechnology has been good at creating intellectual property related to novel therapeutics that have been acquired by big pharmaceuticals or perceived to have high value by financial markets. Therefore a majority of biotechnology value creation, besides revenues from products, also happened through trade-sales or initial public offerings, which may not be reflected in income statements of these firms. Hence, the return on invested capital by biotechnology investors is an alternate way to assess the success or failure of the industry, which is discussed in the following.

THE RATE OF RETURN OF VC INVESTMENTS IN BIOTECHNOLOGY COMPANIES

One way to measure the economic competitiveness of early stage biotechnology companies is based on the rate of return of the invested capital in them. Thus, the rate of return of VC investments in biotechnology companies is analyzed here and compared to VC investments from other industries. The Cambridge Associates LLC U.S. Venture Capital Index[16] (Table 1) shows high deviations in end-to-end pooled net rate of return to the limited partners of VC in general (There is no rate of return provided specifically for biotechnology). While long-term

Table 1: U.S. VC fund (early stage) index summary as of June 30, 2012[16]

Index	1-Year	5-Year	10-Year	15-Year	25-Year
Cambridge A. LLC U.S. VC Index	6.48	4.72	3.95	45.85	21.20
Dow Jones Industrial Average	6.63	2.00	6.01	5.87	9.72
Nasdaq Composite	5.82	2.43	7.21	4.85	8.04
S&P 500	5.45	0.22	5.33	4.77	8.62

(Columns 2-5 show end-to-end pooled return in %, net to limited partners.)

returns for 15-25 years are high (19.38-31.73%), shorter-term returns, less than 10 years, in average are low (2.59-6.72%). The above returns in the short term are similar to returns provided by the stock market, for example, by S&P 500, Nasdaq Composite and Dow Jones Industrial Average, while they are significantly higher for the longer term (4.62-7.24%).

The Cambridge Associates LLC U.S. Venture Capital Index[16] also shows high deviations in pooled gross IRR of companies receiving investment in biotechnology. Although, comparison of the pooled gross IRR of companies receiving investment by specific industries suggests that HealthCare/Biotechnology outperformed VC investments in average[17] it significantly lagged behind hot industries such as Internet-eBusiness and -eCommerce (Figure 1). This is in agreement with a study by Booth and Salehizadeh[17] in which they showed that science start-ups have significantly outperformed other industry sectors in the last decade (pooled gross mean IRR of 15%), conversely to the 1990's when technology investments had superior performance. Booth also showed that venture-backed biotechnology firms who received the most financing do not necessarily deliver the best returns.[18] In fact, superior returns tend to correlate with less equity capital invested, which suggest that smaller and capital efficient firms historically have generated higher returns compared to larger well-funded companies.

A recent study by McKenzie and Janeway[19] found that the relationship between returns to venture capitalist investors is highly influenced by the public equity market. The study found, using a unique proprietary database of the venture capital fund investments made by two major limited partners over the period of 1980-2007, that the single most important aspect that influences most the final IRR of an investment is the time of the exit. Unfavorable exit conditions are associated with a median IRR of 7%, neutral exit conditions result a median IRR of 20%, while favorable exit conditions generated a median IRR of 69% (In fact, exit conditions dominate to such an extent that it seems not to matter if VCs pay "too much" on entry). This suggests that ideally VCs should invest in firms when the market is performing poorly so that they can negotiate the best deals (vice-versa for companies) and exit when market conditions are great. All this implies that financing risk for early-stage companies is lower in periods when there are favorable exit conditions and the opposite when unfavorable exit conditions exist.

Stakeholder Policy Implications and Funding Approaches by Governments

A general belief exists among some policymakers in the United States that VC markets are so vast that entrepreneurs can readily access the capital for early-stage technology companies.[20] Conversely to this belief, there is a lack of capital in the market place for innovative, early-stage, high-risk biotechnology firms. While policymakers' goal is to develop a country's economy, business angles and VCs aim to earn substantial returns for themselves and for their limited partners.

Historically governmental support for funding early-stage biotechnology companies, in general, had been perceived to have limited success. The reason for this is complex and may not come down to simply the quality of the policy or its execution. For example, public schemes that offer tax incentives were exploited for tax avoidance or partisan political control resulting mostly

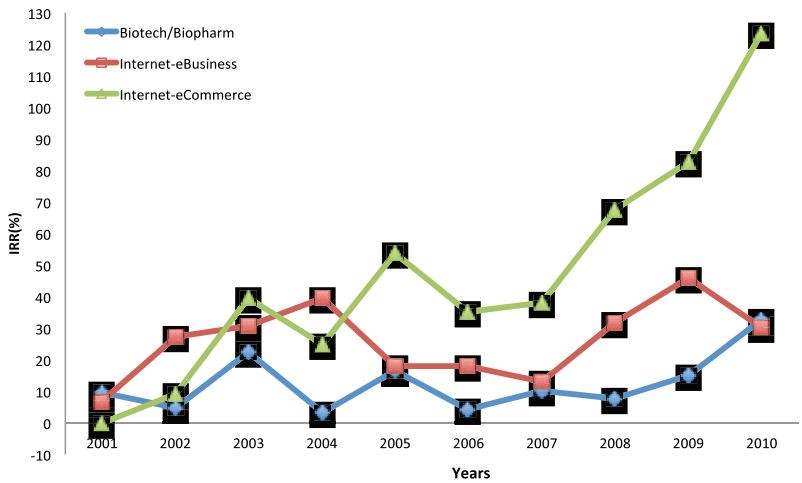

Figure 1: Pooled gross IRR (in %) of companies receiving initial investment between 2001 and 2010 in Biotechnology/Biopharma and Internet Business industries

in unproductive investments.[21,22] Another example is the Small Business Investment Company (SBIC) Program (http://www.sba.gov/INV/) by the U.S. Small Business Administration (SBA) in the United States, which lends funds to private investors such as venture capitalists to augment their funds to invest into small businesses to supplement private investment sources thereby stimulating the economy. Past SBIC program targeting early-stage venture capital has been considered a failure[23] due to structural flaws in the program, for example, profits were distributed before return of capital. Moreover, while SBIC did result in reducing risks for VCs, it provided little advantage for entrepreneurs, for example, it did not lead to the reduction of the high return on investment expected by private investors managing funds from SBIC sources. The SBA has recently revived the SBIC program in a revised structural format.[23]

In the United States, government run funding schemes had long-standing operational issues; nevertheless, most of these programs have matured and are producing positive impact. For example, the Small Business Innovation Research Program (SBIR) in the US is mostly a bottom-up grant program with a budget of up to $2 billion annually, out of which in 2011 the NIH made SBIR grant and contract awards totaling over $609 million. It is designed to fund research and commercialization of research products of small businesses. The SBIR has clearly played an important catalytic role at an early-stage in the technology development cycle and has provided an unprecedented funding bridge between early stage discoveries and the marketplace. The SBIR application and evaluation process can be still improved, for example, it requires a burdensome application process by small businesses, long processing times by the government, and it does limited evaluation of commercialization potential of innovative research solutions.[20]

Governments have created VC-like funds in the past, which work at federal and local levels. For example, federal level funds are the EDBI/Bio*One Capital in Singapore, the Business Development Bank of Canada Venture Capital Fund, the Danish Investment Fund and many others; and local level funds are the Regional Venture Capital Funds in the United Kingdom, the Massachusetts Technology Development Corporation in the United States, Quebec Innovatech Venture Capital Fund in Canada and many others24.[24] Some were closed due to investment decisions made on the basis of political influence or with the lack of relevant technological or business expertise.[25] The management of these funds, however, have improved and new major initiatives, such as the Biomedical Catalyst Fund in the UK, have been linked to governmental science funding agencies.[26] These experiences also resulted in recent funding schemes called hybrid VC funds, in which a government is a special limited partner managed by commercial venture capitalists. Examples of such funds are the Australian Innovation Industry Investment Fund, the German High-tech Gründerfonds and others.[27] These funds can have a variety of profit distribution arrangements that incentivize private VC to participate.[27]

A recent study by National Endowment for Science, Technology and the Arts and British Private Equity and Venture Capital Association investigated the effect of governmental policy and funding schemes on the performance of early-stage firms in the UK. The study found that such funding programs had a clear positive impact on the recipients' performance on the basis of a range of standard accountancy metrics. Specifically, such funding schemes supported the build up of the companies' capabilities and assets leading to future increase in competitiveness and financial performance.[25] The study concluded that hybrid VC funds should be large; systematic approach to policymaking that encourages angel networks and links entrepreneurship and innovation policy has had a positive effect; and that policy focusing on filling narrow funding gaps can be counter-productive. This latter point suggests that a *nonlinear phenomenon* can occur when "noneconomic" investments are made, for example, government expenditures on basic research are made in very early-stage without sufficient attention and resources to the likely investment decisions at later stages of the innovation process.[28]

Paradoxes in the Funding Ecosystem of Early-Stage Biotechnology Firms

Three paradoxes in the funding ecosystem are discussed below, which suggest that the present funding ecosystem is not well aligned with the interests of early-stage biotechnology firms, perhaps the biotechnology industry, and it neglects to consider strategic disease burden needs.

The cost of capital for early-stage biotechnology start-ups is too high, which makes their succeeding even more challenging

The high risks associated with drug development, commercialization, and financing of these activities produce substantial uncertainty in the potential financial success of early-stage biotechnology firms. Therefore, investors of early-stage biotechnology companies such as business angels and venture capitalists demand high IRR on their investment. IRR expectations of these investors, however, may be unreasonably high. For example, venture capitalist aspire for high IRR to satisfy the profit needs

of their limited partners' and their own. Given that limited alternative sources of capital are available for early-stage biotechnology firms, venture capitalists can drive up IRR expectations, perhaps unjustly to biotechnology firms. The high cost of capital for early-stage biotechnology companies, significantly higher compared to cash rich pharmaceutical companies, is a substantial hurdle to overcome, which creates a high barrier of entry and of success. Early-stage biotechnology companies have to compete with pharmaceutical companies, and due to their higher cost of capital they are in significant disadvantage.

It is clear from the data presented herein regarding the IRR of the biotechnology industry that biotechnology investors' IRR expectations are not realistic compared to what the biotechnology industry can deliver (Table 1 and Figure 1 above). Although long-term IRR figures look good, the IRR values for the last 10 years are only acceptable. It is difficult to find a convincing explanation for the difference in long term vs. short-term IRR values. Perhaps this could be due to economic cycles, increase of competition due to fast information exchange, increase in the complexity and costs of clinical trial regulation, etc. On the basis of current data, it is hard to be optimistic about biotechnology becoming again the darling of investors. In contrast to biotechnology, short-term (10 years of less) IRR figures look promising for *hot industries* such as internet businesses. Given current challenging conditions of regulations of clinical trials, capital sources and exits, it is questionable that sufficient number of companies can be as successful as Amgen or Genentech to provide returns that match historic levels.

Most VCs have been focused on finding more efficient ways to operate biotechnology companies, to invest less capital and to exit in shorter periods to maximize returns.[18,29] However, additional goals of the industry that have to do with developing disease modifying therapeutics for untreatable diseases, and thereby saving lives, should also be key elements that drive the industry forward. This is because the likelihood of making substantial returns on this latter example is small due to its high technology risk. Although, this may make sense from an investor's point of view, due to the limited control over research progress, where lots of work and serendipity is a major driver for progress, making "*go* or *no go*" decisions regarding a venture often and early by VCs[18,29] will likely result in most biotechnology firms being shut down after an initial round of funding. Such recipe may be ideal for biotechnology investors to ensure highest returns; however, it does not represent a realistic way forward for the biotechnology industry and for the development of NMEs for incurable diseases. Novel drug discovery research is difficult, most experiments do not work for the first time, and it takes much experimentation and failure to progress projects forward.

Generally, investment practices reward short-term gains while disregarding long-term development of firms and of the biotechnology industry

Current investment practices force biotechnology companies to adopt business models that can be counter-productive for their long-term development. Generally, funding biotechnology companies is similar in process and expectation to funding internet businesses or high-tech start-up. Conversely to these later businesses, the drug discovery product cycle is significantly longer, which limits access to revenues in the short-term. Funding happens in a step-wise fashion in "rounds" and short-term perceived value creation is pursued vs. long-term commercial success. This system may seem to work on the surface, however, it generates high transaction costs due to the need to adapt to different changes. Such maneuvering of biotechnology companies is partially the result of the high IRR expectation of biotechnology investors, who look for short-term returns and neglect long-term growth strategies. The lack of growth in biotechnology VC investments and low IRR of the last decade suggest that such operational mode of biotechnology industry does not lead to past prosperity.

It is clear that the way research and development is done will not change drastically. A detailed recipe for innovation in research of medicine has not been found, and perhaps it will never be. It is well accepted in the industry, however, that it happens most often by hard working small groups of scientists, who are dedicated, creative, risk-taking, free to pursue their interest, and are not afraid to go against *status quo*. Perhaps such ways are natural to us humans and cannot be changed. Therefore, a better way to go would be to accept that current funding practices for biotechnology are out of touch with the natural development process of the industry and change or invent new schemes that can support and fund the natural innovation process and commercialization. Such changes should make the industry more productive, thereby fostering the higher purpose of the industry and also maximize profits.

Profit based investment practices in early-stage biotechnology companies do not consider disease burden needs

Generally, early-stage biotechnology investors fund commercially sound opportunities with almost no regards to the extent of general social need/benefit of the venture. For example, global disease burden is estimated to be the highest for neurological diseases (such as Alzheimer's

and Parkinson's disease), more than twice as much compared to oncology.[30] Nevertheless, biotechnology firms working on neurological disease research and development are less than half as funded by VCs compared to companies with an oncology related diseases[3] focus. The funding practice of the NIH and the pharmaceutical industry are closer in line with disease burden rankings[30] as they fund research and therapeutic development in neurology related diseases the most compared to other disease categories.

The rational for funding early-stage companies focusing on disease areas for which disease modifying drugs have been approved recently makes much sense from private investors' point of view. However, investing money in diseases such as Alzheimer's disease, which are complex and require long and costly clinical trials with little chance of success for a disease modifying therapeutic, does not make much sense for private investors, even though the pay off could be huge. This is because the likelihood of making substantial returns on the latter example is small due to the high technology. Therefore, in the current financial environment, early-stage companies with innovative technologies targeting Alzheimer's and similar type of disease will find few potential backers. Overall, this is leading to a slowdown of the pace of innovation and industrial development of therapeutics for these devastating and costly diseases.

Improvements are needed in investment approaches of early-stage biotechnology firms

On the basis of the existing *funding gap* and the three paradoxes previously described, it is vital that more capital is invested and that investing approaches become more efficient and productive. Below practical suggestions are discussed, which could be useful for improving the funding ecosystem of early-stage biotechnology firms.

More government participation is needed in funding early stage biotechnology companies

Although there is already some participation of governments[26] in supporting early stage biotechnology companies via grants, hybrid VC funds, and different tax incentives, nevertheless, it is necessary for governments to increase their funding even more. There are two fundamental reasons for encouraging more government participation. Firstly, the growth of the industry has an overall positive socio-economic impact. Secondly, the cost of capital for most governments[31] is significantly lower compared to VCs or pharmaceutical firms. In the case when the government is a funder, the general perception should be adopted that investments linked to government funds should have lower IRR expectation compared to private venture capital, and their success should be measured in broader social and economic terms.

One way governments could do more is by setting up flexible for-profit funds connected to governmental or private non-profit science grant agencies.[25] These could behave similarly to VC funds with the difference that industry wide and strategic disease burden needs would drive them as well. In addition, governments should act as limited partners in well-established and successful private VC funds more often, which should be set up for longer periods and with flexibility to ensure that government funds foster the development of business models that are long-term. By funding early-stage biotechnology firms, a government could take partial ownership of some companies and would benefit from their success directly. Profits from such investments could be reinvested in the same sector and thus guarantee funding for next generation of biotechnology companies. Such *evergreen* funding scheme could ensure that funding of the industry is not completely dependent on taxpayer funds. Importantly, funds from governments could be channeled into innovative and novel technologically sound start-ups with a focus on therapies for disease with high economic and social burdens, which are less likely to be supported by private and corporate investors.

Long-term funding schemes are needed to increase IRR of biotechnology companies

It could be beneficial to build in more flexibility in the ending period of VC funds due to high volatility of short-term returns linked to fluctuation of exit conditions in the public markets. If VC have the flexibility to extend the life of their fund for several years then they could attempt to stir away from exiting during bad market conditions. This may be achieved by introducing an option that enables the extension of the life of the fund. During bad market conditions, both venture capitalists and limited partners would be incentivized to postpone the closing date of the fund. In addition, add on funds could be raised in order to supply currently invested firms with more capital to increase the prospects for a better exit. With a descent exit, venture capitalists could end up with a moderately good IRR rather than a low one even after extended investment period if exists happen under good market conditions. This would have a positive overall impact for the funding ecosystem and it may encourage firms to pursue longer-term vs. short-term business strategy. There are several funds out there, which can provide much

flexibility to their companies in regards to exit times. Some of these funds have an evergreen structure, some are mostly family owned while others are derived from institutional profits.

Increase in the role and activity of large pharmaceutical companies is needed

Big pharma could truly be the right investor of early-stage biotechnology companies. It has the technical ability to evaluate whether the science behind a start-up is sound and innovative. It has managed to build up huge cash reserves and its cost of capital is lower compared to private VCs. Although, much of big pharma's cash has been spent on large acquisitions, some of it has also been channeled into corporate VC funds. A benefit for big pharma is that their corporate VC arm can cherry-pick early-stage biotechnology companies of interest, which allows them to pursue high-risk alternative approaches that could be acquired in the future. Interestingly, two recent studies[32,33] provide evidence that corporate VC activity has been effective, which also supports the recommendation of this study that an increase in corporate VC activity is needed. The studies found that biotechnology companies co-funded by corporate VC are more likely compared to other VC supported companies to be successful. (Their measurement of success was to enter into licensing or collaborative deals, median step-up valuation, and be acquired or do an initial public offering.)

This suggests that big pharma should increase their efforts in corporate VC activity by investing even more. One way this could take place is by funding more early-stage biotechnology companies. So far corporate VCs have been funding mostly mid and late-stage biotechnology firms and rarely getting involved in early-stage biotechnology deals.[3] In fact, funding early-stage biotechnology companies should become a priority for them, because big pharma has exceedingly funded basic research activities at several leading universities recently.[34] They may find, indeed, that some of these academic efforts will be fruitful; nevertheless, these will likely mostly provide proof of concept stage findings. Big pharma may not be ready to in-license much of these early-stage projects. Consequently, new start-ups will need to be funded to translate such findings into later-stage and more mature projects. This may enable big pharma to fully take advantage of their recent academic partnerships.

It may also be in big pharma's advantage to engage more with early-stage biotechnology companies. Such partnerships should encourage innovation within big pharma and provide access to novel and alternative therapeutic efforts, which otherwise could not necessarily be develop within a large organization. The challenge with such partnerships is that their formation needs to be driven by researchers at big pharma, only who have the ability to recognize the potential of specific early-stage innovative scientific findings. Therefore, big pharma needs to encourage their scientist to pursue such efforts, and to create practical processes within their organization that can enable these partnerships.

CONCLUSION

The paradoxes in the financial ecosystem of early stage biotechnology companies, outlined in this study, are the result of the sum of following contradictions. Firstly, the cost of capital for early-stage biotechnology firms is too high, which creates a high barrier of success and makes it challenging for early-stage biotechnology firms to compete with big pharma. Secondly, in general, investment practices reward short-term gains while they do not necessarily support long-term development of firms and of the biotechnology industry. Thirdly, the social impact of bringing novel drugs to market opposes the profit based investment approach that fundamentally drives early-stage biotechnology firms forward; no consideration is given to global strategic therapeutic needs due to disease burden and lack of disease modifying drugs. Perhaps, even partial resolution of these paradoxes will enable further growth in the industry and lead to more innovative therapies for untreatable diseases with large social and economic burdens. In this regards, this study recommends that it is necessary to increase funding and improve current financing approaches for early-stage biotechnology companies. It is proposed that improvements in funding approaches should be focused on more government and big pharma participation, because the cost of capital for these two types of organizations is substantially lower compared to VC. More sources of funding for early stage biotechnology firms and more flexibility in investment vehicles for investors should reduce overall risks, stabilize profits, support the growth in the industry, and insure that novel and innovative therapies can be commercialized. A recent development in the funding ecosystem of early stage biotechnology firms is the advancement of the legal framework of crowd funding in the U.S. Crowed funding has the chance to reform and revolutionize the way certain therapeutic efforts and ventures receive financial support. It is yet to be seen how and when this is implemented industry wide.

