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Commentary

Labeling, Lawyers, & Logic

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America deserves access to high-quality health care without avoidable medical errors and complications. This achievable goal begins with harnessing and using the power of information. And that begins with clear, accurate, and usable labeling.

The American health care system is undermined, underserved, and undervalued when labeling is written more for corporate liability protection than as a valuable tool for health care providers.

Today, labeling includes excessive risk information and exaggerated warnings. And this has set into motion a dangerous dynamic: labeling that does not accurately communicate to either the health care professional or the patient the conditions in which any given product can be used safely and effectively. This is nothing less than a grave menace to the public health.

America is suffering from a legal system that is dangerous to its health. Why has this happened? There is, unfortunately, a simple answer - fear of liability.

Manufacturers have significant monetary incentives to add dense and confusing legalese because, under current law in most states, they can be found liable for failing to provide "adequate" warnings about therapeutic products.

Money, not medicine, is driving this dangerous practice. When it comes to labeling written for lawyers rather than doctors, more is less.

LESS AVAILABILITY

The public's access to timely, innovative, and affordable health-care is severely impaired when manufacturers respond to liability costs by withdrawing beneficial products from the marketplace. The signal example of this is Bendectin (pyroxidine HCl/doxylamine succinate), a drug approved by FDA in 1956 to prevent nausea during pregnancy. A quarter of pregnant women once used Bendectin to help prevent morning sickness.

Although the Food and Drug Administration and the scientific community determined that the drug did not cause birth defects, isolated statements to the contrary in the scientific literature beginning in 1969 prompted a flood of lawsuits. Facing more than 2,000 lawsuits claiming birth defects and $18 million in claims, against $20 million in sales, Merrell Dow Pharmaceuticals pulled the drug from the market in 1983. No evidence ever linked the drug with birth defects, and the drug is still sold abroad. Thankfully, birth defects in the U.S. have remained flat in that period, but morning sickness hospitalizations have doubled.

Lyme disease remains an often-misdiagnosed disease that causes severe arthritis-like symptoms and can impair brain function. Less than a year after GSK introduced LYMErix in 1999, attorneys claimed the adult Lyme Disease vaccine caused arthritis. In 2002, GSK withdrew the drug. Lyme disease infections grew by 40 percent.

More liability results in less availability.

LESS INNOVATION

Health care innovation is thwarted when manufacturers choose to devote their finite research and development resources to creating products they believe will not be associated with uncertain and potentially high-stakes liability costs.

Today, developers of new medical products increasingly need to set aside billions of dollars, or redirect their research activities from potentially valuable directions, in anticipation of the potentially unlimited risk of mass tort lawsuits.

Liability risk is inversely related to levels of research and development activity. The lack of innovation in the areas of vaccines, contraceptive products, and "orphan drugs," or drugs for serious and life-threatening diseases that affect small segments of the population - extensively documented by the federal government and others - only

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begins to illustrate the point that more liability results in less innovation.

MORE COST

Higher health-care costs inevitably occur when manufacturers adjust to the out of control tort environment by pricing certain products they perceive as presenting particular liability concerns at a significant premium over others.

Higher prices create pressures to reduce the use of approved products, contrary to the objective of rational prescribing.

More than ever before, rising costs threaten to price the benefits of modern technology out of the range of many of the patients who most need it. And these cost pressures are going to increase as our population continues to age and more treatment options become available.

According to many experts, the differential cost of health care between America and Canada can be explained by product-liability considerations. Higher prices create pressures to reduce the use of valuable, safe, and effective health care options. More cost results in less effective health care.

MORE FEAR

Doctors are, literally, being sued out of their medical practices. Insurance rates are forcing many hospitals and clinics to shutter emergency rooms and trauma centers and cancel other vital services such as obstetrics.

Doctors are moving to specialty areas with lower premiums, moving to states with fairer legal systems, or retiring from the field altogether. Patients are suffering from a legal system that is dangerous to their health.

Consider what's happening in Mississippi. More than a few towns in the state have lost significant access to needed medical care - especially in the Delta, where the economic conditions are such that they need help the most.

Physicians who specialize in family medicine and obstetrics/gynecology in Indianola and in other rural areas of the state have stopped delivering babies and have even moved away because of skyrocketing insurance costs caused by out of control liability. These dedicated health-care professionals are very worried and so are their patients.

More fear results in less care.

LESS EXPERTISE

When it comes to medicine, who should make decisions about safety and efficacy – and on what evidence should those choices be made? At present, the Food & Drug Administration has the responsibility to determine approvals and labeling language based on a scientific review of the evidence. Should this authority be ceded to the tort bar?

Consider the recent spate of litigation against the manufacturers of opioid pain medications. One example is the City of Chicago's lawsuit against multiple manufacturers of opioid pain treatments.[1] In the United States District Court for the Northern District of Illinois (Eastern Division), the City of Chicago's First Amended Complaint ("FAC") seeks to limit the ability of Chicago doctors to treat the chronic, non-cancer pain of patients in the manner doctors deem most appropriate. Although the Food and Drug Administration has approved certain opioid pain medications for the treatment of chronic non-cancer pain, the FAC seeks to deprive patients and doctors of that treatment choice by having six lay jurors determine that "the use of opioids to treat chronic pain is not 'medically necessary' or 'reasonably required' in that their risks do not exceed their benefits."

The FDA has determined that opioids serve an important public health role: "When prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority. Chronic pain is a serious and growing health problem: it 'affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence.' "[2] At the same time, there is no dispute that opioids pose significant public health risks: "Opioids also have grave risks, the most well-known of which include addiction, overdose, even death."[3] The labeling for these products contains prominent warnings about these risks. Moreover, the boxed warning states that all patients should be routinely monitored for signs of misuse, abuse, and addiction.

In September 2013, the FDA ruled on a citizen's petition filed by a group of clinicians, researchers, and health officials called Physicians for Responsible Opioid Prescribing ("PROP").[4] Like the Chicago FAC, the Petition directly challenged the use of opioids for "chronic

1 United States District Court for the Northern District of Illinois, Eastern Division, Case No. 14-cv-04361

2 http://paindr.com/wp-content/uploads/2013/09/FDA_CDER_Response_to_Physicians_for_Responsible_Opioid_Prescribing_Partial_Petition_Approval_and_Denial.pdf

3 Ibid

4 http://www.citizen.org/documents/2048.pdf

non-cancer pain." PROP contended that the "long-term safety and effectiveness of managing [chronic non-cancer pain] with opioids has not been established," and requested that the FDA, *inter alia*, impose a "maximum duration of 90-days for continuous (daily) use for non-cancer pain." The FDA "carefully reviewed" the Petition and "more than 1900 [related] comments." The agency assessed the "relevant literature." It held a two-day public hearing at which it received "over 600 comments" and dozens of experts and concerned citizens testified.

The FDA noted that "the majority of comments" "opposed PROP's requests" and that "many professional societies," including the American Medical Association, "did not support the Petition and stated that the data cited by PROP did not support PROP's requests." After completing a 14-month review, the FDA determined that opioids should continue to be available for the treatment of chronic pain, while also directing further study and certain labeling changes for some opioid drugs. Significantly, after being presented with the same assertions as those now alleged in the Amended Complaint, the FDA made two findings directly at odds with the underlying premises that form the cornerstones of the FAC.

But the lawsuits keep coming.

IT'S TIME TO REPEAL THE "TORT TAX"

While litigation isn't the only means by which pharmaceutical companies' adversaries seek to ignite difficult issues into explosive crisis situations, it certainly has some of the highest and most expensive stakes

Estimates peg the American "tort tax" at $40 billion, an economic behemoth roughly twice the size of Coca-Cola and just "a few billion" shy of the $51.1 billion, invested in 2013 by the pharmaceutical industry for the research and development of new, life-saving therapies.[5]

Pharmaceutical companies are learning, often the hard way, that certain triggering events in the public domain have the effect of setting in motion a well-oiled tort machine. When the FDA posts an adverse event on MedWatch, announces a label change, or tough questions are raised at advisory committee meetings, the plaintiff's bar responds.

Plaintiffs in one vaccine lawsuit sought $30 billion in damages. *The entire vaccine industry's annual revenues total $6 billion.*

Plaintiff firms can churn out dozens of suits across the country, mounting sophisticated, multi-pronged legal, political and mass media attacks. Following closely, in a kind of pincer action, are the media "horror stories" from allied interest groups, high profile media scrutiny, and promises to investigate from sympathetic political figures.

According to the Manhattan Institute's book *Trial Lawyers, Inc.*, "…leading plaintiff lawyers run complex multi-million dollar organizations that use sophisticated and expensive marketing to pursue clients through every commercial avenue."[6] As one lawsuit industry-sponsored website declares: "Seek justice NOW by submitting your class action information online to be considered for a FREE case evaluation!"[7]

Such tactics are designed, according to Trial Lawyers, Inc, "to launch numerous mass tort cases of the sort that have all but replaced the principle of fair and impartial justice with a new governing principle: Winning through intimidation."

Investigative journalist Mike France writes: "As the money has escalated, tort lawyers have succeeded in turning litigation into an all-but-automated process … Empowered by the Internet and enriched by a never-ending stream of lottery-size verdicts and settlements, tort lawyers have built an ingeniously organized industry that operates, for the most part, well out of the public eye."[8]

Attorneys incentivize potential lead plaintiffs by offering a bounty, which can sometimes be as high as $20,000. They also recruit friends and relatives of their firms' employees. The Internet, with its many corporate protest sites, has become a rich hunting ground for potential plaintiffs.[9]

The Attorneys' Information Exchange Group (AIEG) is a virtual warehouse storing, among other things, internal corporate documents uncovered by members of the American Trial Lawyers Association – which has renamed itself "the American Association for Justice" – the ultimate in 21st century Orwellian NewSpeak.

Founded in 1980, the AIEG began as an informal network of plaintiffs' attorneys with Ford Pinto cases. In response to the carmaker's hardball litigation tactics, AIEG began sharing internal corporate documents and trading tactical tips. Since then, its scope has grown. It now has specialized units for everything about autos, from tires to airbags. Other groups are devoted to school buses, motorcycles, boats, and, now, pharmaceuticals.

The AIEG has a Byzantine set of rules "to ensure that the contents of its library remain secret and protected by

5 www.phrma.org

6 http://www.manhattan-institute.org/pdf/triallawyersinc.pdf

7 http://www.triallawyersinc.com/html/print02.html

8 "The Litigation Machine," Business Week, January 29, 2001

9 Ibid

attorney-client privilege. Members of the group are forbidden from disclosing what paperwork the AIEG possesses. Nor are the documents posted online. Plaintiffs' attorneys usually have to travel to Birmingham to see them."[10]

Pharmaceutical companies are not alone in responding to powerful legal challenges with powerful legal responses, allowing counsel to thoroughly research plaintiffs' claims, refusing to comment on legal issues in question, and lining up support, later, from communicators, experts, and third party allies. It's a time-tested approach. And it's likely to fail.

LESS FAIRNESS

Comprehensive studies by the Rand Corporation and others demonstrate that only a small fraction of lawsuits that result in settlement payments or jury verdicts actually involve low-quality care by physicians. Rather, the hallmark of big awards is bad outcomes, not bad care.[11]

Unjustly, only a small fraction of patients who are injured negligently get compensation. And when they do, most of it goes to lawyers and the very high costs of administering this inefficient, unfair, broken system. The system needs to change so that it will deter bad care, not reward bad lawyers.

When the tort system threatened the development of lifesaving medical products in the past, we found creative solutions. Consider the disaster that faced childhood vaccines in the mid-1980s.

Under the weight of litigation, prices for vaccines increased tenfold, and the number of manufacturers dropped to only four from about 20 - and only two in America. So Congress took most child-vaccine litigation out of the tort system and created the well-respected Vaccine Compensation Fund.

Today, it's widely understood that vaccines are safer than ever, not despite these fundamental litigation reforms but because of them.

ALLIES RATHER THAN ADVERSARIES

When public health is put before private gain, tort law and the lawyers who practice it play a very important role in protecting and enhancing America's health.

Tort law, appropriately applied, helps patients get redress for truly negligent care. When product manufacturers provide fraudulent information to the FDA, or deliberately withhold information about safety problems associated with their products, they should be held accountable.

The dedicated members of our legal profession have always provided, and continue to provide, vital protection against those who would prey on consumers or intentionally try to pass off harmful products. The threat of litigation can be an important disincentive to many predatory behaviors.

The problem is that the current liability system doesn't reward lawyers who focus on these real public health concerns. Instead, the most experienced and well-financed law firms know that the biggest payouts regularly go to those who take advantage of the FDA's best efforts to promote the safe and effective use of medications.

More and more often, these "mass tort" firms specialize in taking a new product-warning label or withdrawal decision by the FDA and viewing it as a signal to go forward with all guns blazing. Their bullets, unfortunately but not unpredictably, hit multiple innocent targets and result in a wounded American health-care system.

One woman, speaking to a reporter for the Jackson Clarion-Ledger, summed it up this way: When she read that the drug Propulsid might cause harm, she stopped taking it and signed up for a lawsuit.

"Actually, I didn't get hurt by Propulsid," she told the newspaper. But because she had taken the drug, she said she thought she could join a class-action lawsuit "and I might get a couple of thousand dollars."[12]

Less fairness results in more damages.

LABELING AS THE SOLUTION, NOT THE PROBLEM

Labeling can and must be a valuable tool for improving and protecting America's health. That's the law. Rational prescribing occurs when a health care professional orders an approved prescription drug or biological product in circumstances where the risk/benefit profile of the product is optimal.

The FDA's most potent weapon in the battle for accurate, timely, "rational" prescribing is clear, approved labeling. The FDA's legal and legislative authority over labeling for prescription drugs and biological products is complete, according to federal statute, in almost every respect.

The FDA has the authority, the ability, the means, the mission, and the mandate to manage the health care risks and benefits inherent in the products it regulates on behalf of the American public.

10 Ibid

11 http://www.rand.org/pubs/technical_reports/TR562z17/analysis-of-medical-malpractice.html

12 http://www.fda.gov/NewsEvents/Speeches/ucm053699.htm

A more balanced legal system will occur only when elected officials determine the time has come for real tort reform, as it affects pharmaceutical companies. But that day is likely very far off. Healthcare leaders must devote their most aggressive efforts toward reform.

Maybe when our elected officials understand that it's the health of their constituents versus the pocketbooks of lawyers, our public servants will finally get serious on tort reform.

Commentary

Improper handling of harmful chemicals by small tea growers of Assam: Challenge to heath and local environment

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ABSTRACT

After dominating the world tea market for much of the last 170 years, today India is the fourth largest tea exporter. The state Assam, located in the Northeastern end of the country contributes almost 50% of the India's total tea production and small tea growers of Assam (STGs) produces around 30% of its total annual production and contributes almost 12% of India's annual production. Though the use of harmful pesticides and fertilizers by the STGs of Assam is still not recognized and controversial in the state, it is observed that STGs of Assam hardly follow standard scientific techniques for handling such chemicals. Therefore, maintenance of sound health of STGs and environmental safety is a necessary issue. But, to date no such awareness program was found to be initiated to scientifically teach them about these safety measures. Therefore, there is a great need for immediate implementation of scientific solutions for storing (micro levels of) harmful chemicals and also for a grassroots level safety campaign by scientific communities of India and other competent agencies.

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India, the world's largest tea producer for almost 170 years is now facing rising competition in the world tea market. Today, India is the fourth largest tea exporter in the world and the state.

Assam contributes about 50% of India's total tea production and plays a dominant role in tea exporting.[1] Moreover, the tea industry is the major source of income in the state. Small scale tea cultivation (less than 135 km^2) by farmers is termed as Small Tea Growers (STGs). Small tea growers of Assam produce around 30% of its total annual production and contribute almost 12% of India's annual production.[2,3] Presently, approximately 68,465 STG's are cultivating tea in small scale and nearly 0.5 million families are dependent on it[3]. It is observed that STGs of Assam hardly follow standard scientific techniques for the production of tea. Extensive use of fertilizers (urea, muriate of potash, super phosphate) and pesticides (endosulfan, dicofol, ethion, cypermethrin etc.),[4,5] poor agricultural practices are common for most of the STGs for promoting tea production. Though the use of hazardous chemicals and fertilizers by STGs of Assam are not properly recognized and controversial in Assam, a limited study shows their use by the STGs of Assam. A case study on the STGs of Golaghat district of Assam shows the use of pesticides and fertilizers by 95% STGs of the region.[3] Unfortunately, it is observed

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that most of the STGs are unaware of proper handling of these chemicals. In most of the cases, they do not use masks, hand gloves and other safety measures while handling chemicals, due to lack of knowledge and proper consultation, which may lead them to face great health challenges, apart from other environmental toxicities. Moreover, most of the STGs use to store such chemicals very casually within their living territory and get continuous exposure to them. Lack of knowledge on recommended proportions is another major health threat associated with STGs of Assam.

Therefore, maintenance of sound health of STGs and environmental safety is a necessary issue. But, to date no such awareness program was initiated scientifically to teach them about these safety measures for proper handling of such chemicals. Therefore, there is a great need for immediate implementation of scientific solutions for storing (micro levels of) harmful chemicals and also for a grassroots safety campaign by scientific communities of India including other competent agencies. To overcome such of problems, the cultivation of organic tea can also be suggested. Organic tea cultivation aims for sustainable tea production through ecologically sustainable plantation, in the absence of synthetic fertilizers, growth regulators, pesticides, fungicides, and herbicides, without effecting the natural ecology and natural habitat by polluting soil, air and water. Some of the successful examples of STGs of Assam, such as Gobin Hazarika and Dhiren Phukan shows the importance of organic tea cultivation in the state by finding a good market for exporting organic tea to Canada.[6,7]

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Article

Trends in market access for specialty biologics: Challenges & promises

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ABSTRACT

Specialty biologics are the fastest growing class of bio/pharmaceutical products in terms of the number of new brand launches and rates of health care spending in the U.S. and globally. Innovative biologics meant to treat a range of hitherto untreatable conditions in oncology, inflammation, CNS, endocrinology and other chronic conditions seek to offer radical improvements in efficacy and patient well-being. Such products can command premium prices, often costing over $100K per year per patient - triggering a raft of challenges to ensuring that eligible patients have adequate access.

This article outlines important trends impacting market access to specialty biologics in the U.S. and globally. Particular importance is placed on evolving methods for managing specialty product utilization and reimbursement toward ensuring appropriate access. The reshaping of the specialty product market access landscape in the U.S. through the availability of oral biologic formulations distributed to patients via high-touch, high-involvement specialty pharmacies is examined. The rising role of risk sharing between specialty product manufacturers and insurers as a way to balance rewards of access with the risks inherent in radical new specialty therapeutics is discussed. Challenges posed by specialty biosimilars to traditional ways of ensuring market access and fair reimbursement are outlined. The impact of health care reforms on market access for specialty biologics in the U.S. is discussed in the context of the growing need for comparative outcomes research and the application of the principles of health technology assessments - adapted, in part from their apparent success in ensuring equitable and cost-effective access to biologics in the E.U.

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BACKGROUND

Almost all biotechnology medications are commonly classified as "specialty" drugs. While the precise definition of a "specialty" drug varies somewhat by industry organization, it is widely understood that specialty drugs are used to treat chronic conditions, require special handing, and unique distribution and administration channels. Specialty drugs also usually require a high degree of patient management and counseling. Currently the most common conditions that require specialty drugs are cancer, multiple sclerosis, rheumatoid arthritis and other autoimmune diseases. It is also commonly accepted that specialty drugs are complex and expensive. The Centers for Medicare and Medicaid Services defines drugs that cost more than $600 per month as specialty drugs, while some commercial health plans put the threshold at $1,200 per month.[1]

It is no secret that most specialty drugs cost far in excess of the minimum cost thresholds mentioned in formal definitions. Nine of the 12 new cancer drugs approved by the US Food and Drug Administration in 2012 were priced at more than $10,000 per month. Writing in an op-ed in the New York Times in October 2012, three physicians at New York City's Memorial Sloan Kettering Cancer Center noted that *"the typical*

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new cancer drug coming on the market a decade ago cost $4,500 per month (in 2012 dollars); since 2010 the median price has been around $10,000".[2]

High specialty drug costs are not confined to oncology, however; specialty biologics indicated for treating rheumatoid arthritis, HIV and multiple-sclerosis are among the most expensive medications in the market. To boot, specialty product year over year prices increase the most of all types of medications – causing an ever increasing dent in health care spending. Specialty drugs are the fastest growing segment of health care expenses in the U.S., rising at an annual rate of 15-20% and expected to account for 40% of total drug costs by 2020. By the end of 2015 alone, specialty drug spend is expected to increase by 67% compared to 2013, while spending on other types of drug will decline 4% due to wider use of generics.[3]

Despite high costs however, specialty drugs represent a bright spot in the otherwise bleak landscape for bio/pharmaceutical companies. They represent chances to target hitherto untreatable or partially controllable chronic diseases with the promise of biotechnology, while ensuring substantial financial return - partly due to their price and also due to the fact that they represent chronic, ongoing treatment essential for disease control. It is no surprise then to note that at present four out of every ten drugs in the pipeline of bio/pharmaceutical manufacturers is a specialty drug.