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Original Article

Developing cell therapies: Enabling cost prediction by value systems modeling to manage developmental risk

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ABSTRACT

This work quantifies the highest risk activities and interdependencies in cell therapy new product development (NPD). A simulation model based upon an activates based and information driven approach of the Design Structure Matrix (DSM), using Latin Hypercube sampling methods with discrete event simulation evaluated the interdependencies between critical development tasks. Input data was collected from quarterly financial reports of cell therapy developers and developmental milestones as reported in company press releases and publications. Successfully planning and managing development processes is problematic in an emerging industry lacking precedents and standardised technology platforms. Methods of understanding and reducing developmental uncertainty and risk are needed to aid resourcing decisions. A particular requirement is to understand the impact of process and clinical development, in this highly regulated sector.

Results from the model quantify the probability and impact of process iterations and failures that impact cost and duration of cell therapy NPD. High impact areas quantified are the interdependence of Phase 1 clinical trials and investment, the scaling of the manufacturing process from Phase 1 to Phase 2 and Phase 2 to Phase 3. The model also allows for the calculation of the probability of NPD success for given resource levels, time constraints and market conditions. An application comparing alternative regulatory approaches indicates that the current favoured strategy of targeting an orphan indication gives little benefit for the tested clinic al indication because of reduced clinical trial recruitment rate. While specifically developed for cell therapy NPD this modelling approach has potential application across the wider biotechnology industry.

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INTRODUCTION

The field of cell therapy is rapidly developing, and many clinical trials have been initiated exploring the use of stem/progenitor cells in the treatment of degenerative diseases and cancer and for the repair of damaged or lost tissues. Cell therapies represent an emerging and rapidly developing industry with a unique opportunity to contribute to both health and economic wealth. As the industry has developed from experimental research to commercial growth over 500 businesses have been established to push cell therapies through to clinical development adoption.[1] In spite of this only a small number of cell therapy products have made it to market with the vast majority of companies still engaged in preclinical and early clinical development. The ability of companies to transition their therapies to market will depend on a successful ability to manage risk and cost while creating

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value for all the stakeholders involved in the health-care marketplace. A key issue in boosting commercial success rates involves creating the tools to develop an evidence based approach to picking commercial winners.

This paper is focused on providing analytical and simulation models that assist in the prediction of two of the main drivers of cell therapy product development, cost and risk. We present a value system model that has been assembled to predict the development cost and lead time associated with the clinical and process development activities involved in moving from preclinical testing to completion of Phase III clinical trials.

Cell therapies risk management

Risks to the development and market adoption of cell therapies depend on many risk factors. A common approach to risk assessment and management is to understand the probability of the risk occurring and the impact of the harm caused by its manifestation.[2] A risk factor or hazard is defined as a potential source of harm.[3] Developing cell therapies face two types of risk factor;

1. **Product risk factors:** risks that can harm the patient — including the type of stem cells used, their source, the level of manipulation applied to them and method of use and delivery mechanism. Product risks inform the basis of the regulatory framework that cell therapies must be developed and delivered under[4] as has been discussed in the literature.[5]
2. **Enterprise risk factors:** risks that can harm the introduction of the product and the business that develops it — include financial risks such as cost overruns, market risk, technical risks associated with developing a manufacturing platform and temporal risks associated with completing product development. Products must also be brought to market in a timescale that investors and developers can tolerate.

A thorough evaluation of enterprise and product risk factors, along with their consequences, at the start and during the development of a stem cell based therapy may help to determine the extent and focus of the product development and safety evaluation plans. The differing nature of the two classes of risk defines the amount of effort developers with limited resource will allocate to their management or reduction. The regulatory system cell therapies are developed within rightly dictates that clinical evidence surrounding safety and efficacy is collected by pre-clinical and clinical trials. In addition regulatory authorities demand stringent validation of technologies and processes used in the production of all therapeutic products clinical use.[6] Therapies seeking adoption in the US healthcare market are regulated by the US Food and Drug Administration which dictates when a developer must transition from non-GMP (Good Manufacturing Practise) environments to GMP-validated production during clinical development. Because a phase 1 clinical trial initially introduces an investigational new drug into human subjects, appropriate GMP help ensure subject safety.[7]

How developers choose to conduct these product risk management processes will ultimately influence the enterprise risk however the regulatory system does not account of effects on resource caused by the system. Regulators cannot take account of the difficulty in developing a product over the risks that such a product may pose to a patient population or the cost of developing medicinal products.

The cell therapy value system

It is necessary to include the requirements of developers, investors, healthcare providers and patients along with regulators to gain a true understanding of the enterprise risk associated with cell therapies. These groups represent the actors within the cell therapy value system. We define a value system as the representation of the various activities, actors and resources that are involved in delivering goods (and services) to a market.[8] Resources employed include time, capital, infrastructure and personnel. Actors include, but are not limited to, developers, regulatory authorities, investors, healthcare providers and patients. An overview of the whole value system can be treated as a level of analysis below innovation systems, which often view innovation through the lens of a national, regional or industrial level innovation system[9,10] as it is centred on individual product markets. How a developing therapy navigates this value system influences when costs are committed into a product (for example when a manufacturing facility is built) and relates cost to business development and value creation. As therapies progress through the value system they will ideally increase in value to all stakeholders, including patients, investors and healthcare systems while having a decreasing level of enterprise and product risk.

One method of adding value to any early stage technology based enterprise is risk reduction by either reducing product or enterprise risk by providing more information relating to risk factors to the value system actors.[11] As outlined above product risk may be reduced by accomplishing a significant process development step[12] or moving through preclinical and clinical trials to demonstrate product safety, utility and efficacy.

Enterprise risk may be reduced by the developer proving more evidence surrounding return on investment (ROI) to an investor or shareholder. The extent of the increase in value is sensitive to the amount of information that will accrue (or uncertainty that will be reduced) during development. While the regulatory and scientific communities have provided extensive research and requirements surrounding product risk reduction strategies there is a limited amount of research concentrated on reduction of cell therapy enterprise risk.

This work focuses on the reduction of enterprise risk by prediction of the value cost and price associated with developing cell therapies. This is driven by the need to understand the economics of a product early in the development process. Several recent studies have drawn attention to the increasing need for of early-stage economic modelling for medical products while acknowledging the uncertainties and difficulties intrinsic in such a enterprise.[13,14]

The timely application of economic evaluation in the product development process can provide the manufacturer with a significant amount of useful information, not just on the future economic viability of their new product.[15,16] Traditionally, new technologies have been evaluated at market launch, as a one off exercise by decision makers to decide whether to purchase or invest in a new technology. Developers and investors need to be able to identify candidate therapies with the best clinical and commercial potential and communicate their value to potential investors and the healthcare system ideally before significant investment decisions. As the health services continue to develop robust health economic appraisal methods, developers have started to look at their technologies in the same critical way as healthcare decision makers in order to make better investment decisions.[14] Some proposals envisage ongoing health economic assessment as an integral part of the development cycle.[13]

As the final commercial success of a proposed product will be largely determined by its rate of adoption which is informed by its cost-effectiveness, it is sensible to conduct such an analysis at the outset. While an early assessment may be limited in the accuracy of information it can provide regarding exact cost or price the analysis will help guide developmental targets in terms of product development timeframes, cost and clinical effectiveness goals. The predicament when it comes to the assessment of any innovative medical technology in early stage development is that the available evidence of clinical effectiveness is still lacking or only available to a very limited extent.

By conducting predictive modelling of price and cost at early stage development, when final effectiveness is unknown, and at key stages throughout product development, predictions about the probability of the product being sufficiently affordable can be established and could prove significant in persuading healthcare systems, patients and investors of its value.[17]

To calculate the potential value of a therapy to investors or healthcare systems, three key numbers must be considered; Value, Cost and Price. The difference between cost and price will dictate the potential return on investment by a therapy, i.e. the value to an investor who must judge this against the risk in developing a new cell therapy.

A method has already been presented for scoping the gross commercial opportunity (or "headroom") by establishing a simple price ceiling available to a developer based on an estimate of clinical effectiveness within a cost–utility model.[18] The aim of this work was to provide a quick method for rapid decision-making that would support, for instance, the selection of promising concepts from a larger pool of options. The drawbacks to the "headroom" method are that it is only applicable to healthcare systems where cost effectiveness is measured using the QUALY (Quality adjusted life years) model and does not provide a method to estimate the potential cost of a cell therapy or medical device. The headroom method can be viewed as price appraisal method. What is needed is a range of companion models for the supply side issues surrounding cost and risk.

Linking cell therapy development and cost

The total cost of developing, marketing, manufacturing and delivering a cell therapy to a patient will dictate the final Cost of Goods Supplied (COGS). At the early stages of technology development — when sometimes even the nature of the product is unknown — realistic estimates of cost are difficult. Significant technical and financial uncertainty surrounding the product, its manufacturing system and its supply and business model exists. Product and manufacturing system based cost drivers can be identified as likely to be lowered either through technology improvements such as automation or through economies of scale. Understanding all cost drivers allows developers to identify areas for savings. However unanticipated costs of developing cell therapies have the potential to drive the development cost substantially higher than forecast.

VALUE SYSTEMS MODELING FOR CELL THERAPY

For cell therapies, like all medicinal products, the path to a marketed product involves a long and exhaustive journey through basic research, discovery of a therapeutically effective cell type, preclinical development tests,

process development, increasingly complicated clinical trials and regulatory approval. Several years and significant financial investment is needed to undertake this process.

As a result critical decisions are often made with imperfect information. This can result in the need to redevelop or "rework" parts of the cell therapy development processes causing an iteration of enterprise activity. An example of this would be the need to redo some non-clinical and clinical testing following a change in manufacturing system, process or input. Iteration is a fundamental characteristic of complex and highly regulated product development projects.[19] However, cost predication techniques that rely on past experience or heuristics have very limited capabilities in coping with iterations. The majority of process modelling literature and software is oriented toward production or business processes, where the goal is to repeat a chain-like process without interwoven iterative loops. Shortcomings of standard flowchart presentations of development processes in clearly representing many feedbacks are seldom exposed. However, much of the waste and inefficiency in iterative development processes stems from these interactions and feedbacks — i.e., having to repeat activities because of changes in the information and/or assumptions upon which they were initially executed, or an increase or change in the regulatory environment.

A fruitful way to increase understanding of a process is to look at its parts and their relationships. Decomposition is a possible approach to addressing system complexity — it is generally possible to make more accurate estimates about simpler elements within the system. However, it is generally more difficult to make accurate estimates of the effects on the overall system of relationships between simpler elements. Similarly "bottom up" production orientated cost models often rely on activity based costing that requires a large amount of historic or product specific information to be availably a characteristic that limits its usefulness in maturing industries such as cell therapy. The relationships among elements are an important characteristic that differentiates a system from a mere grouping of elements. As a value system, the development of cell therapies products are defined not only by their decomposition into activities but also by how they interact together.[20,21]

In practice, most product development definitions and models account for a minimal amount of information about the element relationships or interfaces. A single input and output for each activity is often considered sufficient. However, especially in the early stages of product development, people and the activities they execute tend to provide and require a great deal of information to and from each other.[22] A large number of activity interfaces are necessary to document the full range of information flow and dependency. Most process models do not attempt to elicit and represent the actual information flow, even though it is a major driver of product development competence and predictability.[23]

Steward[24] developed the design structure matrix (DSM) method for such purposes. The DSM provides a compact representation of a complex system by showing information dependencies in a square matrix. The DSM method is based on the earlier work in large-scale system decomposition. Eppinger *et al.*[19] extended Steward's work by explicitly modelling information coupling among tasks and investigating different strategies for managing task procedures. Some researchers have used the DSM framework to design iteration modelling to extend its information-based structuring analysis to schedule analysis.[20] Work by Browning[11] shows its increasing use in various application areas including product development, project planning, project management, systems engineering, and organization design in other highly regulated industries such as aerospace.

A design structure matrix (DSM) can be used to represent a process such as product development. The DSM shows activities and interfaces in a concise format. A DSM is a square matrix in which a cell on the diagonal represents each activity. Activity names are usually given to the left of the matrix. A mark in an off-diagonal cell indicates an activity interface. For each activity, its row shows its inputs and its column shows its outputs. When activities are listed in temporal order, super-diagonal marks denote a feeding of deliverables forward in the process, from upstream activities to downstream activities, while sub-diagonal marks indicate feedback. The DSM provides a simple way to visualize the structure of an activity network and to compare alternative process architectures.

We present in this paper the application of a DSM-based simulation model, building on work by Cho et al.[25] that illustrates how model-based design process analysis may be used as an early stage assessment tool applicable to development cost prediction for a cell therapy product.

Model constructs

We follow the information-based view[26] of design projects in which a task is the information-processing unit that receives information from other tasks and transforms it into new information to be passed on to subsequent tasks. The information exchanged between tasks includes both tangible and intangible types such as materials, documentation, learning, etc. Model inputs characterize behaviours of individual tasks and interactions among the tasks from a schedule perspective.

The duration of a task is used to model uncertainty and complexity within the domain of the task. Precedence and resource constraints determine the start times of tasks. Iterations are modelled to depict the patterns of workflows caused by dynamic information exchanges among the tasks.

In order to build such a rich process model, we employ numerical simulation methods. Simulation techniques are effective for the two analytical purposes: sampling of task duration from the known distribution function and modeming of the dynamic progress of a project. We employ the parallel discrete-event simulation method for modelling the progress of a project as a dynamic system, where system variables evolve over time. Note that modelling non-Markovian transitions is impossible to represent as a Markov chain.

1. Task durations

A variety of distributions have been used to represent stochasticity of task duration. This model chooses the triangular probability distribution to represent task durations since this distribution is simple and familiar to many project managers.[27] For each task, the model receives three estimated values for the expected duration of one-time execution — optimistic, most likely and pessimistic. These values represent the duration of a task from the start to the end of its continuous work, even though the task may later be repeated after its initial completion. Remaining duration decreases over time as the model simulates the project's progress.

The model uses the Latin Hypercube Sampling (LHS) method[28] to incorporate the uncertainty of the expected duration of each task based on the three estimated durations. The LHS method divides the range between them into n strata of equal marginal probability, where n is the number of random values for the expected duration representing the triangular probability distribution function. Then, it randomly samples once from each stratum and sequences the sampled values randomly.

2. Precedence constraints

From a schedule perspective, we consider two types of information flow in a task: 1) information flow at the beginning or at the end of the task and 2) information flow in the middle of the task. Accordingly, we define two types of information flow between two tasks. The first type represents the case that the task requires final output information from the upstream task to begin its work. The second type represents the case that the task uses final output information from the upstream task in the middle of its process or begins with preliminary information but also receives a final update from the upstream task.

The first type of information flow is translated to a "finish-to-start" precedence constraint between two tasks, while the second type is translated to a "finish-to-start-plus-lead" constraint. With lead time, two tasks are overlapped so that a successor task starts before a predecessor task is finished.

3. Resource constraints

The model assumes that there exists a fixed, renewable resource pool throughout the entire project duration. It consists of specialized resources and/or resource groups of which constituents exhibit the same functional performance. Each task has its own resource requirement which is assumed to be constant over the entire period the task is processed. The resource requirement for the costing model is represented as a "cash-burn" associated with each specific activity.

4. Iteration

Iteration is defined as the repetition of tasks to improve an evolving development process. It is generally accepted that iteration improves the quality of a product in a design project while increasing development time. Managers must control the project to address this time-quality tradeoff.[15] In this paper, iteration is the rework of a task caused by the execution of other tasks. This definition excludes any repetitive work within a single task's execution (that being considered within the variance in the task's duration contained within the task distribution function). This includes all planned and unplanned iterations that can be modelled probabilistically. Some unplanned iterations cannot be considered because they result in structural changes to the project. For example, a major project failure or addition of different activities imposed by the regulator would involve re-structuring the entire process, not simply reworking the established tasks.

An event is defined as the completion of an active task instead of any information transfer. Thus, when any active task in the current state is completed, the model makes a transition to the next state. The duration of state is defined as the minimum remaining duration of active tasks in the state. Before making a transition to the next state, the model subtracts the duration of the current state from the remaining durations of all active tasks. If all the remaining durations of tasks are zero (the termination condition), one simulation run is complete and the lead time is calculated as the sum of all the state durations. The cumulative cost of the completion of all tasks at the end of the simulation run is calculated by the sum of all the products of individual task

duration and cash burn level. After all simulation runs are complete, the probability distribution of lead time and cost can be constructed.

CASE STUDIES OF CELL THERAPY COMPANY DEVELOPME0NT

Creation of the value systems model required additional information surrounding development costs and timeframes that could not be extracted from the literature. These were needed to provide the initial triangular probability function outlined above and define a cell therapy new product development process to model. Case studies of four cell therapy companies were compiled by recording their historic stock values and outstanding share levels. Company newsflow in the form of press releases, annual reports and analyst coverage were examined to determine key points in the product development process and company development. Instances of financing by licensing agreements, stock offerings and private investment were recorded and examined to determine the strategies adopted by cell therapy companies in financing development and value creation activities. In order to assess the commercial valuation and financial records of these organisations it was necessary to confine the companies studied to those listed on a US stock exchange. This allowed for access to publically available financial information filled with the Unites States Securities and Exchange Commission (SEC).

Company value was measured using the market capitalization of each organisation. Market capitalization (market cap) is a measurement of size of a business enterprise and is equal to the share price times the number of shares outstanding of a publicly traded company. As owning stock represents ownership of the company, including all its equity, market capitalization represents company's net worth.

This value was plotted alongside historic market capitalisation to determine if they had influence on the publically perceived value of each company. This study focused on four companies: Two developing allogeneic therapies and two developing autologous treatments. All are using cell types or products that can be targeted against multiple indications. All companies selected where using adult derived stem cells. This remove any influence US public policy on embryonic stem cell research has on the study.

A cross-case analysis was performed to search for patterns and themes that cut across the individual cases. Results revealed large amounts of NPD rework or iterative development undertaken within the companies studied. A distinctive feature of the cell therapy NPD process is the importance of adherence to regulatory frameworks that dictate the order of clinical and process development milestones. As a result any rework or iterations of tasks that place within tasks during NPD potentially required the rework of tasks both preceding and subsequent to the task that causes the iteration.

Results from the case studies allowed collection of data for development programs surrounding both "Orphan" and "Non-orphan" cell therapies. Orphan therapies refer to therapies with a much narrower market segment resulting in lower numbers of patients recruited to clinical trial activities and possibly higher market prices if the target indication has significant unmet clinical need.