The proliferation of expensive specialty medications is also about the most daunting challenge faced by manufacturers, health insurers, employers and other payers responsible for ensuring access and affordability.[4] For one, the advent of specialty medications poses structural challenges to the traditional ways of assessing drug viability: no longer is it sufficient to rely on manufacturer sponsored clinical trials. Complex specialty drugs require careful, controlled assessments over longer time periods compared to traditional small molecule drugs available in pill formulation; with not insignificant possibilities that adverse events in the real world may well be detected years after the specialty drug is launched. The traditional drug supply chain designed to move small molecule pills from the manufacturer to patients (filling prescriptions in retail pharmacies with copayments of $10-$50) is also ill equipped to optimize on the promise of large molecule (often injectable or infused) specialty medications that require special handling and storage and simply can't be accessed as easily at the pharmacy for comparable copayment amounts.

Like other disruptive technologies in the modern era, specialty medications have caused radical, continually evolving changes in their markets. This article discusses some of the major trends that will likely reshape such markets permanently.

RISING CONTROL OF MARKET ACCESS FOR CANCER TREATMENTS

No other therapeutic area is more reflective of the radical changes wrought by the advent of expensive specialty medications than oncology. At the present time, health care expenditure for cancer care is the highest of all diagnosed conditions. According to industry surveys, manufacturer price increases are the key reason. As a direct consequence, private and public insurers have initiated more mechanisms for controlling access to cancer treating drugs than any other therapeutic area. Payer control over utilization of drugs meant to treat widely prevalent cancers has continued to increase year after year. While some of the controls seek to be consistent with definitions of appropriate use and aim to minimize waste, shifting the rising cost of medication use on to patients is also becoming common. In a recent survey of commercial payers in the U.S., two thirds of the sample reported using patient cost-sharing as a tool to manage cancer drug costs.[5] With more expensive cancer treatments on the horizon, such a trend can be expected to continue.

Relying on manufacturer sponsored cancer patient assistance programs or other forms of copay assistance to absorb rising patient cost burdens will not be the panacea it is held out to be. In fact, to the contrary, the availability of more expensive (and effective) cancer drugs portends the possibility of denying their inherent promise to those who need them most - due to the unrealistic expectations of cost support placed on patient assistance programs. A recent survey of cancer treating clinics in the U.S. indicated that less than one in three of their cancer patients was able to pay the full out of pocket copays for a cancer drug. The same survey reported that just about one out four cancer patients was eligible to receive some form of manufacture assistance to fulfill their copay obligations. Even of those who were eligible, about four in ten did not receive the assistance they expected.[6] It is clear that ensuring equitable market access to promising cancer treatments is a challenge that is only going to become more formidable than ever in the years to come.

Spiraling costs of innovative specialty treatments requiring coverage on payer formularies have had yet another adverse impact on their ability to deliver on their promise. To control utilization of such drugs, payers have resorted to de-facto rationing by imposing strict restrictions on their use. In 2012, over 95% of patients diagnosed with each of the seven most prevalent cancers in the U.S. were subject to some form of control restricting their ability to receive treatment. Between 2010 and 2012, for example, the number of multiple myeloma patients subject to one or more forms of control on drug utilization increased 53%.[5] In the foreseeable future such strict control over drug utilization can be expected to spread to other relatively expensive

specialty therapeutic areas such as rheumatoid arthritis, HCV, multiple sclerosis and cardiovascular diseases.

SITE OF CARE CONSOLIDATION

Patient access to specialty biologics in the U.S. today is also acutely dependent on significant trends likely to determine where specialty care is made available. The economics of specialty care provision is fast influencing a wave of consolidation wherein small, stand-alone community clinics are increasingly being acquired by large hospitals or impelled to join integrated delivery networks and accountable-care organizations. Tightening reimbursement rules of public and private insurers that intend to limit profit margins associated with the acquisition and administration of specialty biologics is one reason why. The advent of accountable-care has also raised the bar on patient care in the community even in the midst of daunting financial circumstances. The requirement to meet pre-defined care quality measures has to be balanced against the need to control costs and maintain an ability to make a reasonable profit – an equation that often fails the test of economic reason. It is no surprise then to see a gradual migration of specialty care from stand-alone, community clinics to larger, consolidated sites of care. For example, according to a report from the Community Oncology Alliance (COA), between 2007 and 2013, 288 community oncology clinics have closed; 407 were financially strapped; and 469 were forced to enter into a contractual agreement or acquired outright by a hospital. In its 2012 Trends report, the COA notes that 50% of reporting community oncology practices have closed or been acquired / managed by a hospital.[7]

Oncology clinics that continue to survive such trends 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.[8]

Many of the large hospitals that have thrived in this era of consolidation are willy-nilly benefiting from otherwise well intentioned changes in how specialty medications are bought and reimbursed. For example, under the 340B drug discount program (1992), hospitals that serve more than a minimum threshold of Medicare patients can purchase drugs at a substantial discount from bio/pharmaceutical manufacturers, while retaining the ability to get reimbursed at the same rates that apply to entities not entitled to such discounts - including stand-along community clinics. Acquiring such clinics, enlarging their patient base (including the proportion of indigent patients), and making astute use of the discounts provided by the 340B program has been a notable trend driving the profitability of large acquirers. While legislators have taken note of such disparity little, substantive action designed to close such loopholes has resulted.[9]

Consolidation of sites of care from small, community clinics to large hospitals and integrated delivery networks is projected to continue unabated. According to a number of sources, by 2015 nearly two out of every three cancer patient will receive care in a hospital or an integrated delivery network as an in or an outpatient.[10]

SHIFTS IN MODES OF SPECIALTY PRODUCT DISTRIBUTION

A preponderance of evidence indicates negative market reactions to current biologic pricing and consequent limits on their market access. A natural outgrowth of this is a de facto need for channels of distribution that are designed specifically for specialty biologics. Failing that, fundamental inefficiencies in the current distribution model will continue to generate unnecessary costs, providing every stakeholder in the supply chain little option but to raise its price. For example, considerable evidence suggests that the buy & bill model for acquiring and administering biologics can lead to excessive utilization, waste and reimbursement. Routing biologics to the specialist through specialty pharmacies – specifically geared to handle purchase, storage, insurance, reimbursement, supply and maintenance requirements of biologics – would eliminate such inefficiencies.[11]

While this mode of distribution has gained some traction lately, it has yet to become the standard. For instance, infusion and injectable products with indications in oncology continue to be distributed widely under the buy and bill model, whereas biologics indicated for treating inflammatory diseases (such as Rheumatoid Arthritis) are widely available through specialty and retail pharmacies. One reason for this is the position espoused by community based oncologists that treating cancer is far more complex, with a lot more potential for toxicity, mandating a far more global, integrated and personalized approach to treatment available only in an oncology office setting. Drugs meant to treat a diverse array of conditions in cancer are better made available through an office inventory on an as needed basis, rather than be reliant on supply through pre-order from an external specialty pharmacy. "*Oncology is unique in that the vast numbers of clinical trials and extensive research in the war on cancer mean that standards of*

care for treatment are constantly changing. New, high-priced, single-source drugs approved for advances in cancer care often are indicated for use in addition to older, established treatments. This trend creates an escalation of cost of care not manageable by the usual specialty pharmacy tradition of buying drugs en masse and driving significant established medical treatments to a few of many alternatives".[12]

While this is debatable there is no question that under a dominant specialty pharmacy driven distribution model, manufacturers can develop preferred vendor relationships with specialty pharmacy chains, generating possible savings which can be passed on to payers and patients in the form of lower prices. In parallel, changing patient insurance structure to cover a biologic under the pharmacy benefit (rather than a medical benefit) to be consistent with the specialty pharmacy model can lead to more transparency in recording costs and dose utilization patterns, as distinct from costs grouped with that incurred for product administration and office visits. This would also enable manufacturers to better control access through, among other means, attractive product pricing via payer specific contracting.

The downside to such a restructuring of biologic distribution is not trivial. For example, attempts to eliminate buy and bill in the U.S. almost always equate to reducing (or sometimes eliminating) the profits specialists take through purchase and administration of biologics. While the larger specialist practices are able to wither such impact, cases of small specialist offices shutting down, merging or selling themselves to larger groups due to reduced reimbursement are not uncommon.

As a result, it not surprising that attempts by some insurers to mandate distribution of specialty products exclusively through specialty pharmacies has lost the impetus of some years ago. Several insurers have instead equalized reimbursement rates for products acquired through buy and bill and the specialty pharmacy. In a recent survey of commercial plans, two out of every three responding plans indicated indifference between routing office infusion therapies through a specialty pharmacy or through acquisition by a physician's office under the buy and bill model.[i]

In any event, future scenarios describing the distribution of specialty biologics are likely to be different from today:

- Insurers are likely to make decisions mandating use of specialty pharmacies on a considered case by case basis, after examining trends in costs, utilization, waste and outcomes, specialists' needs and treatment proclivities, and the relationship between patient adherence and cost of care.
- Specialist physicians are likely to trade the convenience of obtaining specialty biologics on order through specialty pharmacies against the ability to make a modicum of profit under the buy bill model of acquisition and billing, as well as obtaining ancillary reimbursement and patient support services that specialty pharmacies typically provide.
- Manufacturers are likely to consider specialty pharmacies as a viable distributing channel after weighing the need for patient education, adherence, risk mitigation, differential competitive advantages and the availability of rich, patient level data on effectiveness and off label use. A distribution model that emphasizes product flow through specialty, retail and hospital pharmacies as well as traditional buy and bill, in combination with direct-to-patient selling - in proportion to their respective viability in impacting market access and eventual revenues - may be a plausible and pragmatic commercial objective.[13]

THE NEED FOR RISK SHARING

The specter of spiraling drug costs - particularly for innovative, first in class specialty biologics - coupled with limited knowledge about their long term effectiveness outside the realm of controlled clinical trials has raised the level of uncertainty associated with their value to insurers. Like never before, insurers are feeling the pressure to optimize the management of high medical costs and utilization, subject to inadequate understanding of their true value. There is tangible risk in making available costly specialty biologics with no proven record of effectiveness and safety outside of a manufacturer-designed clinical trial conducted in a controlled setting with preselected types of patients. A consequent trend of critical importance to payers and manufacturers is to think of ways that balance paying for costly specialty biologics with rising demands for their access, subject to expectations of sustained, positive real world outcomes that will enable the full realization of the value inherent in them. Such risk sharing is likely to involve clinical and financial metrics designed to measure product safety and effectiveness in comparison to resource spend and utilization.

i Telephone based in-depth interviews with pharmacy / medical directors at 30 U.S. commercial insurers; CRA International

Key developments

Several ongoing developments in the specialty care realm are exacerbating this trend to seek new ways of sharing this burgeoning risk, such as:

- The rapid availability of expensive, oral formulations of specialty biologics designed for niche populations
- A rising demands for proving effectiveness in diverse (often global), subpopulations that could augment a primary indication, thereby increasing the potential of a drug to return revenues that reduce inherent risk
- Increasing pressure from patients and advocacy groups for proven medications that justify high and rising medical coinsurance and copays
- Increasing momentum toward integrated care delivery (e.g. IDNs, ACOs), particularly in the U.S., which equates to higher demand for proven outcomes and performance-based value - not proof of efficacy or safety alone
- Better availability of integrated health information technology (including electronic health records and infrastructure), which increases payer and manufacturer ability to define, measure and monitor outcomes necessary for risk-sharing arrangements
- Rising competition among multiple manufacturers in high risk, high return therapeutic areas (e.g. oncology, autoimmune diseases, cardiovascular diseases), which puts a premium on the need for reliable data about clinical, outcomes and value-based differentiation

Key goals

A common goal of sharing the risk of expensive, potentially valuable, innovative specialty biologics between manufacturers and insurers is to control costs.[14] Trends in the near future, however, point to a number of other types of benefits, including:

- Improving health system sustainability without denying access to new specialty medicines
- The availability of mechanisms to deal with uncertainties related to medicine's effectiveness
- The possibility of speeding access, lowering prices and promoting appropriate use of medicines that would otherwise not be available
- Putting in place means and systems that serve to avoid unnecessary risks to patients
- Ability for manufacturers and payers to make pricing and reimbursement decisions with limited clinical information
- Opportunities for manufacturers, insurers, purchasers, regulators and patient-advocacy groups to collect real-world product use data that can be used in a variety of different ways, and
- Developing methods and infrastructure to avoid excluding reimbursement for some much needed medicines

The success of risk-sharing agreements in single payer systems common to the E.U. can provide valuable lessons to manufacturers and insurers in the U.S. embarking on crafting agreements designed to generate benefits such as those outlined above.[15]

Manufacturer implications

Astute manufacturer of specialty biologics can look to risk sharing as an opportunity to gain rapid market access for specialty products that, in their opinion, truly hold the promise of radical improvements in patient care, thereby justifying premium prices and calls to insurers for wide, unrestricted access and utilization. Such intentions are currently only aspirational. Key steps that could position firms to get ahead of impending trends in risk sharing would include:

- Enhancing clinical trial designs to better capture patient related outcomes
  - Focusing on sub-populations reflecting real-world target patient segments in multiple geographies representing potential for treatment use
  - Actively exploring the feasibility of conducting head-to-head clinical trials versus standard of care
  - Collecting patient-reported outcomes (PRO) data

- Designing clinical trial protocols in collaboration with payers
  - Developing payer-influenced value propositions that inform clinical trial design and expectations
- In product development and launch management encouraging use of technologies that ensure high probability of treatment effectiveness (e.g. use of biomarkers & other diagnostic tests)
- Setting up / enhancing capabilities for patient registries that provide inputs and outputs for measuring the impact of risk-sharing arrangements
  - Tracking patients across multiple payers and sites of care over time
- Improving processes to incentivize health care providers for adequate supply of (often complex) data that ensures success of risk-sharing arrangements.

MANDATING USE OF COMPANION DIAGNOSTICS

The desire to mitigate undue risks due to inappropriate utilization of expensive biologics has also spurred insurer policies that mandate use of companion diagnostics as a necessary condition for market access and reimbursement. In the coming years, payers in the U.S. will increase demands for using companion diagnostics in drug development and utilization as a means to improve clinical and cost efficiencies. In a recent survey of 102 commercial plans, 75% of payers indicated that in the next twelve months, wherever possible, they would require a companion diagnostic test before approving a specialty drug for coverage. In the same survey, 71% of payers indicated they currently restrict the use of a specialty drug based on the use of a companion diagnostic test.[16]

The drive to include companion diagnostic testing within the purview of the process for ensuring market access, however, requires the overcoming of a number of challenges. For one, there is a paucity of reliable information that establishes costs savings associated with the use of companion diagnostics. Clearly, such linkages are likely to be idiosyncratic to a test, the disease and patient state under consideration or, in some cases, the site of care and related administrative processes in use. Second, physicians are not readily incentivized to use companion diagnostics and reduce the number of infusions or injectables administered as a result of negative test outcomes: fewer infusions or office administered injectables mean less income and reduced profits. In some cases, administering a companion diagnostic test is not easy; patients have to be tested in a lab setting external to the treating physician's clinic, requiring separate appointments and costs that are not always covered by insurance. In some instances, the complexity of the diagnostic testing is such that physician clinics have to send patient cultures to an external lab, requiring additional costs and time commitments. Third, pharmaceutical/biotechnology firms that have products tied to mandated companion diagnostic testing can see a reduction in the potential patient population that receives them: smaller addressable patient sizes imply relatively smaller revenues and fewer repeat administrations over a chronic patient's life. Fourth, compared to specialty biologics, companion diagnostic development is not an attractive business proposition. Most current companion diagnostic tests are not protected by patents. Tests developed by laboratories do not require FDA approval, nor are they regulated by the FDA.

Nevertheless, in the foreseeable future, one can expect heightened industry focus on including companion diagnostic testing within the treatment paradigm of specialty biologics. Insurer mandates and the resulting revenue upside from increasing market access in a highly competitive, cost-conscious market will continue to drive efforts that overcome existing barriers.

THE INFLUENCE OF HEALTH TECHNOLOGY ASSESSMENTS

Health technology assessments (HTAs) - a concept that has long benefitted public payers in the E.U. in determining the parameters of drug value assessment, market access and reimbursement - now represent yet another trend gaining rapid adoption in several global healthcare systems with one or two dominant, largely public payer systems. At its core, HTAs are yet another mechanism to determine the cost to benefit, value-defining trade-offs so vital to ensuring adequate coverage and equitable market access. In addition, HTAs represent a means to mitigate the purchase risk inherent in potentially valuable specialty biologics with hefty price tags. One appeal of HTAs is that it is carried out by an independent entity with a wide variety of inputs only some of which are provided by the drug manufacturer.

While there is broad consensus across the board that HTAs are increasingly vital to determining the scope of market access and level of reimbursement accorded a new drug, its adoption as a necessary step in the drug evaluation and coverage determination process is in various stages of evolution around the globe. In some countries (e.g. India, China, Russia, Philippines) there is increasing interest in developing the capacity and skills to formally institute an HTA process and establishing national

guidelines. At present, critical pharmacoeconomic data and analyses are produced by academic or national institutes, with limited impact on drug evaluation decisions.

In some other countries (e.g. Turkey, Mexico, Singapore, Thailand), the principles of HTAs are required by law to influence public payer drug acquisitions. However, a lack of clarity about how, coupled with sufficiently detailed data continues to limit their application in determining acquisition costs and drug reimbursement decisions. In addition to several countries in the E.U., some of the emerging, fast growing health care markets such as South Korea, Brazil and Taiwan have established HTA agencies actively implementing pharmacoeconomic analyses that are a vital input into centralized market access and reimbursement decisions.

As new health care reforms take root in the U.S., the advent of HTA into public and commercial payer decisions is inevitable. According to one estimate, the new reforms will provide funds up to $300M per year for an independent public agency to conduct drug related HTAs in the U.S. While drug approval decisions will continue to stay clear of drug costs, decisions about market access through publicly funded insurance will increasingly rely on advice from HTA analyses. On the commercial side, most insurers have long conducted internal cost / benefit value assessment analyses to determine market access and reimbursement levels. With the increasing emphasis on HTAs conducted by independent, public agencies, the emphasis on cost effectiveness will only heighten with time. In multiple surveys, commercial payers have noted that HTA analyses will be an important means to validate internal inferences.[17]

RISE IN THE AVAILABILITY OF ORAL SPECIALTY TREATMENTS

A significant trend impacting market access considerations for specialty products that will only get stronger with time is the increasing availability of complex specialty treatments available in pill form. Across large and growing disease states such as HIV, Hepatitis C, Multiple Sclerosis, Pulmonary Hypertension, Rheumatoid Arthritis, IBD, Crohn's, Psoriasis and multiple types of cancers, drugs in oral formulations are set to launch and compete with standards of care defined by infusible and injectable products administered in hospitals or clinics. In oncology alone, over 25% of compounds in development will be delivered orally.

The spate of oral specialty products poses key challenges to current ways of drug utilization management, reimbursement and adherence. High priced orals entail stricter utilization management than office-administered injectable or infusible products. The utilization of oral specialty products is typically controlled through restrictions such as prior authorization, step edits and quantity limits. As such, ensuring that an oral product is appropriately dispensed entails obtaining administrative clearance from patients' insurance plans. This comes at an uncompensated cost to the physician office compared to the situation where reimbursement for office-administered medical products is available under the medical benefit. Based on research with physicians' offices dealing with oral specialty products,[18] a related concern seems to be a lack of standardization (e.g. consistent paperwork) covering prescribing, coverage and utilization of orals. In addition, obtaining clearance can cause delays in time when the patient can actually pick up (or receive an oral in the mail) from the pharmacy. Further, some physicians have reservations about the lack of vital hands-on control and interpersonal communication that is otherwise available when patients receive drugs in the office. Such concerns, coupled with a lack of profits from prescribing orals compared to reimbursable in-office specialty products can impede rapid physician uptake of orals, adversely impacting their wide availability to deserving patients.

An equally serious concern is the risk of significant cost sharing incurred by patients for purchasing oral specialty products, entailing co-insurance amounts typically running from 18-30% of list prices.[15] As a result, this sometimes leads to higher than expected economic burden, reduced adherence and poor outcomes. Otherwise manageable side effects in the hands of physicians and support staff cause needless treatment abandonment when patients are left to use orals on their own. This places extra onus on manufacturers, insurers and specialty pharmacies supplying oral products to devise ways and means that ensure uninterrupted use and adherence through costly education programs and tight control on product supply. With the increasing advent of oral products in a wide range of indications, the burden on such stakeholders to fine tune the oral product distribution, access and support infrastructure will increase considerably.

To address the critical question of physician interest in orals versus office administered injectable or infusible products that are reimbursable and impact profitability, oral product manufacturers and insurers will need to evaluate mechanisms that adequately incentivize provider prescribing of oral products. Examples of such mechanisms that are bound to receive more attention in the future include providing payment for administrative / patient support tasks related to oral prescribing (e.g. treatment planning, patient education, care coordination, obtaining prior authorization, managing stipulated restrictions). Another payer strategy entails actively considering coverage of select orals under the medical benefit, thereby ensuring reimbursement to

physicians similar to that for office-administered injectable and infusible products.

Some physician offices have addressed new challenges posed by specialty orals by setting up on-site pharmacies in their clinics that are capable of dispensing oral specialty products. This trend will likely gain wide traction in the near future as well. Onsite specialty oral pharmacies provide clinic based physicians with the potential to receive reimbursement and profits related to oral drug acquisition and dispensing. Having an onsite pharmacy narrows the gap between oral and office administered products in other ways as well – patients receive possession of drug as soon as it is prescribed, and providers have the all too necessary control of patient treatment, monitoring and adherence, since a pharmacy tracking system can be used to monitor patient intake over time through measures such as time between product re-fills, regimen adherence, reasons for non-adherence and participation in manufacturer sponsored education programs.