APPLICATION OF VALUE SYSTEMS MODEL TO CELL THERAPY CASE STUDY

The results of the case studies allowed construction of a candidate new product development process for cell therapies (Figure 1). The process has eight tasks, seven feed forward dependencies and thirteen feedback dependencies. This process has been illustrated using input data from both Orphan and Non-Orphan cell therapy development case studies. The structuring of the tasks was directed by rework loops and iteration observed in

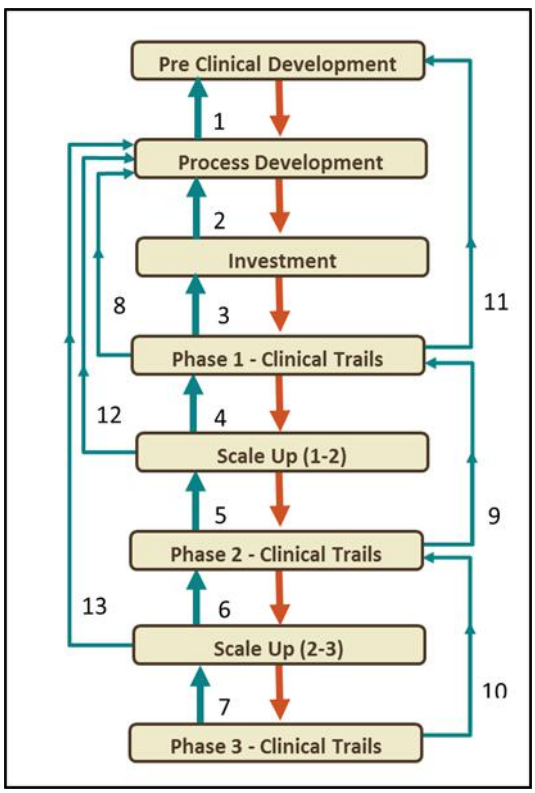

Figure 1: Model structure developed from case studies

the companies studied. The case studies highlighted the feed-forward and feedback dependencies and iteration loops experienced by cell therapy companies.

The case studies also provide triangular probability distributions of the duration of the NPD tasks and monthly "cash burn" levels associated with each development task (See Figure 3), allowing for estimation of development cost within the model. The triangular distributions of duration and cash burn levels were developed from financial reports of the four companies and normalised for company headcount and patient recruitment levels in clinical trials. The rework probabilities and impact factors are shown in Figure 2. The inputted task durations and cash burn levels differed for the Orphan and Non-orphan development pathways. The number of simulation runs was kept high due to the large probability distributions for time and cost — to ensure that the sampled task durations closely follow the inputted triangular distributions.

As with Soo-Haeng Cho, 2005[25] the computer program was written in Visual Basic and subsequently added into a Microsoft Excel 2011 spreadsheet which simplifies model input and control and is used to display analysis results. Extensive numerical experimentation was undertaken to test the simulation program and validate the initial results. Small scale test scenarios were run on individual simulation runs to validate the model code. The input data collected from the case study work outlines above was inputted and ran over 10,000 simulation runs.

RESULTS — APPLICATION OF VALUE SYSTEMS MODELLING TO CELL THERAPY CASE STUDY

The 10,000 model runs for each scenario, orphan and non-orphan produced a frequency distribution of both cost and time required to complete the NPD process. This allow a cumulate probability curve to be drawn that marks the probability of the process completing within a given duration or cost. For a desired probability of completing the NPD process this allows a cost or duration to be generated as seen in Figure 4.

Dependancies

Name		1	2	3	4	5	6	7	8
Pre-clinical `	1		X						
Process Development	2	X		X					
Investment	3		X		X				
Phase 1	4	X	X	X		X			
Scale-up (1-2)	5		X		X		X		
Phase 2	6				X	X		X	
Scale Up (2-3)	7		X				X		X
Phase 3	8						X	X	

Rework Proabilities

Name		1	2	3	4	5	6	7	8
Pre-clinical `	1		0.5						
Process Development	2	0.1		0.9					
Investment	3		0.1		1				
Phase 1	4	0.1	0.1	0.1		1			
Scale-up (1-2)	5		0.1		0.1		1		
Phase 2	6				0.1	0.1		1	
Scale Up (2-3)	7		0.1				0.1		1
Phase 3	8						0.1	0.1	

Rework Impacts

Name		1	2	3	4	5	6	7	8
Pre-clinical `	1		0.5						
Process Development	2	0.5		0.9					
Investment	3		0.5		0.9				
Phase 1	4	0.5	0.5	0.5		0.9			
Scale-up (1-2)	5		0.5		0.5		0.9		
Phase 2	6				0.5	0.5		0.9	
Scale Up (2-3)	7		0.5				0.5		0.9
Phase 3	8						0.5	0.5	

Figure 2: Design structure matrix, rework probability matrix and rework impact matrix for cell therapy new product development process

Input Data - Non-Orphan

	Name	Durations			Learn	$k/Month
		Min	Likely	Max		
1	Pre-clinical `	12	16	24	0.3	428.2
2	Process Development	10	16	20	0.5	440.7
3	Investment	1	3	6	0.9	333.2
4	Phase 1	8	10	12	0.9	578.7
5	Scale-up (1-2)	2	3	6	0.5	618.7
6	Phase 2	9	10	12	0.5	784.3
7	Scale Up (2-3)	1	5	9	0.5	708.3
8	Phase 3	10	24	38	1	1520.7

Input Data - Orphan

	Name	Durations			Learn	$k/Month
		Min	Likely	Max		
1	Pre-clinical `	12	16	24	0.3	435.7
2	Process Development	12	16	24	0.5	398.7
3	Investment	1	3	6	0.9	295.6
4	Phase 1	8	10	12	0.9	458.6
5	Scale-up (1-2)	1	3	6	0.5	618.7
6	Phase 2	18	20	22	0.5	641.3
7	Scale Up (2-3)	1	5	9	0.5	708.3
8	Phase 3	12	24	36	1	1208.3

Figure 3: Triangle probability function and cash burn rates for cell therapy new product development model

	Probability of success	20%	50%	80%	99%
Non-Orphan	Duration	122 Months	155 Months	204 Months	351 Months
	Cost	$146.4M	$176.6M	$227.5M	$365M
Orphan	Duration	114 Months	143 Months	191 Months	338 Months
	Cost	$128.0M	$157.6M	$203.8.5M	$319M
	Δ Duration	8 Months	12 Months	13 Months	13 Months
	Δ Cost	$18.4M	$19M	$27.3M	$46M

Figure 4: The probability of completing the NPD process "success" is expressed against cumulative cost and duration for Acute Myocardial Infarction when developed under orphan and non-orphan processes

The frequency distributions in Figures 5–8 illustrate the frequency distribution of completed simulation runs and the results and duration and costs for each process. Figure 6 summarises the expected costs and durations from the accompanying cumulative probability curves. These results illustrate the leas time (duration) and cost incurred in taking a product from start of pre-clinical research to completion of Phase III clinical trials for a given probability.

This level of investment and duration — while significant — aligns with the current timescales and investment levels seen in the cell therapy community and current expenditure recorded in the input case studies. The probability distribution of the lead time and cost shown in Figures 4 and Figure 5 is skewed to the right because the lead time and cash burn becomes larger as more iteration loops occur and probabilistic sampling will lead to a small number of scenarios with multiple cases of large iteration loops.

Due to the subjective nature of interpreting the rework and impact probabilities associated with the cell therapy case studies and transferring these into the

model framework additional work was undertaken to assess the impact of changing the rework probability on overall duration. Rework probability was varied for each of the thirteen feedback loops from 10% to 70%.

CONCLUSION

There are two key conclusions of this paper.

1. The model presented here should be developed to form part of a larger structured framework that aids in the segregation and estimation of COGS and price for cell therapies early in the development cycle. To develop a comprehensive understanding of the factors that impact cost of goods supplied (COGS) for cell therapies a developer must understand how cost is influences by the entire value system surrounding a cell therapy. Use of the developed framework simulation model can guide this process. Overall, the model provides a framework in which to examine the impacts of a variety of effects on process cost, duration, and risk—yielding several important decision making capabilities. Plus, the basic model is extensible toward providing additional realism, analyses, and insights. Organizations developing new products will benefit especially from being able to illustrate to investors that their cell therapy product development process has an acceptable or at least quantified level of risk.
2. The value systems model accounts for a number of PD process characteristics, including interdependency, iteration, uncertain activity cost and duration, rework probability and impact. The model is used to explore the effects of varying the process risk distribution. This highlights that securing early stage investment is crucial for developing cell therapy companies. It also highlights how critical process development (for the product) is as rework of process development requires rework of clinical trials — with the associated duration and cost penalty. These critical risk points are unlikely to change due to the structure of the cell therapy NPD being dictated by regulatory requirements. The level of potential cost gains is also highlighted in the analytical model presented at the end of the paper and highlights how early decision

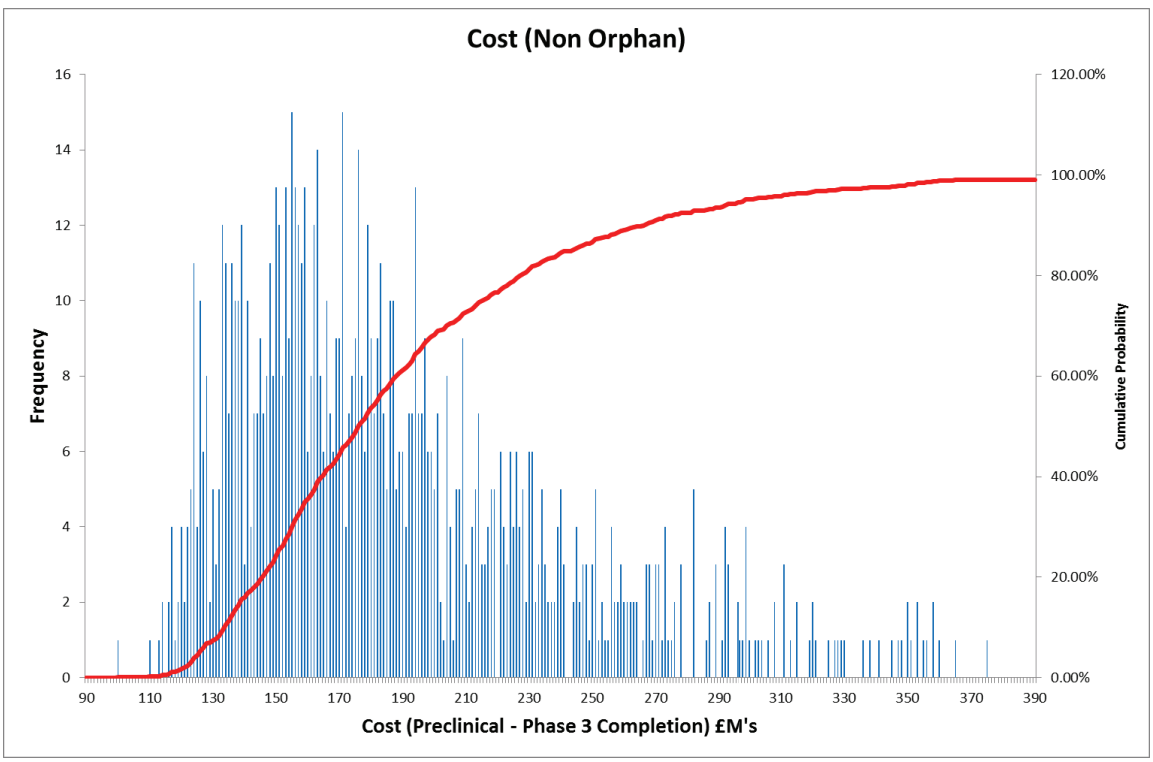

Figure 5: Modelled frequency distribution and cumulative probability curve of development cost for a NPD process for Acute Myocardial Infarction when developed as a non-orphan indication

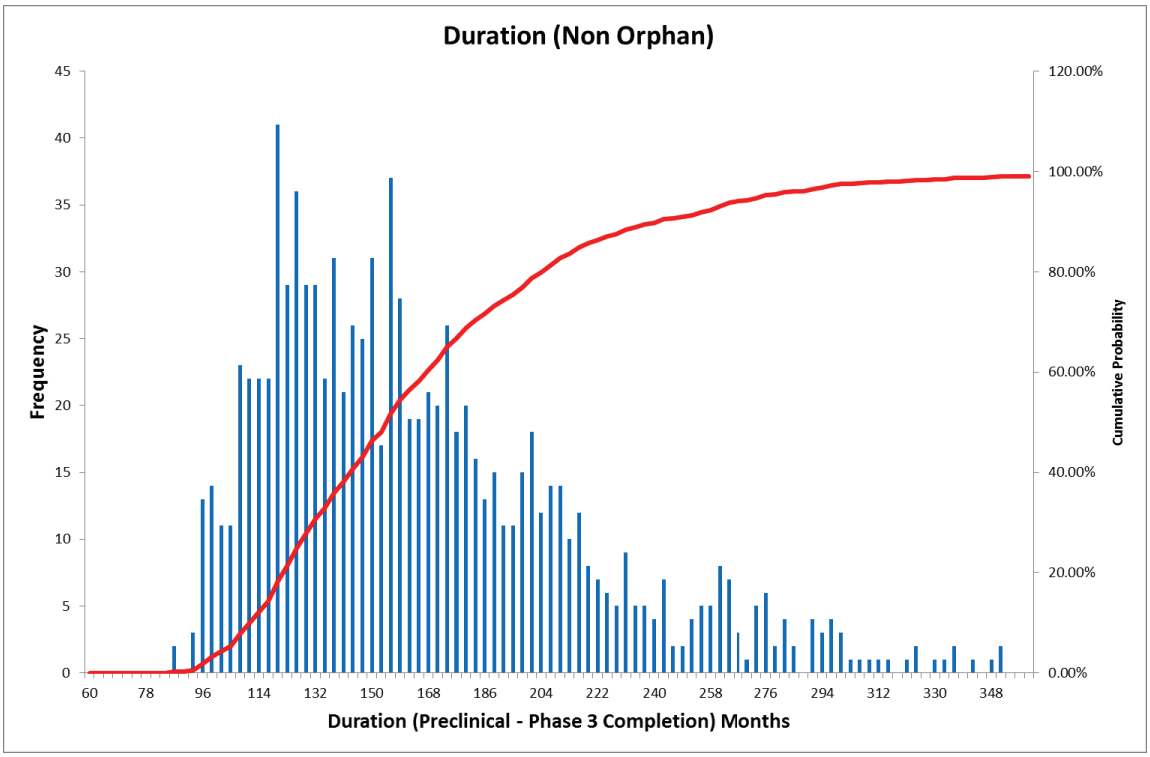

Figure 6: Modelled frequency distribution and cumulative probability curve of development duration for a NPD process for Acute Myocardial Infarction when developed as a non-orphan indication

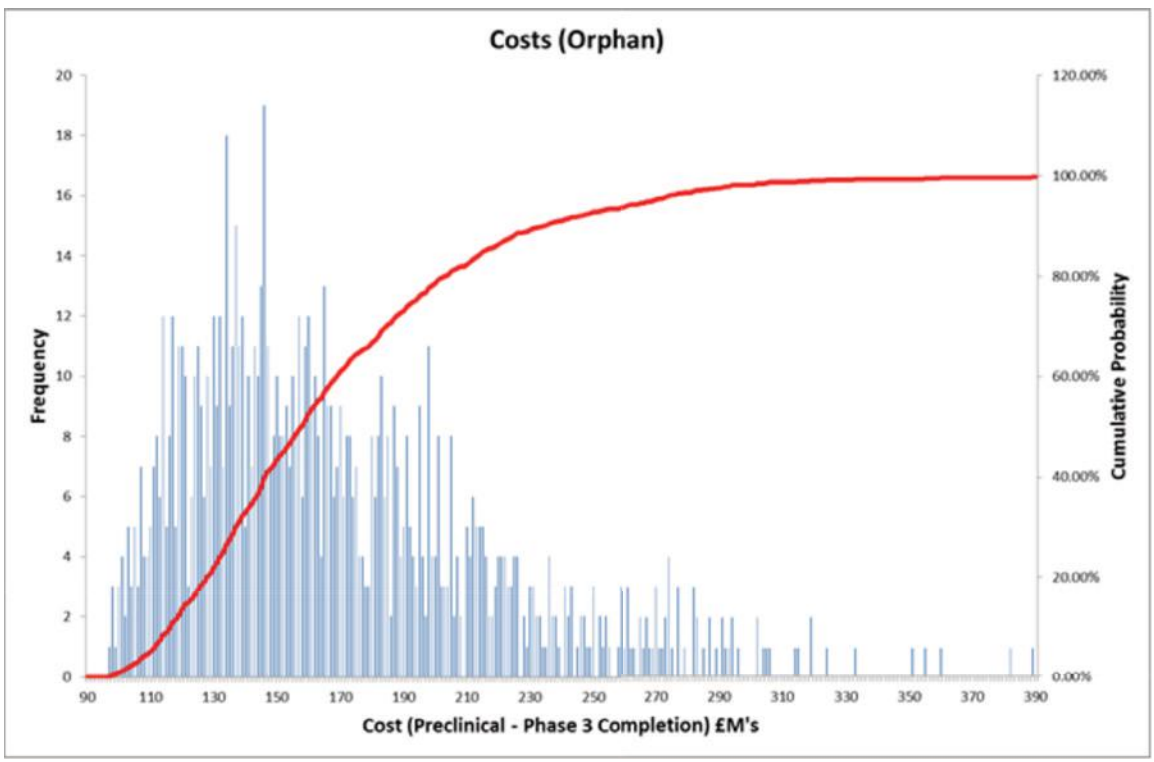

Figure 7: Modelled frequency distribution and cumulative probability curve of development cost for a NPD process for Acute Myocardial Infarction when developed as an orphan indication

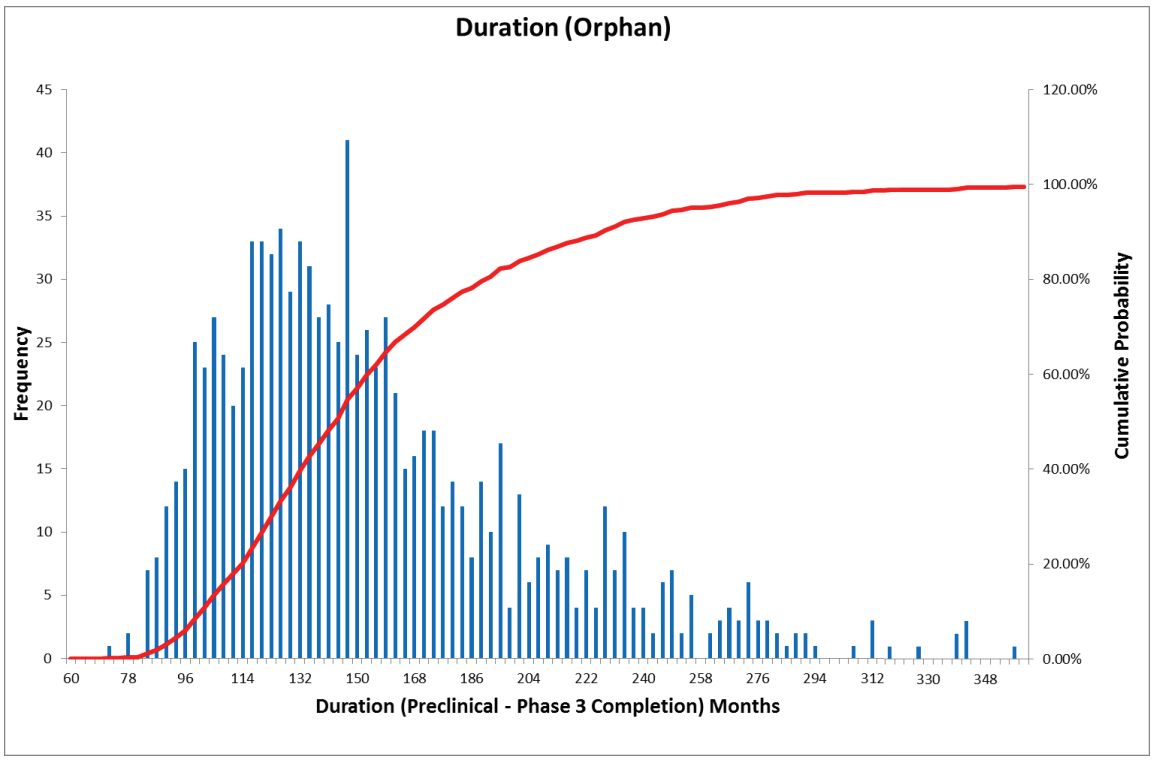

Figure 8: Modelled frequency distribution and cumulative probability curve of development duration for a NPD process for Acute Myocardial Infarction when developed as an orphan indication

support tools can highlight areas for high cost saving.