Insurers - keenly aware of the potential of orals in offering significant efficacy with high convenience and lower physician reimbursement burden - will continue to seek ways that balance such promise of oral products with potential risks created by high cost sharing and reduced adherence. Key steps in this direction include mandating oral product distribution through specialty pharmacies that take on vital tasks such as patient education, constant monitoring of oral use, and implementing adherence programs that minimize waste, ensure appropriate use and eliminate the potential for treatment abandonment.

Manufacturers will continue to take steps that on the one hand reduce patient cost burdens through offering patient assistance programs and on the other collect data from sources such as specialty pharmacies, insurers and patient registries that examine the link between costs and outcomes, thereby providing rational guidance to shape oral pricing strategies that are in the best interests of all stakeholders.

THE ADVENT OF BIOSIMILARS

Between 2014 and 2017, specialty biologics with combined revenues of ~$39B will go off patent in the U.S. All such brands are targets of ongoing developmental work likely to result in the availability of branded biosimilar products over the next ten years. The presence of biosimilars in the U.S. will cause significant changes in how biologics impacting millions of covered lives diagnosed with cancer, rheumatoid arthritis, Type 2 diabetes and multiple sclerosis will be priced, reimbursed and managed for market access. While specific pricing of biosimilars will likely vary by factors such as the therapeutic category, the number of in-line branded competitors and order of biosimilar brand entry, it is widely expected that list prices 20-30% lower than originator branded biologic prices may be the norm. As such, manufacturers of originator branded biologics would face considerable pressure to provide sufficient rationale justifying the pre-biosimilar status quo. It would be common to see such manufacturers make significant investments in conducting retrospective studies that mine valuable in-market data for deep insights about the cost-effectiveness of their brands. Needless to emphasize, biosimilar brands - naïve to the market at launch - would lack similar evidence, and as a result, would have to rely on offering price-related incentives as a short-term strategy for obtaining coverage. One impact of such a dynamic would have insurers setting up a coverage model where branded originators continue to stay on formulary but are only allowed access upon failure of their less expensive biosimilars. Other steps likely to restrict access to branded biologics may include higher patient cost sharing in comparison to biosimilars or, in some cases, not reimbursing use of the branded originator when a biosimilar was available. In situations where the incremental value offered by a biosimilar stemming from lower cost is marginal at best, insurers are likely to continue reimbursing branded biologic originators, but with heightened restrictions such as prior authorizations, limits on quantity used and restricting use to a pre-defined, patient subpopulation based on disease severity, or inability to respond to alternatives.

Market access for branded biologics and their biosimilar counterparts that may be available at retail and specialty pharmacies in the U.S. is also likely to be shaped by public policy decisions. Over the past year, a spate of legislation has swept through a number of states that, if and when effective, would have a decided impact on utilization of branded biologics and their biosimilars.[19] The gist of such legislation is to mandate - like small molecule, generic drugs - the automatic substitution of a branded biologic with its biosimilar at the pharmacy. The key goal of such legislation is to wrest cost savings for private and public insurers (lower utilization of higher priced branded biologics) as well as to patients (lower out of pocket costs for purchasing a lower priced biosimilar, not the originator). As is obvious, manufacturers of branded biologics would stand to gain in that their biologic franchises will be less subject to direct competition from lower priced alternatives. Opponents of legislation that permits such auto-substitution argue that mere biosimilarity (and not complete sameness as in small molecule generic drugs) will be risky; i.e. safety and efficacy differences between the biosimilar and its originator will manifest in patients, leading to unpredictable consequences. The key to effective healthcare should be patient safety and wellbeing rather than guaranteed cost savings; and thus

the prescribing physician, not the pharmacist armed with an auto-substitution law, should be the decision-maker about whether his/her patient should take a biosimilar product. As can be expected, such far reaching legislation has spurred wide debate. No clear consensus is in sight;[ii] consequently, the outlook for biosimilar market access through the pharmacy channel remains murky.

Market access for biosimilars of branded biologics acquired by community clinics (and administered by infusion or injection) is also likely subject to rules by which their acquisition and use will be reimbursed by private and public insurers. If - as is more probable - their reimbursement amount is linked to the average selling price of their originator product through a formula (such as ASP of biosimilars plus 4% of the ASP of the branded originator biologic), it is likely that biosimilars of higher priced branded biologic originators may be reimbursed at higher levels than corresponding biosimilars of lower- priced branded competitors, thereby creating an unfair advantage for the use of one biosimilar compared to another. Insurers, as a result, would need to put in place appropriate controls that seek to negate such utilization behaviors driven purely by profit taking motives. In other words, determining how biosimilar acquisition and administration in the office setting is reimbursed would be critical in shaping their market access and subsequent utilization.

INCREASE IN INTEGRATED CARE DELIVERY

The context in which market access trends outlined in the previous sections will play themselves out is also likely to undergo significant reshaping in the near future in the U.S. The overwhelming need to realize cost savings, higher efficiencies and enhance value of health-care provision across the care continuum has led to system-wide, site-of-care consolidation. The rising adoption of consolidated care models such as Accountable Care Organizations (ACOs) and Integrated Delivery Networks (IDNs) reiterate this trend. Such models, by definition, owe their founding to principles that encourage cost effectiveness and performance assessments driven by notions of value, partly realized through gaining efficiencies via consolidation. As such, manufacturers of specialty biologics intent on securing access on the formularies of these new customer segments will be under increasing pressure to redefine their value propositions in terms that sync with their customers' principles of what matters.

As of August 2013, three out of every four hospitals in the U.S. had plans to join an ACO.[20] Accordingly, one can expect specialty biologic manufacturers to rapidly reconfigure marketing strategies, including those that influence which ACOs to target, how and with what rationale. A critical part of such rationale would now need to focus on an articulation of drug value, providing evidence of cost-effectiveness that could easily manifest in enhanced cost savings and corresponding increases in patient well-being at target ACOs. As mandated by health care reform, improved performance on such measures would translate into higher revenues for ACOs through public and private payer sponsored shared savings programs. In other words, taking steps to recast specialty product value propositions in terms that directly impacted ACO revenues and profits would, in fact, ensure wider and sustainable market access.

In the future, specialty biologic manufacturers will likely serve fewer customers, but each of them would be larger in terms of the number of decision makers that needed to be serviced, more complex in terms of decision making processes likely to impact product acquisition, broader in terms of the types of patients on whom the biologic will be utilized, and more sophisticated in the way drug acquisition, administration, utilization and effectiveness was tracked for a number of purposes, including receiving reimbursement and the reporting of cost and quality measures influencing customer ability to generate revenue, savings and profits.

The path to such a future is not likely to be smooth or predictable. In a recent survey of hospital executives in the U.S., for example, skepticism was the overriding sentiment.[21] Key drivers likely to impede consolidation included a lack of evidence that it would indeed result in the promised increases in efficiencies, savings and profits. Several hospitals with intentions to become part of an ACO had yet to build out the necessary infrastructure that would lay the foundation for such benefits.

ii Six states rejected laws to restrict pharmacists' ability to substitute cheaper biosimilars for their originator branded biologic (Maryland, Arizona, Mississippi, Washington, California and Florida). Three states have passed such a law. North Dakota has passed legislation requiring MD notification and record keeping for biosimilars. Virginia and Utah have also passed such a law, but with a sunset clause, which means that the bill is likely to expire before any biosimilars are approved in the U.S. Nine other states: Oregon, Colorado, Texas, Arkansas, Illinois, Indiana, Georgia, Pennsylvania, and Massachusetts, however, are still considering proposals to restrict the substitution of biosimilar drugs for their branded biologic originators. Nine other states: Oregon, Colorado, Texas, Arkansas, Illinois, Indiana, Georgia, Pennsylvania, and Massachusetts, however, are still considering proposals to restrict the substitution of biosimilar drugs for brand-name biologicals

To specialty biologic manufacturers this period of transition provides much needed room to reconfigure current ways of developing and commercializing promising novel products in their pipelines, particularly to ensure wide market access to them. Key actions likely to reset strategic direction in this regard include:

- Tailoring clinical trials to proactively address the need for pharmacoeconomic data as called for in ACO cost and quality requirements
- Incorporating learning from ongoing ACO pilot programs to streamline evidence development and communication
- Outlining ways to include specific specialty products in established clinical pathways; and to develop new pathways that illustrate the cost / benefit advantages of their products, and
- Working with select ACOs to analyze retrospective cost and utilization data and develop best practices that inform negotiations for purchasing, monitoring, utilizing and reimbursing their products

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Article

Human health biotechnology: Can Brazil advance?

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ABSTRACT

The Brazilian human health biotechnology sector was analyzed according to its spacial and sectorial distribution of the following aspects: (*i*) the scientific production; (*ii*) *innovation: sources of funding for new projects and a lack of innovative capacity regarding the discovery and development of new drugs* and (*iii*) a disconnection between the advancement of scientific output and innovation within the private sector. The picture depicted suggests that, despite the advances being made in science and technology, it is still necessary to overcome many weaknesses to achieve an economic growth based on knowledge and innovation.

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Keywords: biotechnology, innovation, research and development, economic growth

INTRODUCTION

This article presents a new analysis of scientific production and research and technology (R&D) in respect to biotechnology/human health in Brazil. The objective is to provide a better understanding of this sector of the economy.

Science and Technology (S&T) in Brazil has advanced considerably in the last twenty years. The number of graduate students increased tenfold from 1993 to 2011, reaching approximately 43,000 Masters and 12,000 PhDs.[1] From 1996 to 2009, the Brazilian global production of indexed articles tripled, going from 0.9% to 2.7%. In areas such as biology, the country is behind only the United States and China (in absolute numbers), and in clinical medicine, the US, UK, Canada, Japan and China[2]. Moreover, the increase in funding for Science, Technology and Innovation (ST&I) - especially with the creation of sectoral funds since 1999 - and regulatory changes - such as the implementation of the denominated laws "*do Bem*" and "*de Inovação*" - expanded the possibilities of a development process based on knowledge and innovation.