The simulation model provides a tool to assist informed discussion and projection of development task cost and duration including concurrency, iteration and rework, and can take account of learning. Results of the use of the simulation program can be used to compare the relative merits of alternative development and manufacturing strategies and the associated impacts on time to market, cash burn and return on investment. Current limitations of the value system model include reliance on case study input data and a limited resolution view of the development process which limits the information of specific risks that can be highlighted.

The DSM approach discussed in this paper represents an activity based view of the development process. The activities relate to each other as shown in Figure 1. This architecture has a large influence on the appropriate structure of the product development organization as each activity will require different types and levels of organisational resource since organizational elements are typically assigned to develop various product components. This established development architecture can constrain the consideration of alternative product development strategies. The development architecture and product development strategy relationship can affect an enterprise in several dimensions. Better understanding the relationship between product architectures and organization structures is a promising area for further research which may highlight more effect methods of brining cell therapies to market as the industry develops. DSMs will prove helpful in comparing and contrasting development architecture and product development strategy configurations.

The structure of a cell therapy product offering — including manufacturing considerations, supply chain constraints, regulatory approval route — affects how a development process can and should be configured. That is, the product offering structure determines the process (activity) structure. If separate design activities develop separate but coupled aspects of this offering, as in cell therapy, then the need for these activities to exchange information should be noted when designing the design process. It would be interesting to contrast how established NPD processes deal with novel product development when contrasted with new development processes that may take a change in regulatory environment to approve. Again, the DSM can be a useful tool in such research provided adequate input information is available.

Future work will move to collect a higher resolution view of the activities within each development step and

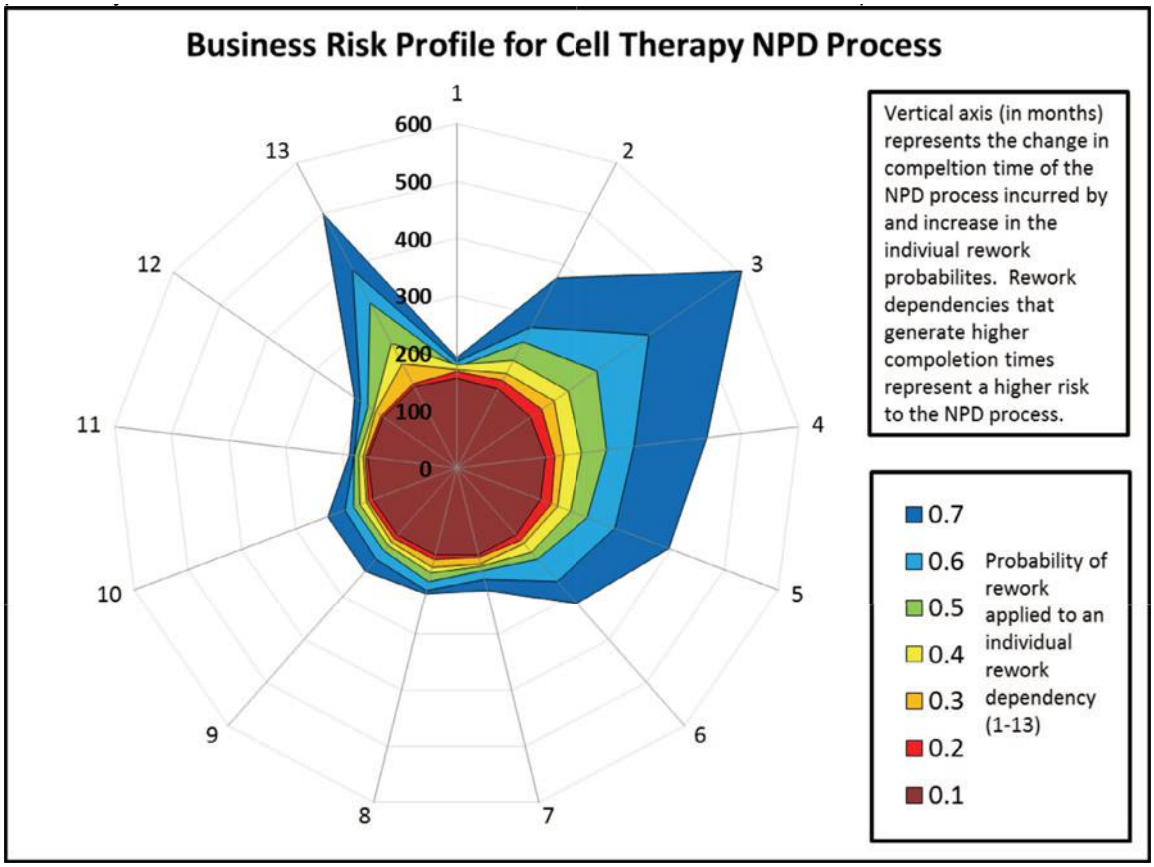

Figure 9: For each of the 13 potential feedback iterations the probability of rework has been modelled from 10% to 70%. The resulting mean durations for the entire NPD process (10,000 simulations) is plotted to show the effect an increase in each risk has on the entire process

will use accepted costs and timescales where possible — for instance regulatory authorities now specific the time that certain regulatory approval steps take.

Increased understanding of the underlying development processes and their interaction with enterprise risk will help develop more efficient development processes for cellular therapies.

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Original Article

A patient centric commercial model for cancer care

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ABSTRACT

Cancer is one of the most challenging diseases of all — not only in terms of the clinical barriers to offering its sufferers respite from devastating consequences, but also to manufacturers and marketers of treatments that attempt to control its impact. Products developed and manufactured through biotechnology dominate the commercial landscape for treating a variety of cancer types. The recent spate of new biologic launches for treating cancer delivered through injections, infusions and oral formulations will only increase in the next five years. The task of developing a viable commercial model for the effective delivery of cancer treatments to its customers lies at the center of ensuring that advances in cancer care are harnessed for their full potential. Both by definition and due to the reality of the cancer landscape, such a model is best conceptualized with the patient at its center. This article describes elements of a patient centric commercial model for cancer care, after recognizing the challenges and opportunities inherent in its commercialization and marketing. The impact of such a model resides in its ability to offer tangible benefits to patients by improving access to leading edge treatments, energizing communication at the point of care, and adequately harnessing the emerging promise of new technology. By viewing the patient at the center of a commercial model, manufacturers and marketers of cancer care treatments can offer products that provide ongoing care for the cancer patient from initiation through palliation, thereby building loyalty and realizing the full potential inherent in such treatments.

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Keywords: patient; cancer; commercial; model; strategy

RATIONALE FOR PATIENT CENTRIC COMMERCIAL MODELS IN CANCER

It is no stretch to say that cancer is one of the most challenging diseases of all. Each year, over 8 million new patients are diagnosed with cancer globally. The estimate could be higher, given that in developing countries the rate of cancer diagnosis is half that in the developed countries.

It is estimated that roughly 50% of cancer patients die of the disease. In developing countries, 80% of cancer victims are diagnosed in late stages of their condition — when the disease is virtually incurable. In the U.S., approximately 577,000 deaths occurred due to cancer in 2012. According to the World Health Organization, cancer diagnosis rates are set to increase at an alarming rate. By 2020, over 15M new cases of cancer are likely to be diagnosed each year globally.[1] In the U.S. alone, over 1.6M new cancer cases were diagnosed in 2012.[2]

It stands to reason that developing cancer treatments is one of the most important priorities of global biopharmaceutical firms. Since 2000 the number of compounds in clinical trials aiming for indications in cancer has nearly tripled. In 2011 cancer treatments had worldwide sales of $82B; projected to increase to >$99B by 2018. The majority of growth in cancer treatment sales is

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estimated to come from new biologics and targeted treatments administered through injection, infusion or oral formulations. In 2011 alone monoclonal antibodies generated >$20B in sales from cancer treatment. It is predicted that of the five highest selling cancer compounds in 2018 four will be biologics; and of the four three will be monoclonal antibodies.[3]

Cancer care as it stands today, however, is fraught with problems. In the U.S. over 85% of cancer patients are treated in their own community in private clinics and small hospitals. Lower reimbursement for oncology treatment and increasing costs partly due to changes in Medicare reimbursement rules, however, is fast turning the practice of community oncology into an unprofitable business. According to a report from the Community Oncology Alliance (COA), over 1000 oncology clinics have been adversely affected. In the last three years alone two hundred community oncology clinics have closed; about 400 are financially strapped. More than 300 practices have been bought by large hospitals, which stand to gain cost advantages.[a] In its 2012 Trends report, the COA notes that 50% of reporting community oncology practices have closed or have been acquired / managed by a hospital.

Oncology clinics that continue to survive are increasingly sending cancer patients to such hospitals, mindful of the adverse financial impact of treating them onsite. This trend has put pressure on the community oncology clinic's ability to provide high levels of care that cancer patients deserve. When needed, cancer patients, for one, have little choice but to travel longer distances, incur more costs and be treated in large, impersonal hospital outpatient centers. The costs to payers of having patients treated in the hospital are also higher.[b]

The advent of accountable care organizations (ACOs) has also raised the bar on cancer patient care in the community, even in the midst of daunting financial circumstances. The desire to provide high levels of patient care as mandated under the ACO schema now needs to be balanced against the realistic ability of an oncology practice to meet quality requirements, while at the same time adhere to specific cost control expectations. Unless this equation is properly balanced, the ability of an oncology practice to join an ACO and reap potential benefits is harmed. Complicating the situation is the hard fact that quality metrics in the ACO framework do not factor for the specifics of cancer care with the degree of comprehension accorded to primary care, nor are the cost control expectations cognizant of the rapidly changing oncology landscape. As outlined in the next section, costs for cancer care will continue to rise in the future, driven partly by the availability of newer and more expensive treatment technologies.

Another disturbing trend of importance to commercial strategists is the diminishing returns to scale from the traditional, sales-force driven share-of-voice model. According to SDI health, between 2000 and 2010, the number of sales representatives selling oncology medicines increased 6.9% per year on average, whereas the number of oncologists they served increased 3.3%. Increasing reps per oncologist only serves to dilute intended effect. As is commonly observed, more requests for rep visits has the unintended consequence of less or no time given to any rep. In a national survey of industry experts, oncologists and payers, inability by a sales rep to see an oncologist was cited as one of the most concerning trends in commercial oncology.[6] There is no doubt that accessing oncologists via sales reps is now more difficult than ever — reducing, in effect, the ability of a cancer product manufacturer to raise awareness of its treatment, provide sufficient rationale for its use and establish the product's value proposition in enabling a necessary modicum of patient care. Equally important, however, is the realization that achieving the ultimate goal of a

a Changes in Medicare reimbursement rules that calculate reimbursement for drug purchase and administration have reduced profits for community based oncology practices. Most commercial insurers have also followed Medicare in revising reimbursement rules that effectively reduce or eliminate such profits for community based oncologists. In parallel, under the Medicare Modernization Act of 2003, Hospitals qualifying under the 340B program can obtain cancer drugs from manufacturers at substantial discounts, higher than what a community clinic could. 340B pricing is not available to stand-alone, community based physician clinics. As such, community based oncologists are sending patients away for treatment to hospitals, which make use of attractive 340B pricing to treat more patients and make larger profits. The 340B Drug Pricing Program is a federal program that requires drug manufacturers participating in the Medicaid drug rebate program to provide outpatient drugs to enrolled "covered entities" at or below the statutorily-defined ceiling price. The purpose of the 340B Program is to permit covered entities "to stretch scarce Federal resources as far as possible, reaching more eligible patients and providing more comprehensive services." Also see http://www.hrsa.gov/opa/faqs/index.html#2.

b According to one estimate, total costs for chemotherapy are 24% lower in the community setting compared to the hospital setting. The cost for treating patients with specialty injectable and infusible products in the hospital is approximately twice that in a clinic setting. See Medical Pharmacy & Oncology Trend Report, Icore Healthcare, 2nd Edition, 2011.

manufacturer to improve cancer patient health requires looking beyond the physician-focused sales-force model. At best, incremental investments to improve sales-force productivity need to be combined with smarter approaches to increasing cancer patient engagement, access, affordability and involvement that extend over the continuum of care.[7]

As a direct consequence, one of the most pressing questions facing the oncology community is how to offer care that puts patients' interests back where it belonged before the onslaught of change. An equally important concern facing leading manufacturers of cancer treatments such as Amgen, Genentech, BMS, GSK, Merck and Novartis is how to develop commercial models of delivering cancer care that are fundamentally patient-centric.

Realigning the practice, access and delivery of commercial care to cancer patients is a pragmatic concept that is widely accepted in principle, but yet to be ingrained in traditional development and commercial paradigms.[8] The rest of this article discusses strategic actions that manufacturers and marketers of cancer treatments can take to design and implement a pragmatic, patient-centric commercial model of cancer care.

IMPROVING PATIENT ACCESS TO CANCER TREATMENTS

Treatments for cancer are among the most expensive of all, regardless of disease. According to one report, spending on cancer drugs could rise at least 10% a year through 2013.[9] Oncology medicines are on track to become the third-largest contributor to increases in drug spending by 2015.[10] Some new cancer treatments can cost as much as $10,000 for a month's supply. A report from Medco cites the fact that 90% of recently approved cancer drugs cost $20,000 or more for a 12 week course of therapy.[11] Even to patients covered by insurance, co-insurance and / or copayments for receiving treatment can be exceedingly high; not to mention indirect costs incurred for travel, lost workdays and presenteeism. According to one survey of breast cancer patients conducted by Duke University and the Dana Farber Cancer Institute, out of pocket cancer related costs can exceed $700 per month for insured patients. The figure includes insurance premiums and costs including lost wages and travel to appointments, as well as co-pays for medications and physician visits.[12]

Treatments for supportive care in cancer are no less expensive. Bone related complications due to cancer metastases are one of the most common consequences of cancer treatment. Sixty percent of cancer patients have bone-related metastases. According to one study, the annual national cost burden for metastatic bone disease (MBD) in the U.S. is $12.6B. Direct medical costs for treating MBD are estimated at $75,329 per patient.[13] In the hospital setting, the costs of treating skeletal related events associated with metastatic cancer are significant as well, ranging from $24,000 to $60,000 per patient, per in-patient hospital admission.[14]

As a result, patient ability to receive appropriate cancer care is severely tempered by health care systems' tendencies to limit access only to those significantly impacted. Such tendencies are manifest in public and private payer restrictions on use, hospital formulary guidelines and physician propensity to follow such norms to ensure adequate reimbursement. Most cancer products are subject to access restrictions. Most are usually only made available under prior authorization and after failure on less expensive alternatives. Other tools commonly used to limit access include restricting the type of patient eligible to receive a drug, requiring strict adherence to published guidelines and rigorous case and disease management. Such restrictions on patient access extend to cancer supportive care. In a recent survey of oncologists and hematologists, "prior authorization" restrictions and "reimbursement only for some diseases / for some patient populations within indication" were the two most common reasons cited for limiting use of Neupogen and Neulasta, the two most widely used CSFs for treating febrile neutropenia due to chemotherapy.[15]

Severe limits on use of cancer treatments currently in place hardly serve the interests of patient-centricity in cancer care. Oncologists are restricted to fewer options and patients and their caregivers often feel deprived of opportunities for receiving adequate treatment. It behooves manufacturers and marketers of cancer treatments to work with payers to ease such restrictions and increase access to what are often perceived as life extending treatments. This can be achieved through multiple approaches. Documenting retrospective use of a cancer product and its outcomes in tandem with direct and indirect costs incurred for such use as documented in reimbursement claims and electronic medical records (EMRs) can form the basis for analyses that establish its cost effectiveness. Rather than a disproportionate focus on cost, establishing proof that the cost is well spent as seen through evidence of effective use is a convincing way to reduce restrictions on access. Data for such analyses are typically hard to compile, but recent partnerships between some cancer manufacturers and large pharmaceutical database providers, clinics and hospital chains are fast making it possible for large, integrated databases to be constructed for such purposes. These databases typically combine claims data with patient registries, EMRs and patient surveys conducted over time to present excellent opportunities for formulating and testing a

variety of cost-effectiveness hypotheses in the context of real patient experiences.[16]

Another activist approach to easing access restrictions to cancer products is to offer insurers economic incentives in return for favorable access. Insurers vary in terms of the cancer patient mix among their beneficiaries and costs associated with their treatment. Cancer product manufacturers would do well to use proven analytics for identifying specific insurers who could make good use of such incentives and make a significant difference in improving access to their products. Ideally, the exact type and level of incentive offered would be idiosyncratic to the insurer and its beneficiaries. The fact remains, however, that actively identifying eligible insurers and designing and negotiating economic incentives that ease access restrictions for specific cancer products offered by them can have a positive impact on the number of patients likely to receive such products, as well as better serve the economic interests of such insurers over the long term.

ENERGIZING PATIENT-PROVIDER COMMUNICATIONS

One of the most important pillars of a patient-centered, commercial cancer care model is patient-provider communication. Poor communication encompasses verbal and non-verbal aspects of the relationship between clinician and patient that have the potential to create unfavorable outcomes. Such outcomes have a direct impact on patient satisfaction, result in unnecessary and inappropriate utilization of medications and services, and higher than necessary costs to the system.[17]

Studies have consistently shown a strong association between poor communication in cancer care and reduced patient satisfaction.[18] Poor communication skill reduces the clinician's capacity to recognize psychiatric morbidity in cancer patients, increases patient anger toward health care professionals and makes them prone to litigation.[19] Poor communication exerts significant burden upon the patient, the clinician and the service delivery system. Patients suffer heightened psychosocial distress, physicians undergo abnormal stress and burnout[20] and their healthcare system faces unnecessary treatment, administrative and hospitalization costs associated with use of needless, alternative treatment paths.

Three large studies have demonstrated that between 35-45% of all cancer patients undergo psychosocial stress.[21] Unresolved emotional issues were associated with five times the frequency of using community health services, twice the rate of visits to an emergency department and also more prevalent use of complementary medicine, as well as third and fourth line chemotherapy. Diversions from the recommended course of treatment are typically not discussed with the primary care provider, and are often associated with unnecessary side effects.[22]

Such problems are reiterated in situations where cancer care is provided by a team rather a single physician; for example, in the treatment of bone metastases in cancer, which requires a coordinated team approach involving primary care physicians (PCPs), oncologists, orthopedic surgeons, radiologists and their support staff. In a survey of health care professionals caring for 1,326 patients at the end of life in 3 countries, one research team documented reports of severe communication problems as part of team assessments in the care of 40% of these patients.[23]

Decisions to design brand marketing programs that emphasize the use of effective patient-provider communication can benefit cancer patients, their care providers and the manufacturers of cancer-treating biopharmaceuticals. There is considerable social and business value in reducing avoidable uncertainty around information patients care about, identifying and explicating the worth of a course of treatment over available alternatives, justifying product and regimen choices and emphasizing the importance of receiving continual patient and caregiver feedback.

Many of the burdens associated with late stage cancer can be ameliorated by physicians willing to listen to and empathize with patients' concerns. In addition, evidence exists to prove that emphasizing patient-provider communication in cancer care reduces health care costs incurred by payers and other key accounts in the health care environment. For example, a study conducted in Canada has effectively demonstrated health plan billings reduction of over 20% at two-year follow up for those breast cancer patients who were offered a cognitive behavioral psychosocial group as compared to those who were not.[24] Other studies have consistently proven the value of psychosocial support for cancer patients in offsetting medical costs and freeing up resources in terms of reduced office visits, medical procedures, diagnostic tests and hospital admissions.[25] Such savings can conceivably be better allocated for the purchase and utilization of proven, safe and effective medications in the oncology portfolios of leading biotechnology firms — often perceived to be expensive in the larger context of health care costs for cancer care.

HARNESSING TECHNOLOGY

The passage and ongoing implementation of health care reform has emphasized the importance of leveraging technology to improve systemic efficiencies, reduce costs and provide better personalized care. The potential exists for leading cancer treatment manufacturers to adopt technology in building a viable patient-centered commercial model for their oncology businesses. For example

- Cancer patients have consistently expressed interest in accessing their electronic medical records for the purpose of improving their care. In an online survey of 8,411 cancer patients administered by LIVESTRONG (the Lance Armstrong Foundation) and the National Cancer Institute's Health Information National Trends Survey (HINTS), 80%-87% of respondents indicated it was very important for patients to be able to obtain their own medical records electronically, since it would improve their care. Respondents who were survivors (on or post-treatment) comprised the greatest proportion of those who believed this was important.[26] Another survey of 173 cancer patients found that "*for successful patient engagement to occur, patients need to be connected to their healthcare team, have access to their health information, receive personalized tools and resources specific to their condition, and have it all integrated as part of the provider-patient relationship process.*"[27] Specifically, survey data indicated that approximately 75% of respondents wanted to engage in their care by having access to their medical records and by reading education materials. Devising creative branded and unbranded tools that use technology to facilitate patient engagement and involvement specific to their condition, treatment and ongoing care in the light of such demand can only better serve the needs of cancer patients and firms that provide medications for their care.
- Considerable discussion in the recent past has advocated the development of cancer navigating portals by oncology practices. Such portals are one-stop destinations for cancer patients to acquire personalized information and literature, interactive tools and social means to take charge of their care in a context provided by their care-providers. Recent models of care such as the ACO (Accountable Care Organization) and the PCMH (Patient Centered Medical Home) also require more patient engagement to reduce overall costs — which such leveraging of technology can enable. A demo patient engagement portal designed by Navigating Cancer includes a health tracking tool for patients to record psychosocial measures such as anxiety, energy and stress. Patients can easily share this information with their healthcare team, which allows clinic staff to be alerted sooner to potential issues so they may intervene when necessary, even if it's between appointments. Over time this data can be used to measure performance to see if patients are experiencing less psychosocial distress as practices implement initiatives to address specific issues. As patients identify specific issues, the portal has a robust library of expert resources that can be shared with them via private message to help them cope. If a practice has outside providers they refer patients to for palliative care or genetic counseling, they can have them stored in their clinic resource library and ready to send to patients and/or their caregivers when appropriate. When patients see outside specialists during treatment, the portal can be used to generate and send a treatment care summary. This can also be used when patients complete their cancer journey and transition back to their primary care physician.[28] Enabling such portals through proactive involvement, providing branded or unbranded sponsorship, ensuring adequate availability of information on (and encouraging appropriate use of) cancer bio/pharmaceuticals in such a channel can genuinely serve the interests of cancer patients, their providers, and bio/pharmaceutical manufacturers and marketers who are interested in becoming more patient-centric in their commercial activities.

EMBRACING THE ONCOLOGY MEDICAL HOME CONCEPT

The medical home concept envisions patients receiving accessible, comprehensive, longitudinal and coordinated care in the context of families and community. The concept emphasizes the role of the patient in collaborating with the care provider to ensure effective care.[29]

Adapting the medical home concept to the provision of care in oncology is gradually taking root through several small-scale pilots in various U.S. geographies. Ostensibly meant to streamline patient care, introduce efficiencies and control costs, the medical home concept is clearly suited to the development of a patient-centered commercial model in oncology.

A successful application of the medical home concept in oncology discussed in the media emphasized several aspects of patient care including[30]

- coordinating all aspects of cancer care related to evaluations and services beyond the medical oncology office using online patient navigators
- proactively promoting an interdisciplinary approach to cancer management
- constant collaboration between the clinical support and treatment teams
- stressing the importance of patient education, engagement and compliance
- enhancing patient access to allow proactive management of symptoms via extended hours, telephone triage services and physicians on call
- fixing accountability for care delivery at the physician-patient locus
- assuming ownership of cancer-related needs in a highly personal way

Effective medical home pilot applications in oncology have relied upon the development and implementation of evidence based pathways — which recommend proven treatments, regimens and supportive care that ensure desired patient outcomes while minimizing waste, thereby contributing to patient wellness as well as cost-effectiveness of care. By virtue of offering comprehensive, one-stop, coordinated cancer care, effective oncology medical home pilots have also streamlined patient care from evaluation and diagnosis to treatment including chemotherapy, supportive care, hydration and nutrition, as well as providing ongoing patient education.[31]

As can be expected, such benefits offer patients higher quality of care, while reducing costs and garnering payer support. For example, one pilot increased the number of cancer patients treated by 29% with the same number of physicians and a decrease in office staff, reduced ER admissions by 51%, reduced inpatient admissions by 68%, while also reducing the number of incoming clinic calls resulting in an ER referral by more than 50% over a 5-year period.[32]

In order to ensure that their products realize their full potential in providing meaningful patient care, biopharmaceutical firms need to embrace the medical home concept. It is not enough — and less than worthy — to solely aim at realizing incremental sales through this new channel; rather, the goal should be to take advantage of the medical home, its structure and processes to provide holistic patient care founded on appropriate use of its products. A biopharmaceutical firm interested in developing patient-centric commercial models for cancer care can adopt the medical home concept through means such as

- Sponsoring oncology medical home pilots in regions where there is a high density of patients requiring treatment by its products
- Conducting studies in such pilots that lead to the recommendation of evidence-based, clinical treatment pathways incorporating its products, so that such pathways are adopted into the day to day treatment regimens of cancer medical homes, clinics and hospitals everywhere
- Monitoring the use of its products over time in such pilots in a test / control context so that data on costs, utilization and outcomes can be compiled, analyzed and made available for commercial and public benefit, and
- Using such pilots to understand cancer-specific, product driven quality of care provided by its products, and define practical quality metrics that could be used in a broader population to assess and possibly differentiate its products along the all-important quality-of-care dimension.

INCORPORATING PALLIATIVE CARE IN THE COMMERCIAL MODEL

The treatment of cancer presents unique challenges in that requirements for patient care stretch far beyond relieving symptoms and achieving control or remission. Even when treatment is completed and no cancer remains, serious residual effects such as depression,

anxiety and post-traumatic stress disorders impair patient ability to perform activities of daily living, limiting capacities to function as responsible members of families, and adversely impacting adherence to necessary medications. Impaired quality of living is one of the most debilitating effects of treatment for bone metastasis in cancer. Providing cancer care for the whole patient — rather than focusing on disease progression alone — is an important (and under-recognized) opportunity for a patient-centric commercial model in cancer care.

According to a study published by the National Academy of Sciences[33], *"Although family and loved ones often provide substantial amounts of emotional and logistical support and hands-on personal and nursing care (valued at more than $1 billion annually) in an effort to address these needs they often do so at great personal cost, themselves experiencing depression, other adverse health effects, and an increased risk of premature death. Caregivers providing support to a spouse who report strain from doing so are 63 percent more likely to die within 4 years than others their age. The emotional distress of caregivers also can directly affect patients. Studies of partners of women with breast cancer (predominantly husbands, but also 'significant others,' daughters, friends, and others) find that partners' mental health correlates positively with the anxiety, depression, fatigue, and symptom distress of women with breast cancer and that the effects are bidirectional."*

Large sample surveys of cancer survivors conducted by LIVESTRONG in 2006 (n = 2,307) and 2010 (n = 3,129)[34] outline a host of physical (e.g. loss of energy, lack of concentration, impaired sexual functioning), emotional (e.g. fear of recurrence, sadness, depression) and practical (e.g. employment, debt, insurance, education) effects that linger well after treatment ends. The surveys further emphasize the fact that such physical, emotional or practical concerns receive little or no attention from their care providers. The surveys also note a decline in the number of survivors who received care for their physical concerns from 2006 to 2010.

According to a survey of executives at cancer centers in the U.S.[35] the barriers to providing adequate palliative care are lack of reimbursement and insufficient resources. Further, focusing oncology medical research, education and training on the benefits of palliative care is imperative.

Beyond the obvious altruistic goal of better patient care, building a palliative care component into a patient-centric commercial model holds potential economic benefits. According to studies conducted by The Palliative Care Leadership Center, adding palliative care consultation to the standard of care for patients avoids unnecessary tests or treatment and reduces costs associated with ICU and hospital stay. Cost savings in the study attributed to palliative care range from $1,696 to $4,908 per patient.[36]

A patient-centric commercial model that explicitly incorporates mechanisms to address the palliative care needs of cancer patients is likely to succeed both for its champions within the oncology commercial organization at a manufacturer as well as with the customers of its products. Key elements of such models may include features such as

- Influencing national policy and research priorities emphasizing the benefits of palliative care in oncology
- Influencing public and payer policies that provide for adequate reimbursement of palliative care, especially when provided in parallel with the use of the manufacturer's products
- Encouraging demonstration projects that integrate palliative care into treatment regimens of interest to the manufacturer
- Sponsoring reliable academic research that develops the necessary evidence base for highlighting the clinical, social and economic value of palliative care, and
- Developing patient registries to study the impact of palliative care on patient quality of life over the entire patient-care continuum (from treatment initiation to palliative care) experienced by patients taking the manufacturer's products[37]

OTHER RELEVANT ELEMENTS OF PATIENT-CENTRICITY

Improving adherence

In health care systems such as the U.S., the relatively high costs of cancer medications invariably trickle down to cancer patients in the form of high out-of-pocket payments for drugs and indirect costs associated with their administration. The risk of high cost burdens is significantly greater for patients with cancer compared with other chronically ill and well patients.[38] The consequences of high out-of-pocket costs include debt, higher chances of bankruptcy and decisions to abandon treatment.[39] Poor adherence to oral oncology treatments (due partly to high out-of-pocket costs) is well documented; as is the impact of low adherence on cancer patient decisions to postpone or abandon care — allowing the worsening of the cancer, leading to higher rates of hospitalization and other emergency care.[40] With the advent of oral biologic treatments for cancer care, the importance of adherence

to maintaining patient health, ensuring positive outcomes and realizing the full sales potential inherent in a drug's value proposition has never been more critical to a commercial model.

Reshaping clinical trial programs

It is no stretch to recommend a re-envisioning of oncology clinical trial programs that emphasize patient outcomes and effectiveness in multiple patient segments (e.g. based on severity, co-morbidity, geographic location) rather than clinical efficacy in highly specific subpopulations through impact on short term survival alone. Conducting parallel studies that focus on developing evidence of cost effectiveness in select patient segments in comparison with previous standards of care, taking, where possible, a lifetime view of treatment benefit in conjunction with palliative care will also serve the interests of patient-centricity while developing an evidence base with value for health technology assessors, regulators, payers and clinical practitioners.

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Original Article

Challenges and prospects for monoclonal antibodies in China

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ABSTRACT

The technology of monoclonal antibodies (Mabs) has been developed since the 1990s and is attracting more and more attention in China during the 21st century. While foreign Mabs dominate the Chinese market domestic universities and companies are taking efforts to catch up with the strong support from Chinese government. The first monoclonal antibody product was introduced by the Chinese local producer in 1999, and presently seven products are listed, of which three are humanized products. There are several technical constraints that are affecting the development of monoclonal antibodies in China: limitations to the number of drug targets, restricted biological diffusion, limitations to administration routes, and species-specific issues, as well as China's own limitations in production and R&D capabilities. This article provides suggestions relevant for the Chinese development of monoclonal antibodies. In the long run China is expected to catch up with its own technology roadmap and market opportunity.

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INTRODUCTION

In 2010, CANCER replaced cardiovascular disease as the world's deadliest disease, taking 7 million lives every year.[1] In China millions of people suffer from the disease.[2,3] In the search for a drug to prolong survival and relieve pain with fewer side effects for rising cancer patient population, the monoclonal antibody (Mab) is attracting tremendous attention from industry and academia.[4,5]

Based on immunological principles and relying on antibody in vitro amplification techniques to produce therapeutic antibodies primarily for tumor therapy, Mabs are the most important element in the bio-pharmaceutical system.[6,7] The ability of Mabs to recognize specific targets (such as tumor cells and pathogenic microorganisms) can be exploited to enhance the diagnosis, prevention, and treatment of diseases.[8] For example, in the treatment of tumors, Mab drugs can target the

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cancer cells, gather around them, block their growth, and shrink the cancerous parts.[9,10] As a result, a low-dose treatment of low toxicity can be achieved. A Mab is like a biological missile in the human body that is constantly looking for the receptor.[11] Once it finds a cancerous cell, cohesion, combination, and blocking the growth of the cancer cell take place.[12] As a result, the major therapeutic areas of Mabs are in cancer treatment, which accounts for more than 40% of Mab sales.[13]

Compared with small molecule drugs, the biggest advantage of Mab products is their accuracy.[14,15] They can simultaneously treat a specific target, with minimal side effects, and enhance efficacy. The mechanisms of Mab treatment can be divided into two categories: one is the combination of Mab itself with the target protein, followed by use of the human immune system to clear the target protein; and the other is the combination of Mab with a therapeutic small molecule drug or radiotherapy drug, thereby directing the drug towards lesions and achieving specific therapeutic purposes.[16,17]

As a result, with the development of biotechnology, many pharmaceutical giants and emerging biopharmaceutical firms invested more and more resources and efforts in Mabs, which has led to notable development of Mab products to market.[18,19] Recently, in the first decade of the 21st century, Chinese pharmaceutical companies have put much emphasis on Mabs, and have already realized much advancement in technology and product development of Mab.[20,21]

CHINESE CONTEXT FOR MAB

With its rising economy and huge population, China is becoming a more influential pharmamerging market for global pharmaceutical industry. Especially cancer has been a major disease threating people health in China, and the incidence rate of cancers including lung cancer, liver cancer, stomach cancer, colorectal, esophagus, and breast cancer keeps rising in the past decade.[22] Such kind of increasing patient population with considerable consumption capability provides unique opportunities for Mab products. It is estimated the Mab market in China will grow to 32.5-65 billion yuan by 2015.[23]

Attracted by the enlarging Chinese market foreign Mab producers try to introduce their Mab products into China. Until now nine Mab products of foreign companied are listed in China (see Table 1). Among these nine Mabs five are humanized products, showing that foreign companies are using their most advanced Mab products to obtain market control. In fact before 2006 the whole Mab market in China is mostly dominated by foreign Mab products.

Because of their distinguished medical efficacy, the foreign Mab products are widely accepted by physicians in China. But Mab products are not included into the National Social Security and have to be paid by patients themselves. Consequently foreign Mab producers generally concentrate on the high-end market in China.

Realizing the great medical and financial value of Mab, the central and local governments in China have tried to support the development of Mab, especially through providing research funding to universities and academic institutes. Consequently laboratory research and development of Mabs is fairly strong in China.

Table 1: Background information on nine foreign Mab products in China

Non-proprietary name	Firm	Market time	Type of antibody	Target	Therapeutic areas
Daclizumab	Roche	2001	Humanized	CD-25	Kidney graft-rejection
Rituximab	Roche	2001	Mosaic	CD-20	Non-Hodgkin's lymphoma, Rheumatoid-like arthritis,
Trastuzumab	Roche	2003	Humanized	HER-2	Mammary cancer
Basiliximab	Novartis	2003	Mosaic	CD-25	Kidney graft-rejection
Cetuximab	Merck	2006	Mosaic	EGFR	Colorectal cancer
Infliximab	Johnson & Johnson	2007	Mosaic	TNF-α	Rheumatoid-like arthritis, ankylosing spondylitis
Bevacizumab	Roche	2010	Humanized	VEGF	Colorectal cancer
Adalimumab	Abbott	2010	Humanized	TNF-α	Rheumatoid-like arthritis
Etanercept	Amgen	2010	Humanized	TNF-α	Rheumatoid-like arthritis, ankylosing spondylitis

Table 2: Mab patent applications in China up to 2011

	Patents for inventions	Utility model patent	Appearance patent	Invention authorization
Has patent right	1005	136	0	1005
No patent right	1912	40	1	317
Under review	2314	0	0	0
Total	5231	176	1	1322

According to the number of patent applications to the State Intellectual Property Office of China, applications for Mabs grew by more than 5,000 (up to 2011), as shown in Table 2, indicating good technology development as well.

The Mab patent applications in China mainly focus on anti-cancer and biological toxin detection. From academic point of view, monoclonal technology in China is not far behind world leaders in this area due to its world-class gene technology researchers. Currently, Mab technology in China is keeping pace with its foreign counterparts (mainly in the USA). Nevertheless more than 50% applications among all the Mab patent applications in China are from universities and academic institutes rather than firms, implying possible lag between academia and industry.[24]

DOMESTIC MAB PRODUCTS

The domestic Mab producers are also taking efforts to enter into this market and have obtained 20% of the Mab market in China from global pharmaceutical companies. Now there are seven Mab products are manufactured and marketed by domestic producers (see Table 3). Unlike its chemical drugs that struggle in the generic market, some Chinese Mab products have already taken a leading position. Among the seven listed Mab products three Mab products are humanized. Since it began focusing on products with minor side effects, Shanghai CP Guojian Pharma has marketed two humanized products. Meanwhile, Biotech Pharma, in collaboration with a Cuban group, has produced Taixinsheng® and the humanized level is as high as 95%, which makes Taixinsheng® a leading Mab product in the market.

Three Mab products in China are used to treat cancer, but only one of them is a humanized product; the other two are used for the treatment of lung cancer and are murine. Perhaps because the survival of individuals diagnosed with lung cancer is brief, it is not necessary for China's existing research organizations to continue humanized research. Consequently, compared with foreign products that are almost humanized, China still adheres to its own technology path.

Aiming to catch-up the frontiers of international Mab products, the Chinese producers try to acquire Mab technologies from diversified sources: three Mabs are input from overseas; one is from domestic university; and the other three Mabs are from self-development. As Table 4 shows, the Chinese producers also have innovatively developed the various characteristics of Mabs based on the original Mab technologies input from outside to distinguish themselves from current Mabs in the market.

To support these Mab projects, the Chinese producers have to make use of varied financing models to cover the huge Mab development cost and meet the requirements of different types of stakeholders (see Table 4). The Chinese government provides strong finance support by direct investment or indirect investment through state-owned enterprises. Some domestic private pharmaceutical companies and venture capitals also have interest on Mab projects but feel hesitant about investment required and failure risk.

CONSTRAINTS OF MAB DEVELOPMENT IN CHINA

Because of the increasing number of cancer patients, researchers are confident that Mabs have a promising future. However, there are several technical constraints that are affecting the development of Mabs throughout the world, including limitations to the number of drug targets, restricted biological diffusion, limitations to administration routes, and species-specific issues (see Table 5).[25] These four aspects are also the main bottlenecks restricting the development of Mabs in China.

Despite Chinese strengths in technological development, the introduction of few innovative Mabs to the market may imply a lack of cooperation between enterprises and research institutes. Compared to foreign companies, China has its own difficulties in the development of Mabs (as shown in Figure 1).