However, despite the progress made, many weaknesses need to be overcome in order to cultivate an economic growth based on knowledge and innovation. The expenditure on R&D, for example, is still low in relative terms - 1.1% of GDP. The lack of more substantial funding from the private sector results in a persistently low number of patents registered – most of which are generated in governmental institutions. Despite the increase in the number of Masters and PhDs, 68% work in academic research institutions, all of which are, with rare exceptions, governmental.[3]

The trade deficit of the Brazilian Health-Industrial Complex rose from $3 billion in 2003 to $10 billion in 2011.[4]

The productive structure and infrastructure of biotechnology ST&I in the biotechnology/human health field in Brazil are solid and in expansion. However, they are geographically concentrated and very dependent on public funding. Clustered in southeastern Brazil, especially in a few cities in the state of São Paulo, the biotech/human health field is sectorally concentrated, with cutting-edge scientific production and innovation focused on a few areas of expertise, such as cardiology, cancer

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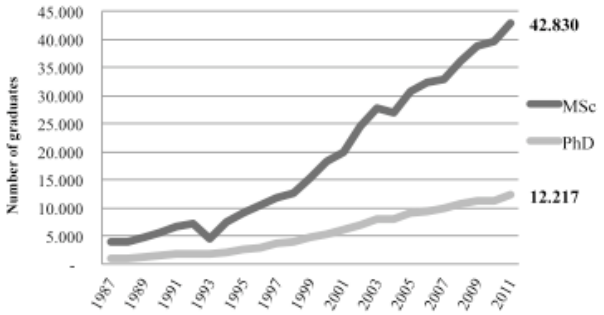

Figure 1: MSc and PhD graduates per year, Brazil 1987-2011
Source: Capes

and infectious diseases. Finally, almost all of the companies, mostly micro and small,[i] depend on public funding for R&D.

(i) Scientific production in human health

Brazil has a well-structured post-graduate system, which provides conditions for advanced training of human resources in some areas of science, though still quite uneven in terms of sectors and distribution across the country.

Human resources for research

In regards to the training of human resources at the graduate level, growth in Brazil over the last two decades was significant. In 1987 the country produced 3,865 Masters (MSc) and 1,005 PhDs. In 2011, it was approximately eleven times more Masters (42,830) and twelve times more PhDs (12,217) than 24 years earlier (Figure 1).

Three points must be emphasized in relation to this growth trend. The first is that there is a strong concentration in the State of São Paulo: 25% of the Masters and 40% of the PhDs came from institutions based in São Paulo state. The second is that, though the ratio of researchers to the total population is improving in Brazil, it is still relatively low (660/million) compared to those in developed countries - 4,500/million in the United States and in South Korea and 5,500/million in Japan.[2] Thus, Brazil contributes only with 1.7% of the researchers in the world, much less than all of the developed countries, as well as China, India and Russia. The third is the fact that researchers find few opportunities in the Brazilian job market, being largely employed by universities and research institutes (68%), and not in the private sector (with only 26.5%), as is typical in developed countries. [3]

i Companies that have up to 50 employees or revenue up to R$ 2.4 million.

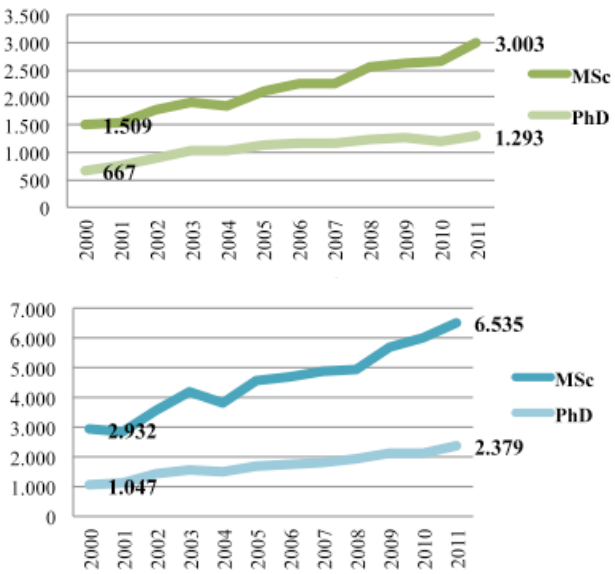

Figure 2 Top: Biological Sciences MSc and PhD graduates per year, Brazil 1987-2011; Bottom: Health Sciences MSc and PhD Graduates per year, Brazil 1987-2011
Source: Capes; Prepared by the authors.

Nevertheless, the increase in the training of human resources in Brazil was significant in the principal fields of study related to human health /biotechnology.[ii] If we use the

ii Capes stands for *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* or Coordination of improvement of personnel with a Bachelors' degree. It has a classification system that is divided in knowledge areas that start with more general/comprehensive areas to more specific ones: big areas, descriptive areas and evaluation areas. In this paper, we considered the following Capes knowledge areas related to biological sciences: biophysics, general biology (includes molecular biology), biochemistry, pharmacology, physiology, genetics, immunology, microbiology, morphology and parasitology. Regarding health sciences the following Capes knowledge areas were considered: pharmaceutical sciences and nutrition, several areas in medicine, such as allergies and clinical immunology, anatomical pathology and clinical pathology, oncology, cardiology, surgery, infectious diseases and parasitology, ophthalmology and medical radiology. Finally, in engineering, we selected chemical engineering and biomedical engineering. Biotechnology is a recent addition to the areas of knowledge from Capes and was selected in this paper as well. The database from Capes has the following information: Number of Masters and PhDs (graduated and enrolled), faculty, institution, municipality and State of a given program.

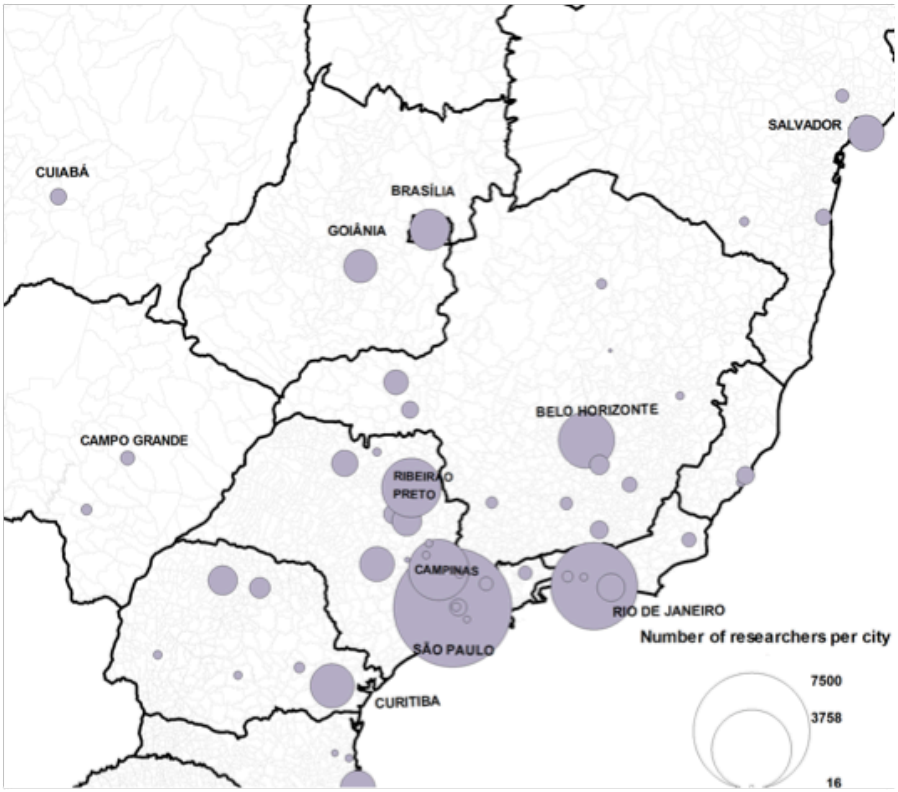

Figure 3: Faculty and researchers in Masters and PhD programs in biotechnology-related areas in human health. Southeast, Brazil. 2011.
Source: Capes; Prepared by the authors.

year 2000 as our starting point, the number of Masters and PhDs has increased, in 2011 was almost double in the areas of biological and health sciences. In relation to the total in 2011, 22% of the 42,830 new Masters and 30% of the 12,217 PhDs in the country were in the disciplines of biological and health sciences (Figure 2).

Research potential in human health and biotechnology

Considering the number of faculty and researchers in Masters and PhD programs as proxy for scientific production in academia,[iii] there is a clear potential for development of new technologies and know-how in biotechnology-related areas in human health, but that is highly concentrated in certain cities, with advanced research in only a few areas of expertise. There are currently 11,813 faculty and 29,115 researchers enrolled in graduate and doctorate programs in the areas selected here[1]. This represents 18% and 17% of all faculty and graduate students in the country, respectively.

São Paulo state has 37.5% of the 40,928 researchers (enrolled in Masters, PhD programs and faculty), well ahead of other states such as Rio de Janeiro (12.5%), Minas Gerais (8.6%) and Rio Grande do Sul (8.2%). In addition to the Southeastern/Southern axis, all of the northeastern states combined make for a total of 15% of the researchers in fields related to biotechnology in human health (Pernambuco, 4.2%; Ceará, 3.4%, and Bahia, 2.9%).

This is reflected in a more disaggregated spatial analysis, since only 79 municipalities (out of 5,565) contain all of the 40,928 researchers. Among the five cities with more researchers, three are from São Paulo state: the capital, São Paulo (19%), Campinas (5.6%) and Ribeirão Preto (5.3%). The other two are the capitals of the states of Rio de Janeiro (10.8%) and Rio Grande do Sul (5.6%). Belo Horizonte (4.9%) is ranked sixth, just above Recife (4.1%) (Figure 3).

iii It is important to emphasize that we are not considering that all researchers/faculty working under the Capes knowledge area biotechnology are working with human health. In addition, because we are only considering faculty enrolled in graduate programs, we are underestimating the research potential, given that there are researchers that are not enrolled in a given program.

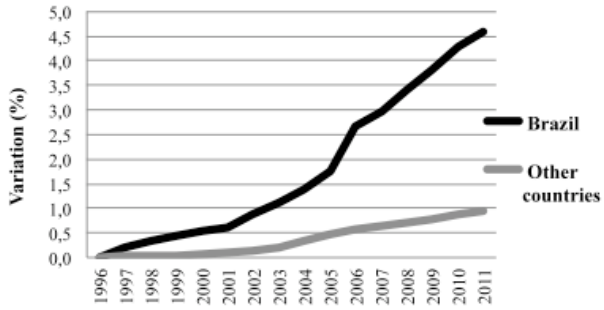

Figure 4 Scientific Articles published in Brazil and in other coutries. Variation (%), 1996-2011.
Source: Scopus; MCTI. Prepared by the authors.

In regard to the fields of study selected here, the highest number of researchers is in medicine. The sum of medical specialties represents 6% of all researchers in Brazil, with the majority in surgery, pathology, oncology and cardiology. Other groups with significant numbers of graduate students and faculty, are in fields related to human health-focused chemistry: biochemistry, pharmaceutics, pharmacology, and chemical engineering which totaled 9,123 researchers, or 4% of the total. Researchers in microbiology, immunology, infectious diseases and parasitology amounted to 4,393 - 2% of the total. One area that has grown significantly in recent years is genetics, at 1% or 2,166 researchers.