In addition, several other troublesome problems constrain the development of Mab in China. The main direction of Mab R&D in China is still following that of

Table 3: Background information on seven domestic Mab products

Non-proprietary name	Firm	Market time	Type of antibody	Target	Therapeutic areas
Mouse anti-human CD3 antigen of T lymphocytes for injection	Wuhan Institute of Biological Products	1999	Murine	T lymphocytes CD3	Protects against the rejection of certain organ transplants
Anti-human interleukin-8 cream	Asia Space pharma	2004	Murine	IL-8	Psoriasis vulgaris
Recombinant human tumor necrosis factor-receptor	Shanghai CP Guojian Pharma	2006	Humanized	TNF-a	Moderate and severe active rheumatoid arthritis
Recombinant humanized anti-CD25 injection	Shanghai CP Guojian Pharma	2011	Humanized	TNF-a	Organ transplant rejection
Iodine [^{131}I] tumor necrosis therapy injection	Shanghai Meien Biotech	2007	Murine	Nucleus of tumor cells	Lung cancer
Iodine [^{131}I] metuximab injection	Huasun Biotech	2007	Murine	HAb18G/CD147	Lung cancer
Nimotuzumab injection	Biotech Pharma	2008	Humanized	EGFR	HNSCC, colorectal cancer

Table 4: Technological characteristics of Mab products in China

Non-proprietary name	Technology source	Technological characteristics	Financing model
Mouse anti-human CD3 antigen of T lymphocytes for injection	Self-development	A pioneer in the Chinese Mab market; direct effect on T cells that play a major role in organ transplant rejection.	Investment from government
Anti-human interleukin-8 cream	Input from Canada	To introduce the world's first therapeutic Mab for external use; convenient	Joint venture
Recombinant human tumor necrosis factor-receptor	Self-development	Similar to the world's best-selling Mab (Enbrel) and has fewer side-effects	Investment from state-owned enterprises
Recombinant humanized anti-CD25 injection	Self-development	High humanization; can be used alone or as combination therapy with other drugs.	Investment from state-owned enterprises
Iodine [^{131}I] tumor necrosis therapy injection	Input from US	The first lung cancer irradiation immune targeted therapy in the world; significant effect on patients with advanced lung cancer that failed to respond to radiotherapy and chemotherapy.	Venture capital from US and domestic
Iodine [^{131}I] metuximab injection	Input from domestic university	The world's first Mab radioimmunoassay targeted drug for liver cancer.	Investment from domestic private enterprise
Nimotuzumab injection	Input from Cuba	Highly humanized; targets the epidermal growth factor receptor (EGFR)	Joint venture between China and Cuba government

Table 5: Four technological bottlenecks to Mab development

Technological bottleneck	Detailed description
Limited drug targets	Mab is specific. Each Mab can only bind to one target or the cell types of one disease.
Biological diffusion limitations	Mab is a large protein molecule that cannot enter solid tumors. It has good efficacy in suppressing surface tumor cells.
Species-specific	Humanized antibody really can minimize side effects and allergic reactions but has a long R&D time. However, it is not necessary for some malignancies with a short survival period.
Route of administration limitation	The human body will metabolize drugs during the administration process. There are considerable limitations to drug absorption. Meanwhile, some Mab molecules of large size could not penetrate through certain body tissues and organs.

foreign countries (mainly USA). Nevertheless, a major problem restricting the development of the Chinese pharmaceutical companies is lack of finance, which might be attributed to the small size of these pharmaceutical firms in China. This fundamental problem prevents China from making greater progress in R&D in Mabs.

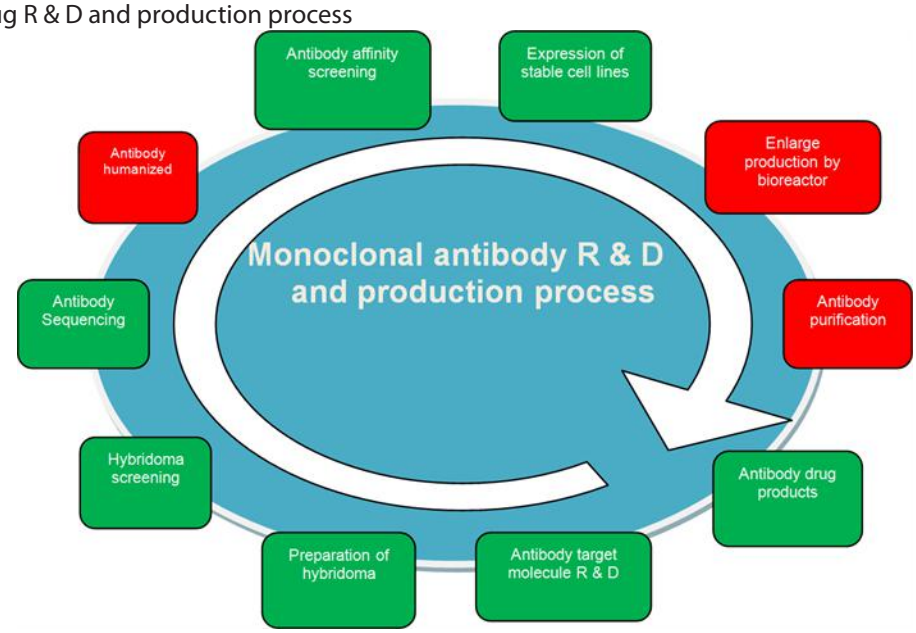
The second but most vital problem is the production processes. The production of biological products is very different from that of chemical drugs. Mab production processes have strict production requirements. In addition, an antibody used in cell culture technology and production requires precise controls. A slight mistake will cause the whole production process to fail. Currently, foreign Mab production fermentation tanks and other equipment have a scale above 3000 L, but in China the highest attainable scale is 2500 L (Biotech Pharma).[26] Consequently, China's production output lags far behind that of the more sophisticated pharmaceutical companies.[27]

Finally the price of Mabs constrains the Mab development in China. Because of their huge R&D investment and higher production cost the price of Mab products in China remains at a high level that can't be easily afforded by ordinary patients, which limits the sales of Mab products in the less developed areas of China where cancer incidence rate is much higher.

FUTURE OUTLOOK

By the year 2020, bio-medicines are expected to completely replace chemical products.[28] As a key component of biological drugs, Mab is a primary prerequisite for achieving this goal.[29] New breakthroughs are expected

Fig 1: Mab drug R & D and production process



***Red areas** are the difficulties for Chinese companies in developing Mab.

to solve the four previously mentioned global technology bottlenecks. The Chinese pharmaceutical sector also looks forward to contributing to the development of Mab.

According to a systematic analysis of the technological and economic environment, several solutions for China's own R&D and production technology bottlenecks can be suggested. In R&D, Chinese pharmaceutical firms should be encouraged to cooperate with universities, colleges, and other agencies, not only to reduce R&D cost and time, but also to improve technological innovation capabilities. A production-learning-research system can effectively promote technological innovations in Mabs. Cooperation partners should not be confined to China, but should also include foreign advanced scientific research institutions, such as the cooperation on Taixinsheng® between Biotech Pharma and its Cuban partner as well as the cooperation on Enboke® between Asia Space Pharmaceutical (Dalian) and Anogen-Yes Biotech Laboratories (Canada). In addition, licensing of antibody technology that has already been developed by a foreign laboratory can help to develop China's Mab market. Some Chinese pharmaceutical enterprises have already realized this and are making efforts in this regard (e.g., Qilu Pharmaceutical).

In production areas, Chinese biopharmaceutical factories ought to expand production capabilities and solve the problem of low production yields. Otherwise, even if the technology becomes readily available, it still cannot be industrialized and might never be profitable. Today, most domestic production equipment is purchased from foreign countries, which offers great opportunities for domestic enterprises to enhance the strength of their own production. Moreover, China's Mab firms should focus more on raw material selection: Biotech Pharma offers a good example in this field.

The global biopharmaceutical market is undergoing tremendous change. China possesses some unique potential advantages, especially in fields of cutting-edge research such as genomics and stem cell research. Having recognized the value of these technologies, the Chinese government is providing financial support to create a healthy environment for the biopharmaceutical industry. Particularly the planning inclusion of cancer treatment into National Social Security may provide greater opportunities for Mabs in China. With the development of Mabs, Chinese pharmaceutical companies are expected to devise their own technology map and business model with their own solutions.

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From the Board Room

A business perspective on IP: Open innovation vs. open source in commercializing biomedical opportunities

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ABSTRACT

In this article, we address the issues that are involved when developing a strategy for commercializing a discovery that is novel, useful, and non-obvious to someone skilled in the art. Patent(s) may be used as one means of providing a competitive advantage, and in addition this method is quite common as a means to monetize the intellectual asset. Alternatively, a more "open-source" method may be employed as is more typical in dealing with software products or services — thereby opening up the field to collaboration and widespread use. However, other means must then be developed to monetize the asset whether it involves a "hardware" component, software, or both. We argue that to answer these questions, one needs to be very strategic in framing the business model that would be most successful in commercializing the particular discovery keeping in mind that wide dissemination of the innovation is the objective. We focus on issues prevalent for innovation in biopharma, medtech, and medical IT, where high risk, long life cycle, capital-intensive investments are required for commercial introduction.

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INTRODUCTION

It is not uncommon in academia for researchers to take the position that patenting of inventions would preclude wide dissemination of a technology embodied in a drug, medical device or diagnostic. Why not use an open source approach as is common in the software industry to ensure the widest, and free access to the technology?[1–3] Some argue that open source is the ethical approach since everyone may benefit equally from free access to a breakthrough technology (even though open source may be insufficiently documented and developed to serve as a validated basis for investment as a commercial product). It is often asserted that this approach yields greater societal benefit, since anyone in need of a drug or medical device would somehow have access at a lower cost anywhere in the world. The counterargument is that the use of an open source approach, while altruistic, would result in just the opposite in the field of biotechnology (or medtech). This is a direct result of the structure, and strategy of the industry and the tremendous uncertainty with developing drugs, and also to a certain extent medical devices and diagnostics. Therefore these industries require a certain level of validation of potential products prior to entering the commercialization pathway in any significant way. Even with open source software, it is cited that products such as MySQL did not reach its commercial potential as an open source approach as a stand-alone entity. The financial viability (and extent of market penetration) was questionable at best prior to acquisition by Oracle.[4]

The biotechnology industry, and other technology intensive industries are characterized by a very long, high risk, and extremely capital-intensive development cycle. Therefore, the organization that develops the technology will be required to invest a considerable sum of money to move the technology down the commercialization life cycle spanning discovery, preclinical and

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clinical testing before it is even clear that the potential invention will demonstrate efficacy and suitability for the market. Drug development requires hundreds of millions of dollars (taking into account failures, this amount is estimated to exceed $1B).[5] Medical devices require less, but still significant amounts of investment ranging from tens of millions to fifty million or more. Who would make a multimillion-dollar, high-risk investment without some ability to generate a fair return on that investment? While government funding is helpful in this regard, private sector investment is necessary for commercial introduction. Private sector funding may come from the pharma or medical device industry, from venture capital or both. So shareholders or limited partners who put up the risk capital need to be satisfied. Without risk capital, innovation cannot proceed, hence no one benefits from a discovery or breakthrough.

Another complicating factor is the business model employed in these industries, which we discuss in more detail below. Value creation most often results from the contributions of multiple partners along the value chain, in addition to the value added by the pharma or medical device organization that actually brings the product to market and deals with the distribution of the end product to the patient and provider.

One of the underpinning factors for the success of any business model is that the product be differentiated, and a sustained competitive advantage developed. Patenting is one method for achieving this objective (at least in part). Note in particular the requirement for novelty and utility in exchange for a 20-year period of exclusivity granted to the patent holder. In the biomedical field patents are necessary, but often not sufficient in this regard, and most venture investors in biotech or medtech will not invest in any potential drug or device where a patent (and most probably freedom to operate) is not available.

Below, we discuss the pros and cons of patenting in the biomedical field. We also consider some of the business ramifications in this field, since as noted it is common (and increasingly more common given the move towards collaborative innovation typified by open innovation business models – not to be confused with open source), that multiple parties may be involved to ultimately bring a drug to market.

In the language of strategists and economists, each of the parties involved along the value chain will "seek rents" for their contribution to creating and sustaining value in the market. How will value be measured and shared to best ensure balance of risk and reward? One may think of licensing of patents to partners as simply "renting or hiring" the business model of the partner to create and deliver value for the technology, c.f. Chesbrough in his book entitled Open Innovation.[6] Therefore the fundamental breakthrough is often valued lower by the partner who "owns" the business model since that organization has already invested quite heavily in development of other key parts of the business model, e.g., key activities and resources, customer channels and customer relations. To optimize the "rent" it is beneficial for the technologist (university or early stage company) to raise money from the government and private sector to decrease the development and/or market risk and thereby increase the value prior to partnering. Patents are a vehicle by which monetization of an intellectual asset can be conveyed to a partner via a license whether the license is exclusive, non-exclusive or otherwise restricted by the owner.

THE OPEN INNOVATION BUSINESS MODEL AND MONETIZATION OF INTELLECTUAL PROPERTY

There are many sources of extensive information on development of winning business models, c.f. Osterwalder & Pigneur[3] Chesbrough[7], Christensen[8], for example. Basically, the business model is defined as the components that must be assembled by an organization to create, capture and deliver value to customers (those who pay for the product or service). Of course in the biomedical field it is well understood that customers and users may be different entities since there are the 3Ps (patients, providers and payers). The chapter in the excellent book edited by Burns[9] (c.g. Chapter 4, Biotechnology business and revenue models) illustrates the common models in the healthcare industry. These include FIPCO (fully integrated pharmaceutical company), RIPCO (research intensive pharmaceutical company), and FIDDO (fully integrated drug discovery/development organization). These characterizations are useful for categorizing the companies in the biomedical field, however it is more illustrative to take a more fundamental look at the various components of the business model itself. For this purpose one can adopt the very straightforward (and graphical) framework described by Osterwalder. This approach is applicable to any industry. Over the last decade the business models employed in the healthcare sector have been questioned since the industry had difficulty with driving and sustaining innovation; c.f. Pisano.[10]

Osterwalder[3] framed the business model as consisting of 9 separate and necessary parts. On the "*customer side*" there is the (1) customer, (2) the value proposition, (3) the channel to reach the customer, and, (4) the customer relations necessary to sustain and nurture the customer for awareness, consideration, choice and repeat business. Also on that side of the model is (5) the revenue

model, which describes how revenue is actually generated (thru one or more of the 3Ps in this case). For example revenue can be generated by selling a product to the consumer, or by licensing that product to another company who has the ability to interact directly with the customer. For software products, the Software as a Service (SAAS) model could be employed. Download the software and pay a fee — the owner controls the software. Alternately, the so-called Freemium model could be employed whereby the software is provided free (open source) and revenue generated by other means, such as providing a service to the customer or alternately selling a premium version to paying customers, with a free version to others. Osterwalder and Burns cover many different business models (which is beyond the scope of this short article).

The "*company*" side of the business model deals with costs, and the resources, processes and values needed to carry out the business, i.e. (6) key activities, (7) key partners, (8) key resources, and (9) the costs incurred to acquire, build and deploy those assets. Generating and developing intellectual property would be a key activity, as would be the resources involved (people and partners).

The historical business model in biopharma is a "vertically integrated" FIPCO where all of the 9 components were "owned" by the pharma company, with some licensing or partnering providing the company with new drugs for commercialization (along with those discovered and developed in house). With medical devices and medical IT a similar approach was employed. Most medtech/medical IT companies employ a combination of in house development along with partnering and acquisition of new technologies/companies. Over the last decade, however, a more open innovation model has been employed with the pharma or medtech companies partnering extensively across the value chain to acquire, and bring new products to market. In effect an extensive, emerging biotechnology/medtech industry (consisting of RIPCOs, FIDDOs and other startups) has developed to eventually partner with (and be acquired by) the larger organizations that have become much less vertically integrated (still called FIPCOs).

The open innovation business model involves partnering globally, whereby academia, emerging companies and larger organizations that "face the customer" have collaborated to bring innovation to the marketplace. In this paradigm, the existence of intellectual property (particularly in the form of a patent) is considered as necessary conditions for these smaller, emerging organizations to monetize their assets and convey rights to the larger organizations via a license or actually selling part of the ultimate product to the larger partner. Indeed a recent *Journal of Commercial Biotechnology* article by Boni[11] titled "Project, Product or Company", discusses the multiple options or paths to the market that must be considered when developing the commercialization strategy to be employed for translation of a technology or invention into an innovation.

A REAL ILLUSTRATION

The points argued above are illustrated below in a "mini case" on Stentor, Inc. This case is based on a real commercialization opportunity that arose when the author was director of technology management at the University of Pittsburgh. A company, Stentor, Inc. was formed around a patent; a novel medical technology was brought to market successfully; and, Royal Philips Electronics eventually acquired the company after it demonstrated market traction (the Stentor product was adopted in the Phillips product portfolio and is continuing in use today) — a successful outcome for all parties.

So as not to divulge any private data, this mini case uses only publically available information that appeared in the press just before and after the acquisition, or in the public stock-offering prospectus (S-1) filed by the company with the U. S. Securities and Exchange Commission (SEC). As discussed more fully below, a breakthrough technology was developed in a university laboratory. The inventor/technology developer argued that the technology should be "open sourced" to promote wide dissemination, since he was most familiar with the software industry. The "secret sauce" that enabled this invention was based on a software algorithm, and it is common to try to apply a typical software (or digits) approach to monetization instead of what is more common with hardware (widgets) or chemical/biological entities where patents are almost always employed. In fact the situation described in the Stentor case involves both "digits and widgets", therefore both methods of monetization can be applied. The revenue model employed by Stentor was Software as a Service (SAAS), but the business model itself would necessitate patenting of the algorithm, and thereby enabling the customer to apply the technology to "commoditized" computers — in this case low-cost PCs and not more-expensive workstations. Those of us charged with managing the IP of the university argued that the technology should be patented to promote successful commercialization — as discussed in this article.

Stentor mini case

In the mid part of the 1990's companies such as GE and others utilized specialized computer workstations to transmit and view medical images. These Picture Archiving and Retrieval Systems (PACS) cost well over

$100,000. Dr. Paul Chang, a radiologist at the University of Pittsburgh and UPMC Health System developed a software solution that made it possible to achieve the same objective (managing high quality medical images and information across multiple facilities) at a significantly lower cost, and with an easier to use system that could be deployed in a doctor's office via an ordinary network of desktop PCs. This is a classic disruptive innovation opportunity, c.f. Christensen.[8] Pamela Gaynor, Staff Writer for the Pittsburgh Post-Gazette reported the following in an article published in 2000.[12]

"The high cost of the PACS systems made them prohibitive for all but the nation's largest medical centers, and even then only in the radiology departments. (Christensen would eventually characterize this as a disruptive innovation–provider and point of care). PCs did not have the capacity to handle the volume of data in medical images, and the workstation manufacturers, but only with severe degradation of the image quality. The Chang breakthrough employed a "just in time approach" whereby only those parts of the image needed at the time were handled by a software solution (in effect a compression/decompression algorithm). This was inspired by his visit to a factory that had done away with its parts warehouse by adopting "just in time" delivery of its supplies. Chang argued that this technology would give all physicians at a health system, not just the radiologists' access to top-quality electronic images (and at an affordable price). Chang's initial approach was to develop the software and give it away to the PACS manufacturers with whom he had a working relationship".

So, Chang approached the office of technology management at the University of Pittsburgh, and also officials at the UPMC Health System since he was also part of their radiology department. We all quickly came to the conclusion that while working with the PACS manufacturers was a possible route, there were some downsides to taking that approach so early in the development cycle. Since there were multiple manufactures, there was little incentive for any of them to commercialize the technology for several reasons. First, why disrupt "themselves" and their current product offering, c.f. Christensen?[8] Their business models were not consistent with selling a lower-cost, easy to use solution inherent in the PC/algorithm solution. Secondly, they would be competing with each other with an undifferentiated solution, and without barriers to entry by their competitors (aside from their existing business channels and arrangements). An alternative would be to form a startup company, develop the technology, begin implementing it at UPMC and other hospitals, and then license or partner with selective PACS organizations. With either alternative, a patent would be required to protect the algorithm.

As reported by Ms. Gaynor, Dr. Chang did not want to form a startup company since his principal interest was to develop the technology. As reported, he also wanted to give the technology away for free (essentially the open source approach). Eventually we all agreed that the best approach here was to form a startup company and license the technology to the company that would carry it forward into the marketplace. Coincidentally, UPMC had invested in Lancet Capital, an early stage venture capital group, who agreed to provide the seed funding for Stentor, Inc. Both Pitt and UPMC received equity as a result of the investment and also co-invested in subsequent financings. The partners of Lancet Capital formed a management team with the expertise needed to commercialize the technology.

Stentor was formed in 1998 and set up operations in Silicon Valley and R&D operations in Pittsburgh. Just two years later, in 2000, they made a "big splash" at the Radiological Society of North America meeting and appeared to be "pushing the industry" according to a clinical radiologist and professor at the University of Pennsylvania, as reported by Ms. Gaynor. After additional investment by Lancet and others, a public offering was planned as the company was gaining market traction. Prior to the IPO, Philips acquired the company for $280 million in cash in 2005, providing a good exit for the investors and originators of the technology ($45.1 million for UPMC — $36 million over their investment of $9.1 million — and $10.8 million for the University of Pittsburgh, c.f. (http://upmc.com/media/NewsReleases/2005/Pages/stentor-release-05.aspx).

From a commercialization perspective the startup, Stentor, brought a truly revolutionary technology to the market via a disruptive innovation (both technological, and point of care), and its products are widely available to the medical community. The public thereby benefitted since cost was reduced and the method of deploying radiological images and data was made more efficient and widespread. It could be argued that human health was improved substantially as well. Could this all have been achieved with an "open source approach"? Not likely. If an open source approach had been taken, it is likely that the "state of software development" would not have been accepted or sufficient for the key commercial players in the market at the time to proceed with commercialization (aside from differentiation and competitive advantage provided by IP). Indeed, even the Google Android open source software approach was insufficient to incentivize key partners to proceed with commercialization (much of this work had to be done in house, and in the case of Stentor, universities/medical centers are not set up to support products. Patents are an essential part of the biomedical business model and provide part of the competitive advantage required to acquire

resources and deploy breakthrough technologies — and improve human health. In this case moving forward with a startup company provided the means and resources to demonstrate the value of the technology and a suitable partner for on open innovation business model. Thus, in the spirit of open innovation, a promising technology was acquired by a larger partner and the product was made available to benefit the public.

ACKNOWLEDGMENT

I wish to acknowledge that while serving as director of technology management at the University of Pittsburgh and leading up the Stentor transaction, I worked very closely with two other individuals who assisted significantly in what became a noteworthy success. I am very grateful for the insights and assistance provided by Scott Lammie of the UPMC Health System and David Kalson, an attorney with Cohen & Grigsby, PC. It took a collaborative team approach to work through the complexity of the process (especially to convince the inventor that the "fork in the road taken", i.e. the startup pathway and the patent filing was the best choice).

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From the Board Room

Getting social with biotechnology business development

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ABSTRACT

Social media is becoming increasingly important in business. While the lack of regulations makes marketing online to consumers a challenge in the life sciences, social media offers significant opportunities to the industry by complementing traditional business development and capital raising activities.

With relatively little effort and expense, companies can build networks, gain trust, and obtain introductions with previously inaccessible targets and distant markets. In embracing social media, individuals themselves become more approachable and open themselves up to business growth that might otherwise have been unattainable.

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Keywords: social media; online; business development; capital raising; biotechnology; twitter; video

INTRODUCTION

Social media use is popular in industries where products are sold directly to consumers. Online tools such as Facebook and Twitter allow increasingly targeted marketing to individuals in a way that traditional mass marketing could never allow, with messages aimed specifically at a particular demographic. Despite this, marketing pharmaceuticals remains a challenge. There are only two Western countries that allow pharmaceutical companies to market their products direct-to-consumer — the United States and New Zealand. In addition to this, the FDA issued draft guidelines for social media marketing to the industry in 2011, but it has been slow to introduce formal regulations.

This doesn't stop pharmaceutical companies from undertaking unbranded awareness campaigns globally without including specific drug information. All top ten pharmaceutical companies in the US (by sales) have a corporate presence on Facebook, Twitter and online blogs. Pfizer has 40,000 people actively following them on Twitter, GSK has 20,000. They use social media to interact and engage with individuals, promote their consumer brands, announce press releases, and raise their profile by discussing their current disease research and support for charities.

Social media is a useful and valuable tool for marketing, corporate relations, employee and patient recruitment, and for business development. I believe the latter is the most underutilised opportunity that social media can offer the life sciences industry, yet with only a little work it offers the greatest reward — particularly for those start-ups who may not have money to burn on traditional methods.

Executives in the pharmaceutical, biotechnology and life sciences industries need no education on the importance of a network, and I would be surprised if any successful executive is not present on at least LinkedIn. As well as acting as a modern day Rolodex, LinkedIn is an excellent platform to find and connect with business development targets. Other corporate social media tools including blogs, Twitter, and YouTube are not used nearly as widely — and yet they should be.

THE VALUE OF TWEETING

Twitter originally was used to allow a direct line of communication and marketing between businesses and celebrities to consumers and fans. The early adopter phase has long since moved on and with latest estimates

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at 250 million users, more and more influential people are using the platform. It is surprising what can be covered in up to 140 characters, and selectively following people is an easy way to keep up to date with development in your area of interest — whether that is diagnostics, therapeutics, capital markets, or a particular disease indication.

The short character limit means that it has never been easier to reach out to someone who might once have been impossible to spend time with — it is amazing how many celebrities, politicians, philanthropists, companies, and business targets will respond when the barrier to reply is low.

A COMPETITIVE ADVANTAGE AT CONFERENCES

Large conferences play an important role in allowing businesses to meet, reunite and engage with companies. They can also be one of the more challenging environments to locate your niche and get time with your hit list. In 2009 at the BIO International Convention in Atlanta I was one of very few attendees tweeting. Twitter has become so popular that just three years later in 2012 there were 14,150 tweets during the week of the convention — without even considering the conversations taking place during the lead up. The annual JP Morgan Healthcare Conference has even run a popular meeting for the last three years exclusively for those on Twitter.

Some of my most opportune business meetings have taken place at a conference by sending a quick tweet to an attendee or speaker. Some of the more interesting people I have met are those who tweet humorous quips during lengthy conference presentations. Although you're already there, social media makes people more accessible. They wouldn't be on social media if they didn't want to be social — and it's a far better use of time than seeking them out in a crowded exhibition hall.

THE ADVANTAGES OF VIDEO

A succinct 90 second video pitch is inexpensive to produce. Even a video from a mobile phone, as long as it's interesting, can be more likely to engage a viewer from beginning to end than a traditional presentation or document. Whether used for exploring partnerships, investment, or to attract media, video allows the viewer to see the founder, the scientist, or the management team, and gives a true insight into the technology, the business model, and the opportunities a business has on offer. It can be the next best thing to meeting a team face to face, and could provide a foot in the door that would otherwise not open. This is particularly pertinent for companies operating from outside major markets. I spent time in New Zealand working with executives of bioscience companies on digital strategies. These companies had a range of successes, with one of the most exciting being a small company that signed on a much sought after distributor in Asia — a 12 hour flight — by getting noticed through Facebook and YouTube, and never leaving the country.

TARGETING INDIVIDUALS

Although social media is traditionally used to reach out to a large audience, we are starting to see it being used to target smaller numbers. For companies with very specific or crucial targets, the natural extreme of this is to reach individual decision makers with tailored marketing material. By intimately understanding a person's interests and online activity, you can offer tweets, videos, blog posts, and messaging that plays to their specific requirements or preferences.

TRUST AND KNOWLEDGE

Social media allows you to connect with and get to know a person in a far more personal way than a quick introduction at a networking function would ever allow. Using online tools has the added advantage of letting people understand the person behind the company — people increasingly share information online about their own beliefs, opinions, passions and emotions. At the same time, by being visible as an individual on social media you are making yourself more accessible and approachable. Most people you interact with online you may never meet, but social media can help you approach a business meeting with enough background on a person to substitute a warm introduction.

No matter where in the world, people do business with people they know, like and trust. This is particularly relevant as we look toward the East, where trust in people arguably takes even more priority than it does in Western business decisions. Even though China has no access to Facebook, Twitter, or YouTube, it has alternatives to each of these. With the largest internet user base and social media activity in the world, online engagement in China is just as important for business, if not more so, as in the United States.

CONCLUSION

Online developments will never replace traditional business development methods — the best contacts I

have made were serendipitous run-ins in the Starbucks line at a convention center. But as far as business development goes, social media offers an excellent complement. Considering that businesses can pay thousands of dollars for the privilege of pitching to a group of investors or to attend a conference, free online tools can be remarkably effective at exposing your business to the world. After all, in business development you have nothing to lose and literally everything to gain.

Legal and Regulatory Update

Bowman v. Monsanto: Revisiting the Exhaustion Doctrine and its application to biotechnology and digital technologies

Received: February 25, 2013

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has extensive background relating to intellectual property and knowledge-economy issues in advanced developing countries including India and South Asia, Latin America and the Middle East North Africa (MENA) region, working with innovative companies through Finston Consulting, LLC since 2005. She also works with governments, and NGOs through BayhDole25, with education and outreach activities including submission of amicus briefs to the U.S. Supreme Court in both *Bowman v. Monsanto* and *Microsoft v. AT&T* (2007). Together with biotechnology pioneer Ananda Chakrabarty, she also is co-founder of Amrita Therapeutics Ltd., an emerging biopharmaceutical company based in India with cancer peptide drugs entering in vivo research.

ABSTRACT

On February 19, 2013, the U.S. Supreme Court heard oral argument in *Bowman v. Monsanto* – the first case to directly present the question of how the exhaustion doctrine should apply to patents relating to biotechnology and digital technology inventions. The Petitioner, Vernon Hugh Bowman, asserts that the exhaustion doctrine should be extended to advanced agricultural technologies where the technology itself is contained in genetically modified seeds that may be reproduced through successive generations of seeds without limitation, and that companies like Monsanto can instead rely on remedies found in contract law to protect their commercial interests. The Respondent, Monsanto Corporation, supported by the U.S. Government, (not surprisingly) disagrees, contending that an extension of the exhaustion doctrine of this magnitude would undercut effective patent protection for inventions that may reproduce perfectly over generations, undermining R&D in innovative technologies.

During the *Bowman v. Monsanto* oral argument on February 19th, the Justices focused on the broad scope of the exception sought by Bowman to patent rights for GM seed as an extension of the exhaustion doctrine to biotechnology and digital technology inventions, and did not appear persuaded either that the only reasonable use of the soybeans by Bowman was to plant them or that right holders would find effective modes of protection through contract law. The Justices noted that this was the first case to present the intersection of the exhaustion doctrine and effective protection for inventions that may be reproduced across generations. That intersection between exhaustion and effective patent protection for reproducing inventions appeared to be the issue of greatest interest to the Court in *Bowman v. Monsanto*, where the Court may be unlikely to create a sweeping exception to patent rights for biotechnology or digital technology inventions that has not been contemplated by the Congress.

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Keywords: Bowman v. Monsanto; exhaustion doctrine; self-replicating inventions; GM Seed;

INTRODUCTION

Bowman seeks a substantial change in the current reach of the exhaustion doctrine and the balance of benefits between patent-holders and purchasers or licensees, including the right to reproduce the invention without limit and without payment of royalties to the patent-holder. The root cause of this dispute is the

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straightforward commercial interest of Bowman in Roundup Ready® technology and in gaining continuing access to the technology beyond the agreed use under the Technology Agreement in place between the Parties, for his second season planting. Monsanto's Roundup Ready® technology is a patented gene sequence that provides resistance to the effect of the related Roundup® glyphosate herbicide, with substantial commercial and environmental benefits for farmers. Monsanto can't recoup its investment in the patented technologies through outright sale, and instead provide access to the Roundup Ready® technology to farmers through a rolling, multi-year contract known as the Technology Agreement.

As one of Monsanto's licensed seed producers, Pioneer Hi-Bred ("Pioneer") sold Pioneer Hi-Bred® brand seeds containing the Roundup Ready® technology to Bowman over a number of years. Pioneer required Bowman to execute the "Pioneer Hi-Bred Technology Agreement," restricting Bowman's use of the soybeans. The Pioneer Technology Agreement contains language and restrictions identical to Monsanto's Standard Form Technology Agreements. Specifically, Bowman agreed:

> (1) "[t]o use the seed containing the subject technology for planting a commercial crop only in a single season";
>
> (2) "[t]o not supply any of this seed to any other person or entity for planting, and not to save any crop produced from this seed for replanting, or supply saved seed to anyone for replanting";
>
> (3) "[t]o not use this seed or its progeny or provide it to anyone for crop breeding, seed production or research (other than to make agronomic comparisons and conduct yield testing)."[1]

Between 1999 and 2007, Bowman legally acquired the technology in accordance with the Technology Agreement for his first-crop planting. For his second-crop planting, however, he planted Roundup Ready® soybeans purchased from a commodity grain elevator as undifferentiated soybeans not intended for use as seed, as well as (from 2000 onwards) seeds saved from prior years' second-season harvests.

DISTRICT COURT AND APPELLATE COURT FINDINGS OF PATENT INFRINGEMENT

After Bowman's activities beyond the scope of the Technology Agreement came to light, Monsanto brought suit against Bowman in the Federal District Court for patent infringement,[2] and was awarded damages in the amount of $84,456.30 on summary judgment. *Monsanto Co. v. Bowman*, 686 F. Supp. 2d 834 (S.D. Ind. 2009).

The U.S. Court of Appeals for the Federal Circuit upheld the district court decision, holding that "[P]atent exhaustion does not bar an infringement action", and explaining that "The right to use does not include the right to construct an essentially new article on the template of the original, for` the right to make the article remains with the patentee." (quoting *Jazz Photo Corp v. International Trade Commission*, 264 F3D 1094, 11-2 Fed Cir. 2001), Cert Denied, 536 U.S. 950 (2002) (Brackets in Original). *Monsanto Co. v. Bowman*, 657 F3d 1341 (Fed Cir.2011). The U.S. Court of Appeals also disagreed with Bowman's suggestion that planting of the commodity seed is the "only reasonable and intended use" of the soybeans (quoting *Quanta Computer Inc., v. IG Elecs., Inc.*, 553 U.S. 617, 631 (2008)). In sum, both the district court and the Court of Appeals for the Federal Circuit rejected Bowman's defense of patent exhaustion.

QUESTIONS BEFORE THE U.S. SUPREME COURT

Following the Court of Appeals decision against Bowman, Bowman filed a Petition for Writ of Certiorari to the U.S. Supreme Court, presenting the question:

> "Whether the Federal Circuit erred by (1) refusing to find patent exhaustion in patented seeds even after an authorized sale and by (2) creating an exception to the doctrine of patent exhaustion for self-replicating technologies?" Petition for a Writ of Certiorari, *Bowman v. Monsanto Co.* (Dec 11, 2011).

While the case may have commenced as a straightforward dispute over the failure of Bowman to pay for the continuing use of Monsanto's patented technology over several years, it has taken on greater importance with high stakes on both sides as it reached the U.S. Supreme Court. When the U.S. Supreme Court granted Bowmans' Petition for a Writ of Certiorari on October

1 Pet. App. 6a-9a, 21a; JA27a; see also Fed. Cir. JA A0284-A0315.

2 Infringement of two patents relating to the Roundup Ready Soybeans: U.S. patent Nos. 5,352,605 and RE39,247E.

5, 2012, following successive losses at the district court and appellate court levels, opponents of patents for GM seed hoped that the Bowman case could provide a vehicle for the Supreme Court to revisit patentability of genetically modified seed (e.g., *Diamond v. Chakrabarty* (1980)), or at least to curtail the impact of biotechnology patents through expansion of the exhaustion doctrine to allow farmers to go back to older practices of saving, buying and selling their seeds freely as was the case prior to the advent of patented seed technologies in the late '70s, while still gaining commercial benefit from the advanced agricultural technologies now included in GM seeds.

Bowman v. Monsanto has attracted a great deal of media attention, with Bowman portrayed as a David standing up to the Goliath of agricultural biotechnology, and with many amicus briefs filed on both sides. Both Monsanto and the U.S. Government have confirmed that this case does not affect any farmers who find GM seeds accidentally growing in their fields, which appears to be unlikely, at least in the case of soybeans.

TESTING THE LIMITS OF PATENT EXHAUSTION

As noted by the U.S. Government in its brief in support of Bowman, the exhaustion doctrine as currently applied under U.S. jurisprudence extends to the actual item(s) purchased, not to future or successive generations of products. In other words, an authorized sale serves to exhaust the patent-holder's rights with respect to that item itself, and does not enable the purchaser to use the technology to reproduce new copies of the original.[3] Vernon Hugh Bowman advances an alternative interpretation of the exhaustion doctrine as defense against allegations of patent infringement for Monsanto's Roundup Ready® technology.

Even before he had a chance to frame the argument, Chief Justice Roberts challenged the underlying logic of Bowman's argument: "Why in the world would anybody spend any money to try to improve the seed if as soon as they sold the first one anybody could grow more and have as many of those seeds as they want?" Counsel for Bowman sought to distinguish the case by raising the use of contracts in place of patent rights, initially asserting that the exhaustion doctrine already provides protection to Bowman, as "part of the patent policy is to protect the purchaser, and that's been part of this Court's law for more than 150 years."[4]

Bowman, however, was not seeking continued use of the soybeans purchased from Monsanto's authorized agent, and instead has been using the Roundup Ready® soybeans acquired from the commodity grain silo to make an entirely new generation of soybeans. Based on the statement of the facts most sympathetic to Bowman, he is not using the products of the Roundup Ready® seeds initially purchased from Monsanto, because he has conveyed them to the commodity grain elevator prior to re-purchasing soybeans for his second-season crop.

In other words, while the traditional exhaustion doctrine would govern the scope of Bowman's rights with respect to the Roundup Ready® soybeans acquired under the technology agreement, Bowman argues that it should protect against claims of patent infringement relating to the Roundup Ready® soybean purchased from the commodity grain silo. The Justices noted this distinction, as summed up by Justice Ginsburg:

> [T]he exhaustion doctrine was shaped with the idea of an article; there was an article that you could use and then you use it and its used up. But we haven't applied the exhaustion doctrine when you have a new – when you create a copy of the original. So it's – it's not that we have law in place. We've been dealing with an item with the exhaustion doctrine and now we have hundreds of items, thousands of items, all growing from that original seed.

After initial demurral, Bowman's counsel conceded the point: "This is obviously a brand-new case where we're dealing with the – doctrine of patent exhaustion in the context of self-replicating technologies."[5] Further, under the proposed extension of the exhaustion doctrine proposed by Bowman, whether or not the farmer has ever entered into the Technology Agreement, s/he would be free to acquire seeds from a third party and to utilize the Roundup Ready® soybeans without infringing Monsanto's patents.[6]

3 Brief for the U.S. Government Supporting Affirmance, *Bowman v. Monsanto*, p. 6., citing the language of *Jazz Photo Corp v. International Trade Commission*, 264 F3D 1094, 11-2 Fed Cir. 2001), Cert Denied, 536 U.S. 950 (2002)) as cited in the Court of Appeals for the Federal Circuit opinion in *Bowman v. Monsanto Co.*

4 Mr. Walters, Oral Argument Transcript, p. 4.

5 Mr. Walters, Oral Argument Transcript, p. 12.

6 JUSTICE GINSBURG: Well, suppose he – he had never bought any Monsanto seeds. He just goes to the grain elevator and 90-odd percent of those seeds have the genetic composition. So – and he planted that and he harvested it. Would he be infringing on Monsanto's patents?
MR. WALTERS: No.
JUSTICE GINSBURG: So he never has to buy any seed at all from Monsanto. (Oral Argument transcript, p. 10.)

ABOUT THAT SELF-REPLICATING TECHNOLOGY …

Bowman's second line of argument – that the only possible use of the Roundup Ready® technology as a self-replicating technology is to plant it for successive generations of soybeans – appeared tautological during oral argument and was also challenged by the Court.

Although the commodity grain silo sells soybeans for a variety of uses including for animal feed, food processing, etc., Bowman asserts that the only reasonable use of the invention that Bowman could make is to use the soybeans as seed. After several quips (including mention of possible uses for the seed including as tofuturkey), Justice Breyer noted in a more serious vein:

> Now, there's another law that says you cannot make copies of a patented invention. And that law you have violated when you use it to make generation 3, just as you have violated the law against assault were you to use it to commit an assault. Now I think that's what the Federal Circuit is trying to get at. And so it really has nothing to do with the exhaustion doctrine. It has to do with some other doctrine perhaps that – that somehow you think should give you the right to use something that has as a basic purpose making a copy of itself. Maybe you should, but I don't see that. Where is that in the law?[7]

Based on Bowman's initial brief and reply brief filed with the Court and representations at oral argument, the source of that right in the patent law remains unclear, at best. On the other side of the argument, counsel for the United States appearing as amicus curiae pointed out that the U.S. patent law does not include exceptions for seed saving or research, and both counsel for the United States and counsel for Monsanto pointed to the logical consequence of Bowman's argument: that even the sale of the first progeny of Monsanto's Roundup Ready® technology for initial breeding purposes prior to retail sale to farmers would exhaust its patent rights, making it impossible to recoup its investment of hundreds of millions of dollars over thirteen years of research and development. (This imbalance in the positions of the two sides contributed to an overall feeling that the oral argument was somewhat one-sided.)