Biotechnology as a specific area of study in the Brazilian graduate system is recent. Given its interdisciplinary nature, much of biotechnology's research occurs in areas not related to human health, but, still it is worth mentioning that the number of researchers in biotechnology and biomedical engineering totaled 3,281 (1.5% of the country's total).

Scientific production: more publications in areas related to biotechnology

According to the last "SIR World Report", Brazil occupies the 10th position in scientific performance[5]. This is due in part to growth in recent years, the number of Brazilian publications in general, and the relative share of the country's total production worldwide. According to the Scopus basis, in 2011, Brazil published 46,933 articles, 2.3% of the 2,062,532 in the world (more than half of Latin America, 54.1%)[6].

Regarding information on the number of articles published in scientific journals indexed from another source, the Thomson/ISI, in 1996, Brazil produced 6,000 articles. This number jumped to 32,000 in 2009, an increase from 0.9% to 2.7% in the participation in publications worldwide.[3] Along with China, South Korea, Turkey, and Taiwan, Brazil ranked among the five countries with the highest percentage growth in the publication of articles between 1981 and 2009, in absolute terms; only China, the U.S., South Korea, India, and Canada had greater variations.[2] According to this source, Brazil now ranks 13th in the world, behind countries with smaller economies and populations such as France (65,000), Canada (55,000), Italy (51,000), Spain (44,000), South Korea (39,000), and Australia (38,000), in addition to the countries quoted above.[7]

The number of publications further illustrates the regional concentration of science in Brazil: only seven universities (all public) account for 60% of the articles in international journals, and USP (University of São Paulo) is responsible for about a quarter of the total [7] (Table 1).

Of the eleven fields in which the country has the highest rates of published articles indexed in the worldwide total, seven are related to human health and/or biotechnology. More importantly, the Brazilian share of the global output has increased between 2004 and 2009 (Table 1).

Although the impact factor of Brazilian publications is still low, it improved from 1.45 citations per article, in 2000, to 2.05 citations in 2007.[7] The fields of study that stand out the most are precisely those related to human health, originating mostly from the state of São Paulo.[8]

Finally, it is worth mentioning the evolution of Brazil over the past two decades in terms of patent applications. There was an increase in the number of patents pending in the United States (at USPTO) between 1988 and 2011, with 71 requests in 1988 and 586 in 2011 by Brazilians - 725% increase. Concessions rose from 29 in 1988, to 254 in 2011 (775% increase).

However, this growth in absolute numbers was not significant in relative terms, as many other countries also increased their number of patents, and some, such as South Korea, China, and India, have performed well above Brazil. For this reason the country, that held 30th place in the ranking of patents granted in 1988, moved up only to 29th in 2011. In other words, Brazil continues to occupy a minor position in the ranking of countries in terms of international grants of proprietary technology. In addition, most patents are generated in universities and public research institutes, and not in the private sector and half of them originated in São Paulo state.[9]

(II) Innovation on human health: sources of funding for new projects and a lack of innovative capacity regarding the discovery and development of new drugs.

The Brazilian private sector invests little in R&D: 0.5% of the GDP, with about a third of that investment from tax breaks.

This low record of private investment is especially obvious when the sources of R&D funding of

Table 1:

		% of Brazil in relation to the world	
	Areas of Knowledge	**2004**	**2009**
1	Agricultural Science	2,9	9,9
2	Plant Science/Veterinary Medicine	3,4	7,0
3	Pharmacology and Toxicology	2,3	4,0
4	Microbiology	2,2	3,3
5	Social sciences	0,9	3,3
6	Ecology / Environment	2,4	3,0
7	Biology / Biochemistry	1,9	2,8
8	Neurosciences / Behavioral Science	2,1	2,8
9	Medical Clinic	1,4	2,7
10	Immunology	2,0	2,3
11	Molecular Biology / Genetics	1,3	2,3
12	Physics	2,6	2,0
13	Chemistry	1,6	2,0
14	Space Sciences	2,1	1,9
15	Mathematics	1,8	1,8
16	Multidisciplinary studies	1,6	1,8
17	Materials Science	1,5	1,8
18	Geology	1,4	1,7
19	Engineering	1,5	1,5
20	Psychology / Psychiatry	0,4	1,5
21	Computer Science	1,6	1,2
22	Economics and Business	0,4	0,9
	Total Brazil share	**1,8**	**2,7**

Source: National Science Indicators (NSI), Thomson Reuters Scientific INC; Prepared by the authors.

biotechnology/human health companies in the country are analyzed: most are completely dependent on governmental resources, a difficult problem, given the limitations that that imposes on the growth of the industry.

The Brazil Biotech map 2011, identified 237 biotechnology companies in the country, 53% (125 companies) have human health and reagents as their main area of expertise.[iv] Of this group of biotechnology companies working with human health, 79% use public resources for R&D, of which 61% use FINEP, 40% programs from CNPq, and 44% use state foundations that support research (FAPESP and FAPEMIG, for example). As the study indicated, these are companies both young (67% created after 2000) and small (70% have revenues under $2.4 million, and 83% have up under 50 employees).

Three federal agencies have an important role in the distribution of grant funding for innovative biotechnology / human health projects: FINEP, now the Brazilian Innovation Agency, which publishes announcements for grant proposals (see analysis below), BNDES, the National Bank for Economic and Social Development, which has a variety of programs encouraging innovation - Funtec is their non-refundable fund and CNPq (Conselho Nacional de Desenvolvimento de Científico e Tecnológico), which has a special program denominated RHAE (which stands for human resources in strategic areas), that provides fellowships for professionals that have completed a Masters and/or PhD degree to work in companies that develop innovative projects. The goal is to stimulate companies to hire professionals that can participate and be responsible for innovation. 69% and 25% of all approved RHAE projects go to micro and small-sized companies, respectively. Again, the southeastern region of the country approves more than half of all projects (51%), of which 14% is in biotechnology and 10% in human health (on line presentation made by CNPq, May 22nd, 2014).

Federal investment in R&D: the case of economic subsidies from FINEP

In order to better understand the nature and geographic location of innovative projects in human health developed in Brazil, we analyzed the projects approved by FINEP, within the scope of economic subsidy, which is the instrument for granting non-refundable resources

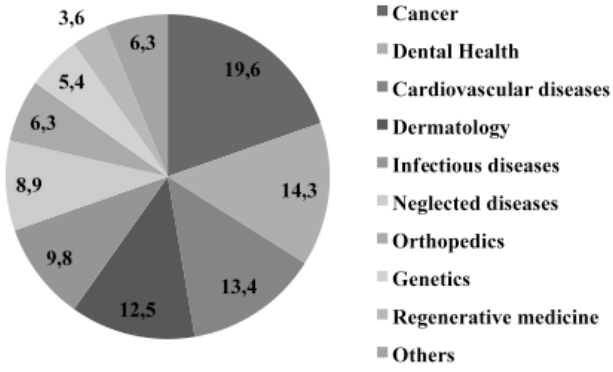

Figure 5 Number of human therapeutic projects approved by FINEP
Source: Finep; Prepared by the authors.

by the institution.[v] The first finding is that companies from the state of São Paulo submitted half of all the projects. Rio Grande do Sul was in second place with 10% of the grant awards, and in third place, Minas Gerais and Paraná, both with 9%. Rio de Janeiro had 7%, and Goiás, Santa Catarina, Ceará, Brasilia, Amazonas, Paraíba, Pernambuco and Piauí together added up to 15%.[vi]

As human health encompasses very diverse areas, we categorized the projects by therapeutic area. It was then possible to group them into 13 categories: cancer, orthodontics, cardiovascular diseases, dermatology, infectious diseases, neglected diseases, orthopedics, genetics, regenerative medicine, inflammation, endocrinology, chronic pain, and respiratory diseases. Cancer is the category with the highest number of projects, 20% of the total, followed by orthodontics (14%), cardiovascular diseases (13%), dermatology (13%) and infectious diseases (10%) (Figure 5).

Although the highest concentration of projects approved are in the state of São Paulo (especially in

iv The information on biotechnology companies presented in this paper are from a new analyses from the databank made for the *Brazil Biotech Map 2011*. For the methodology, Cebrap, available at http://www.cebrap.org.br/v2/items/view/419

v Data from FINEP's databank collected searching for projects related to human health (no filter for this search was available, projects related to human health were selected based on their titles. If the title was not informative (a minority), projects were not considered) and for each State (there are filters for selecting different States), from 2007 (first year of approved projects under *Subvenção econômica*) until 2010. http://www.finep.gov.br/pagina.asp?pag=programas_subvencao>, accessed on 06/2014.

vi The same company can have more than one project approved in different programs rom FINEP. The majority of the projects are from the call *Subvenção econômica*, but some are from other programs such as *Juro zero* (this program was discontinued) or *ICT-Empresa*. Additional programs were introduced by FINEP, *Inova saúde*, for exemple, that were not considered for this analysis.

cancer, cardiovascular diseases, and neglected diseases), the South of Brazil (Paraná, with ten cases, and Santa Catarina, with five) excels in innovative projects in orthodontics.

FINEP is also the main sponsor of venture capital funds in Brazil through its program "*Inovar fundos*". The institution conducts public requests for proposals to raise capital to foment the growth of the venture capital industry. The goal here is to increase the amount of the private funds share in the development of high technology companies. Nevertheless, a brief analysis of the track record of the funds approved by the program shows that: (i) only 25% goes to seed capital, which is what the biotechnology/human health sector mostly needs (companies are young and small); (ii) considering the seed funding and venture capital with involvement from FINEP, few have focused on biotechnology, and when they do, human health is not a priority area. Of one hundred companies, we identified five in human health. Among them, three are dedicated to services (oncology clinic, CRO and IVF) and only two to human health biotechnology; one in orthodontics and another dedicated to the discovery of new drugs for human health.[10]

Venture capital in Brazil is not investing in companies focused on human health biotechnology, as was the case with BNDES' seed money fund, *Criatec I,* which has closed. The portfolio of biotech companies that received funding included agribusiness and human health, but in this case, equipment companies and information technology in health and services. The "risk" investment has shown more interest in direct applications in healthcare, such as hospitals, diagnostic companies, equipment, and information technology applied to healthcare, than in biotechnology projects, which are technology heavy and involve high cost and risk. With the exception of the old example of Biobrás, national biotechnology lacks success stories in human health.