7 Oral Argument transcript, p. 3.

INHERENT WEAKNESS OF CONTRACTS TO PROTECT GM SEED

On the issue of whether contract law could substitute for patent rights, the Court did not appear persuaded that companies could protect innovative biotechnology inventions through contract alone, and extended this logic to digital technologies, via discussion of *ATT v. Microsoft* (2007)[8] in colloquy with counsel for the United States (amicus curiae), and counsel for Monsanto. As expressed by Justice Kagan, "all that has to happen is that one seed escapes the web of these contracts, and that seed, because it can self-replicate in the way that it can, essentially makes all the contracts worthless."[9] Again, there did not appear to be a clear response to the concerns raised on this issue by the Court.

CONCLUSION

Bowman v. Monsanto appears to be of interest to the Court as the first case to present directly the intersection of the exhaustion doctrine and effective protection for biotechnology or digital technology inventions that may be reproduced perfectly and endlessly. The implications of Bowman's proposed extension of exhaustion to include the right to make new generations of the invention appear daunting. While it is not possible to know what is really in the minds of the Justices now or next June when the case will be decided, Bowman appeared to face substantial skepticism over the viability of a business model for R&D requiring substantial investment over a period of years, where the first sale would enable the purchaser to reproduce the invention with impunity. The Court's preference to not act in the absence of strong signals from Congress (as in *Microsoft v. AT&T* (2007) on the issue of extraterritoriality), may further reduce the likelihood that the Court would extend the exhaustion doctrine to products that may be re-invented, thereby creating exceptions for seed saving and/or research where none currently exists in the U.S. patent law.

8 Bowman's counsel noted that that case did not turn on the issue of patent exhaustion, given that the Court found no patent infringement due to extraterritoriality. Nonetheless, the Court appeared sympathetic to the specter of limitless perfect digital copies that could be produced without obligation to the patent-holder under the proposed expansion of the exhaustion doctrine.

9 Oral Argument transcript, p. 19.

Legal and Regulatory Update

Should the HHS decision to overrule FDA on Plan B be reversed?

Received: February 2, 2013

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ABSTRACT

On December 7, 2011, Secretary of Health and Human Services Kathleen Sebelius overruled a decision of the Food and Drug Administration (FDA) on the over-the-counter (OTC) status of emergency contraception.

What will be the repercussions of Secretary Sebelius's action? Why is the act itself of far greater long-term significance than the transitory regulatory action it impacts?

By reversing an FDA decision, the Secretary has set a dangerous precedent for all-comers to lobby Congress, the Department of Health and Human Services (HHS) and the White House on any and all FDA decisions—directly inserting politics into what must be a scientifically driven process.

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Keywords: FDA, HHS, Plan B

INTRODUCTION

On December 7, 2011, Secretary of Health and Human Services Kathleen Sebelius overruled a decision of the Food and Drug Administration (FDA) on the over-the-counter (OTC) status of emergency contraception.

What will be the repercussions of Secretary Sebelius's action? Why is the act itself of far greater long-term significance than the transitory regulatory action it impacts?

By reversing an FDA decision, the Secretary has set a dangerous precedent for all-comers to lobby Congress, the Department of Health and Human Services (HHS) and the White House on any and all FDA decisions—directly inserting politics into what must be a scientifically driven process.

BACKGROUND

Secretary Sebelius's overruling of FDA's decision to permit OTC sales of emergency contraception without any age restrictions marked the first time that an HHS Secretary has ever usurped FDA's authority over a regulatory decision.

Despite the high-velocity nature of reproductive rights and their potential political repercussions during a presidential election cycle, the more important issues relate to the erosion of faith in FDA's authority by both the communities the agency regulates as well as the public at large.

This decision directly and unambiguously injects politics into the FDA regulatory process. Even if this specific decision was made with the most altruistic of intentions, the precedent is clear—FDA is not the master of its own regulatory decisions.

If this decision stands, the obvious next question is, do we even need to have an FDA? And that's a dangerous proposition.

MAJOR ISSUES IN DISPUTE

What are the unintended consequences of a Health and Human Services Secretary overruling an FDA regulatory decision?

Secretary Sebelius's unprecedented overruling of FDA's decision makes one thing clear—the door is now wide open to anyone to lobby Congress and HHS regarding any FDA decision not to their liking.

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When asked directly if the White House had weighed in on this matter, the HHS press office refused to comment. This refusal to comment is surprising, considering the high-profile nature of this particular product and that this is the first time that a politically appointed official at HHS has overruled an administrative decision by FDA. As the New York Times opined in a December 7 editorial:

> *After a careful review, the F.D.A. was about to approve the drug for all females of childbearing age, based on evidence that it is very safe and effective and that adolescent girls can understand how to use it and what it does (prevent pregnancy) and doesn't do (protect against sexually transmitted diseases). That was the considered judgment of agency scientists. The agency's commissioner, Dr. Margaret Hamburg, concurred after conducting her own review.*

Kathleen Sebelius, the Secretary of Health and Human Services, reversed the decision, arguing that younger girls, those 11 or 12 years old, have different cognitive and behavioral skills than older girls. She offered no evidence to challenge her agency's in-depth analysis. And it is hard not to see this as anything but an effort to blunt Republican criticism in the presidential campaign or shield the F.D.A. budget from retaliation. Unfortunately, the losers will be young girls who need easy access to the pill."[1]

Having served as Associate Commissioner at the FDA during the first round of Plan B hysteria, I can personally attest to the heat and scrutiny it generated—and, appropriately so. The significant difference about the last time is that it was a debate internal to the agency. There were differences of opinion to be sure—and you can argue whether or not there was political pressure brought to bear—but the decisions (whether you agreed with them or not) were FDA decisions.

Why don't the arguments in support of the Secretary's decision pass either scientific or political muster?

Two studies, described by FDA Commissioner Margaret Hamburg as "designed specifically to address the regulatory standards for nonprescription drugs," clearly "hit their endpoints."[2] In other words, both studies (of girls aged 12 to 17 and 11 to 16) demonstrated sufficient understanding of the package by those age cohorts to take the medication without a doctor's supervision.

Here's the regulatory logic as explained by Commissioner Hamburg:

> *The Center for Drug Evaluation and Research (CDER) completed its review of the Plan B One-Step application and laid out its scientific determination. CDER carefully considered whether younger females were able to understand how to use Plan B One-Step. Based on the information submitted to the agency, CDER determined that the product was safe and effective in adolescent females, that adolescent females understood the product was not for routine use, and that the product would not protect them against sexually transmitted diseases. Additionally, the data supported a finding that adolescent females could use Plan B One-Step properly without the intervention of a healthcare provider.*[3]

That's a key OTC question—can the patient understand how to use the product without the supervision of a physician?

Asked and answered. Yes. Efficacy was never an issue and safety is always (it is important to understand) a relative concept.

Perhaps it's better, in the context of Plan B, to refer instead to benefit and risk. The benefit is a reduction in unwanted pregnancies. The risk is a medical/scientific question. And the risks are minimal enough for this product to already be available OTC to older teenagers.

Then Commissioner Hamburg put the issue into its proper perspective:

> *It is our responsibility at FDA to approve drugs that are safe and effective for their intended use based on the scientific evidence. The review process used by CDER to analyze the data applied a risk/benefit assessment consistent with its standard drug review process. Our decision-making reflects a body of scientific findings, input from external scientific advisory committees, and data contained in the application that included studies designed specifically to address the regulatory standards for nonprescription drugs. CDER experts, including obstetrician/gynecologists and pediatricians, reviewed the totality of the data and agreed that it met the regulatory standard for a nonprescription drug and that Plan B One-Step should be approved for all females of child-bearing potential.*[4]

And then Dr. Hamburg reminded us of her personal responsibility, "I reviewed and thoughtfully considered the data, clinical information, and analysis provided by CDER, and I agree with the Center that there is adequate and reasonable, well-supported, and science-based evidence that Plan B One-Step is safe and effective and should be approved for nonprescription use for all females of child-bearing potential."[5]

The regulatory science experts at FDA were satisfied. The FDA Commissioner was satisfied. Both were satisfied as to the sound scientific basis of the agency's

decision. From a nuts-and-bolts perspective, this decision was not of the overly nuanced variety. But, what of the moral implications? Well, not to put too fine a point on it, who cares? The first thing we need to stipulate is that FDA does not (and should not) render its decisions based on morality. Morality is important, but it is not science. That's why FDA doesn't do death panels.

(Speaking of which, you may ask, what about expanded access programs for oncology medicines? I believe there is a fundamental difference between access to potentially life saving medicines and every other category of FDA regulated products. That is why, in PDUFA V, there is general consensus that the patient voice must be taken into more careful consideration during product reviews and factored into the still nascent FDA concept of a more formalized mechanism for risk/benefit analysis.[6])

So, was the decision to override FDA based on a different view of benefit and risk? Here is the explanation the Secretary gave for her decision:

> *Today's action reflects my conclusion that the data provided as part of the actual use study and the label comprehension study are not sufficient to support making Plan B One-Step available to all girls 16 and younger, without talking to a health care professional.*[7]

In other words, Secretary Sebelius—a lawyer—studied the Teva data and decided they were not robust enough to meet the standard for approval. That's right, the Secretary studied the data and reached a different conclusion from the experts at FDA.

And maybe she did. In fact, let's give her the benefit of the doubt and stipulate that she did. This raises two important questions: 1) why did she study the data in the first place and 2) what are her qualifications to do so? Does she regularly study data on FDA decisions?

If so, did she study the data on Avandia? Did she study the meta analysis on the potential for cardiac risk for children taking medications for ADHD? And if not, why not? What about Avastin? (Even before FDA announced its recent decision to remove that drug's breast cancer indication, the Centers for Medicare & Medicaid Services announced they would continue reimbursement for this use—regardless of the FDA's decision.[8])

Why intercede on the Plan B decision when, from a risk/benefit proposition, so little is at stake? (Another issue at play here is some sort of official BTC (Behind-the-Counter) designation—but that's another discussion for another time.)

Then there's another, more troubling, question: how is this happening? I don't think the Secretary would ever claim to be an expert in regulatory data analysis, so to whom is she turning for advice on these matters? Is there some double secret shadow-FDA deep within the bowels of the Humphrey Building? And, if there is, who is staffing it?

According to the December 7 statement by Secretary Sebelius, "I have directed FDA to issue a complete response letter (CR) denying the supplemental new drug application (SNDA) by Teva Women's Health, Inc."[9] She added in a subsequent interview, "There are always opportunities for the company to come back with additional data."[10]

If Teva decides, based on the contents of the CR, to resubmit their application, should they also send a copy to Secretary Sebelius? Perhaps they should bypass FDA altogether? After all, the agency has already signaled that they already approve—based on data already submitted—of broader OTC availability. And how closely will Secretary Sebelius and her secret FDA monitor the drafting of this CR? Will the CR be drafted in White Oak or at 200 Independence Avenue?

Senator Patty Murray has asked the Secretary to testify in front of a Senate committee to explain her scientific views on the matter. Senator Murray stated, "I want to know what the scientific evidence is that the secretary made this decision on in overriding the FDA … Pharmaceutical companies here in this country make some very expensive decisions, and they need to know that the FDA is going to base a decision based on science."[11]

In fact, 13 senators (Kirsten Gillibrand, Barbara Boxer, Richard Blumenthal, Daniel Akaka, Carl Levin, John Kerry, Tom Harkin, Al Franken, Frank Lautenberg, Bernie Sanders, Ron Wyden, Maria Cantwell and Jeff Merkley) joined Senator Murray in a rather terse letter to the Secretary asking, "that you share with us your specific rationale and the scientific data you relied on for the decision to overrule the FDA recommendation. On behalf of the millions of women we represent, we want to be assured that this and future decisions affecting women's health will be based on medical and scientific evidence."[12]

All this to say that it's pretty tough to believe that Secretary Sebelius made this decision minus any consultation with the White House. And if she did, well, she's got a lot of explaining to do. Qui bono? Certainly not Secretary Sebelius.

Now let's address some relevant social science to add some spice and context to this historic decision.

According to the Guttmacher Institute, a nonpartisan research institute that studies sexual health, less than 1 percent of 11-year-olds are sexually active, but almost half of teenage girls are having sex by age 17. Importantly, there's no evidence to suggest that making Plan B available OTC without respect to age will somehow cause younger teenagers to start having sex

in greater numbers. Looking north to Canada, where Plan B is sold over the counter and without age restrictions, there has been no increase in teen pregnancy, no outbreak of promiscuity in junior high school, no uptick in any drug-related adverse events. From a public health perspective, it's important to note that the United States has a teen birth rate three times that of Canada.[13]

Secretary Sebelius's claim that she's standing up for better science instead of pandering to American fears about teenage sexuality becomes more and more suspect the more and more you consider the facts.

WHAT HAS THE PRESIDENT DONE TO EITHER MITIGATE OF ENFLAME THE ISSUE?

Whether or not the President will receive any political benefit from this is certainly open to debate. Consider his statement on the issue. First he said, "as the father of two daughters," he supported the Secretary's decision.[14]

Really? If he had been the father of two sons, would be have felt differently? As the Feminist Majority Foundation commented, "Who needs lengthy scientific review, when apparently father knows best?"[15]

The President believes that 10- and 11-year-olds should not be able to buy Plan B "alongside bubble gum or batteries."[16]

Such a non-serious statement should generally go without comment, but let me make just one: how many more adverse events are caused by a plethora of other OTC products? Should they all be withdrawn beyond the proximity of bubble gum and batteries? In fact, there are likely more adverse events related to bubble gum than for Plan B. (In December 2009, Ukrainian media reported that a chemistry student from the northern city of Konotop was killed when a stick of chewing gum exploded in his mouth. You can never be too careful.[17])

Finally the President commented, "I think it is important for us to make sure that we apply some common sense to various rules when it comes to over-the-counter medicine."

Whatever that means. Does it mean that "common sense" should overrule, um, science? Is "common sense" a wink-and-a-nod placeholder for "politics?"

According to an article in the Washington Post, "One former White House official familiar with decision-making on such issues said the scientific evidence clearly supported the FDA's findings that it was safe for girls younger than 17 to use Plan B without a prescription—adding that this was a higher standard than that applied to any number of potentially lethal medications offered over the counter. One of the President's first executive orders was that we will use science to guide decisions and not politics, said the official. And I don't understand how this can possibly square with science."[18] Transgenic salmon anyone?

The Secretary's reversal of this specific FDA decision must be reversed by direct order of the President in order to maintain trust and respect for FDA's regulatory authority.

Leaving aside the peculiar politics of reproductive health, this reversal by the Secretary of an FDA decision must itself be reversed by direct order of the President in order to maintain trust and respect for FDA's regulatory authority. Left standing it will severely undermine the authority of the FDA and embolden those who think that political arm-twisting should be used to influence agency decisions. Unless this action is undone, there will be a continued diminishment of faith in the FDA as the expert and ultimate arbiter of issues put before the agency.

A MODEST PROPOSAL

So that this can never happen again, and to signal the importance of FDA's integrity and authority, Congress must act to remove the ability of the Secretary of Health and Human Services to reverse FDA decisions.

When one considers the mission of FDA—to independently protect and advance the public health—it is not at all clear whether the Commissioner should be a Senate-confirmed political appointee "serving at the pleasure of the President."

I think that the American people would prefer he or she be nominated by the President for a fixed 6-year term—similar to that of the Director of the FBI—and then approved by the Senate. Think about it—why should the safety of food additives, the integrity of the blood and vaccine supply, and decisions on drug labeling indications (to name only a few FDA responsibilities) be considered Democratic or Republican issues? The boss of the FDA Commissioner is and should continue to be the Secretary of Health and Human Services—a politically appointed, Senate-confirmed cabinet officer.

Let the person chosen as FDA Commissioner serve as free of the political current as possible. Selection of career officials should not be dismissed out of hand. Such selections have led to excellent choices at, for example, the Centers for Disease. Control and Prevention and the Food Safety and Inspection Service, two complex, important, and large organizations with critical public health missions—and both overseen by cabinet secretaries.

CITIZENS PETITION DENIED BY FDA; RENDERED "MOOT " BY JUDGE

In a related matter, FDA has denied a citizen's petition from the Center for Reproductive Rights to allow broader access to generic versions of the Plan B contraceptive for girls under 17. At issue was whether the Teva product should be taken out from behind the pharmacists' counter, making it available outside pharmacy hours—and without a prescription for girls younger than 17 for the first time.

In a letter explaining its actions to the center, FDA points out that the application to approve access to girls 16 and younger without a prescription was denied because Teva provided data for Plan B One-Step, a single-dose tablet, not Plan B. (Plan B One-Step is an OTC pill for women ages 17 and older and is available by prescription for those under the age of 17. Plan B, on the other hand, uses a two-dose regimen, as per the FDA.) According to the FDA, "In particular, because Plan B One-Step consists of a single tablet, the dosing data for Plan B One-Step could not provide support for an OTC switch of Plan B as that data would not adequately address the ability of subjects to correctly follow the directions related to the timing of a second dose that is required for proper use of Plan B."

U.S. District Judge Edward Korman said that FDA's response rendered moot a complaint to hold the agency in contempt of court. But, the court is willing to hear arguments on whether FDA should stop requiring prescriptions for girls younger than 17 to buy morning-after pills. Judge Korman invited the Center for Reproductive Rights to file appropriate legal motions in the case, and said that Secretary Sebelius could be added as a defendant.[19]

Which raises an interesting question—will FDA experts testify against the Secretary? Will Commissioner Hamburg?

CONCLUSION

As a veteran of the regulatory wars, my argument is that the rocky seas began to roil when the position of FDA Commissioner was converted from a career position to a political position in the late 1960s. Prior to that time, the FDA chieftain was generally someone who had advanced through the ranks of the agency gaining experience and seasoning along the way.

When the Commissioner's position became Senate confirmable in the late 1980s, some believe an adverse change took place. Others believe that politics is just more contentious than ever before. Both of these notions are correct.

Having had the honor to serve our country and our President as an FDA Associate Commissioner, I can unequivocally state that the unwelcome infusion of politics into science makes an already difficult job virtually impossible. To have the job of Commissioner open and only partially filled for extended lengths of time grinds progress to a halt. Low morale, lengthy delays, and even postponements often characterize an open Commissionership. This is not acceptable. Unless and until we address this and the other issues discussed in this paper, December 7, 2011, will be a day that lives in regulatory infamy.

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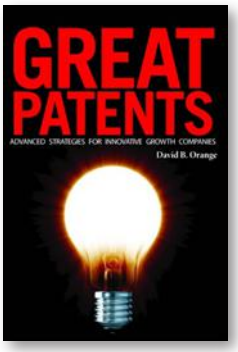

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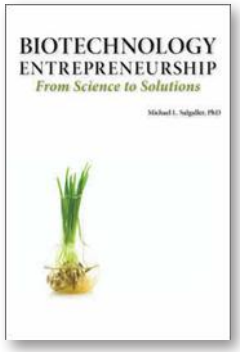

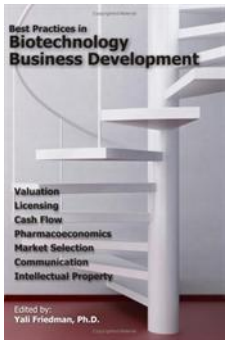

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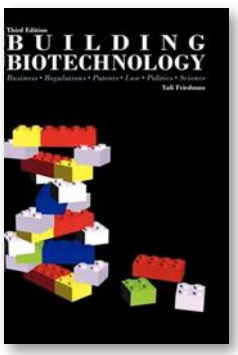

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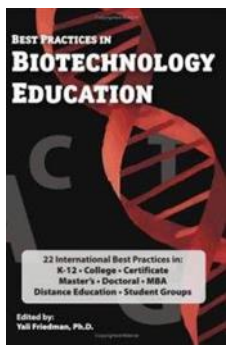

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