Innovative capacity: an analysis based on clinical trials

We conducted a search for clinical trials in the predominant knowledge bases found in the projects approved by FINEP and that needed clinical trials to bring a product to market, namely cardiology, cancer and infectious diseases. To contextualize the national scene, we did the same search in Brazil and the United States, a leading country in innovation in human health. For each knowledge area and country we filtered the searches by: (1) industry-sponsored phase 0-2 open trials; (2) Open trials phase 0-2 sponsored by other institutions; (3) Phase 3 open trials sponsored by industry, and (4) Phase 3 open trials sponsored by other institutions.[vii]

Following these parameters, the totals were 10,589 selected trials underway in the United States and 352 in Brazil in these three areas. As expected, the highest proportion of clinical trials in the United States was in phases 0-2, while in Brazil the largest proportion was in phase 3 (Figure 6). Within cancer in the United States 79% of the tests were in phases 0-2 (with 46% sponsored by non-industrial institutions and 34% by industry); 56% of all trials in cardiology (with 37% for non-industrial institutions and 19% from industry); and 60% of the trials in infectious diseases (with 37% for non-industrial institutions and 23% from industry).

In Brazil, the largest proportion of clinical trials is phase 3 and sponsored by industry (mainly foreign multinationals): 48% of trials for cancer, 39% of those in cardiology and 55% of the trials in infectious diseases. In cardiology, the participation of non-industrial institutions, mostly Brazilian, is also significant (33%).

Two important findings came to our attention during the analysis. The first refers to the trials in phase 0-2 - those that indicate greater innovation - in Brazil, where cancer is the area that has the highest proportion: of 41% of the trials, 28% were sponsored by industry and 13% by other institutions. Cardiology, for example, appears in 29% of the trials. The difference is that in cancer, the greatest part of phase 0-2 trials is sponsored by foreign multinational industry, and in cardiology, sponsors are mainly national research institutions and hospitals. This may be a reflection of the greater interest of the international market for innovations in cancer than in cardiology.[11]

The second finding is that the involvement of Brazilian companies, either as sponsors or contributors, is very minor in the three therapeutic areas that were analyzed. In cardiology, one of the areas in which Brazil has a good international reputation for basic and applied science, of 142 open clinical trials, only five (3.5%) have participation from Brazilian companies: Scitech Medical Products, ProCardiac in partnership with DASA group, the service provider LAL and the pharmaceutical company Eurofarma (with two trials). Several national research institutions such as USP, INCOR, UFRJ, UFBA, UFJF, among others, are sponsors. In cancer, the pattern is similar. Amidst a variety of leading multinational companies with clinical trials in Brazil, there are only a few national companies:

vii Data is from clinicaltrials.gov. Searches were made for the following keywords, cardiac, cancer and infectious diseases. First we used the filter for open studies in Brazil or USA and then filters were used for the results: phases 0-2 or phase 3, and industry or all others. We considered all trials open until 03/30/2013.

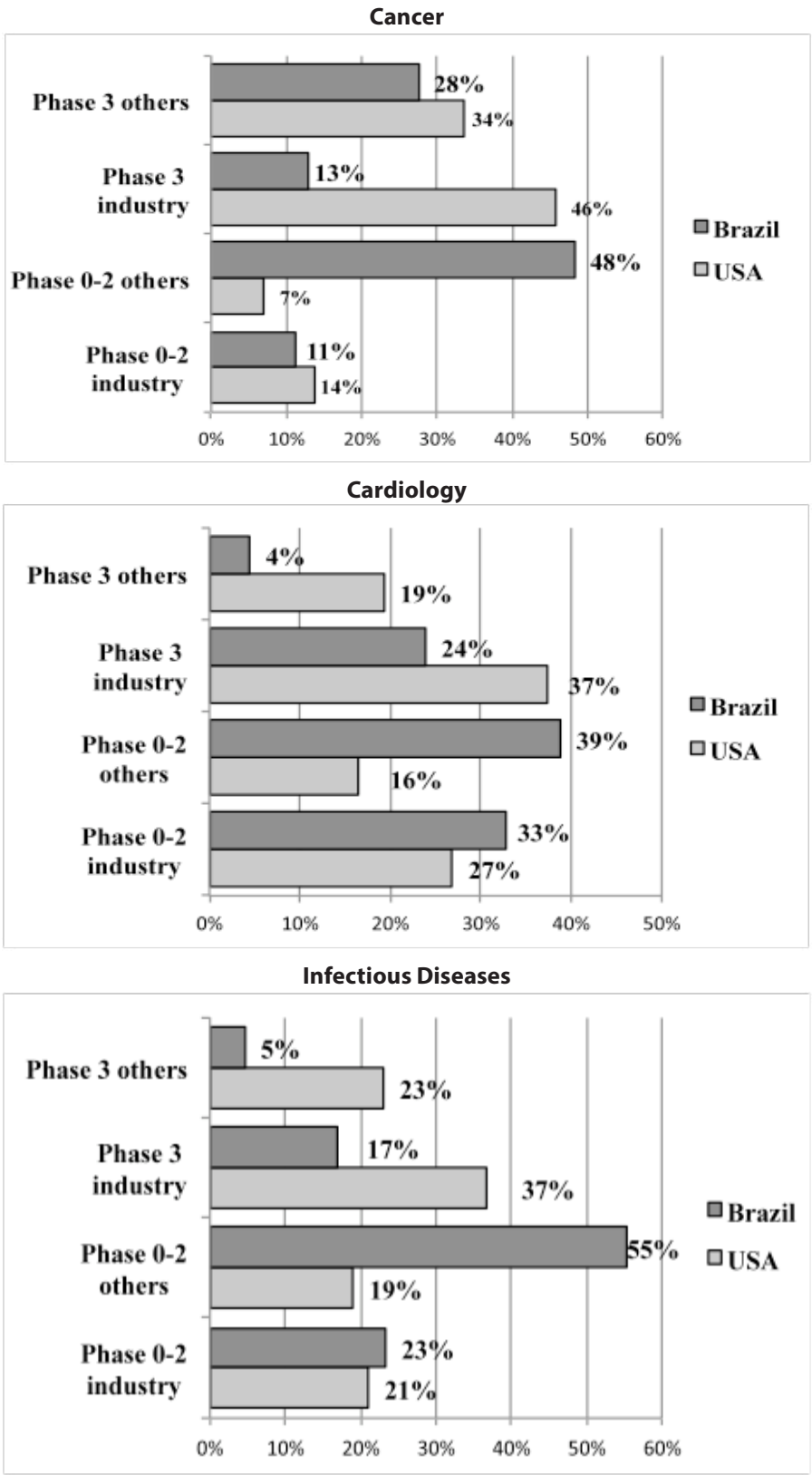

Figure 6 Proporation of clinical trials by therapeutic area and phase, in Brazil and the United States
Source: clinicaltrials.gov; Prepared by the authors.

Eurofarma, Recepta (with monoclonal antibodies), and Lavilabor (with natural products), and LAL.

It was surprising to note that this pattern was not much different in infectious diseases. The majority of these trials had sponsors from foreign industry. Of 166 open trials, only eleven were sponsored by Brazilian companies: EMS, Laboratório Teuto Brasileiro, Adapt Ophthalmic Products, Biolab Sanus, Zodiac Pharmaceuticals, Zurita Pharmaceutical Laboratory, and LAL.

(iii) A DISCONNECTION BETWEEN THE ADVANCEMENT OF SCIENTIFIC OUTPUT AND INNOVATION WITHIN THE PRIVATE SECTOR

These findings from clinical trials confirm what appears in literature on the subject in Brazil: the low innovative capacity of the private sector in human health. For Gadelha, for example, one of the essential problems of the Brazilian health industrial complex is the low innovative capacity of the national pharmaceutical industry, which is detached from the Brazilian technological and scientific base.[12]

Despite the growing number of Masters and PhDs, our publications still have little impact and the number of patents registered by the Brazilian scientific and technological base is low. The lack of connection between the domestic pharmaceutical industry (which should be responsible for the output) and the Brazilian scientific and technology base (the input) can also be the result of the fact that much of the investment in the training of human resources does not necessarily have a direct relationship with the generation of interesting technologies to create products for the market.

The Brazilian pharmaceutical industry has a unique feature: the existence of state sponsored laboratories nationwide, geared primarily for the production of medicines listed in government health programs. Together, official laboratories are able to produce about 11 billion pharmaceutical units per year, with 195 products, encompassing more than 100 active ingredients. The production of these laboratories represented, in 2006, close to 3% of national production in value and 10% in volume, which amounted to about 10% of total purchases of medicine from the Ministry of Health. Although the dependence on external supplies for the production of medicine is a common problem in developing countries, Brazil is one of the few countries to have state-owned drug production facilities, installed in various regions of the country.[13]

The role played by official laboratories, however, goes beyond the production of medicine, representing an important form of market regulation. By offering medicine, these labs help to increase competition in the sector, develop research in areas of less interest to the industry and, above all, facilitate the access of medicine to the low-income population.

There is considerable expertise in our hospitals and research institutions to conduct R&D in strategic areas, such as cancer and cardiology, but the development of new technologies for human health is hindered by the lack of involvement in the private sector. This is consistent with the low amount of innovation within the national pharmaceutical industry and a biotechnology sector still comprised of very young, and poorly funded, companies.

The high reliance on public funding and the low innovation capacity of businesses is evidence that relates directly to the literature on the topic, which point out major challenges when it comes to human health biotechnology in Brazil: 1) the centrality of production in public laboratories; 2) the relationship between the high trade deficit and the low technological capacity and innovation in the national industry and 3) the need to improve the purchasing power of the government as a strategy to stimulate technological development.[14] To deal with such challenges, public policy in the health sector can stimulate technological development in the health industrial complex, in general, and specifically in biotechnology/human health.[15]

In 2012, the federal government launched the *National Strategy for ST & I*, which, according to Costa, "emphasizes the need to promote mechanisms to stimulate innovation in health and the intensification of technological transference to national public laboratories."[16]

According to the Ministry of Health, by December 2013, 104 agreements were reached for the production of 97 new products in Brazil including, vaccines, anti-retroviral drugs, oncology drugs, drugs for neglected diseases and biosimilars. The agreement involved 19 public and 60 private laboratories, 30 with national, and 30 with foreign capital.[17]

In order to put Brazilian industry on a path towards technological learning in regard to biosimilars and reduce the trade deficit of human health in the country, the federal government intends to use its purchasing power to stimulate local production of medicine and biosimilars.[18] The fact that the government will pay up to 25% more when these products are manufactured in the country has encouraged the private sector. Two joint ventures that aim to manufacture biosimilars are BioNovis and Orygen Biotechnology.

Despite the efforts and advances, much of the innovation in human health biotechnology arises from the discovery of new drugs, something that Brazil isn't doing very well. The Brazilian deficit in human health is especially related to biotechnology products, those with higher added value and primarily prescribed for chronic

diseases, the major problem of the country's population today.[19] The deficit is a problem that the federal government tries to attack with the above-mentioned efforts. However, an overview of the sector in other countries shows that there are other challenges. The country has a strong academic background, as mentioned in this article, and a sophisticated biomedical community. The discovery of new drugs is a long, difficult process, involving high risk and high costs, requiring a closer relationship between academia and the private sector. In this field, it seems that there are still more roadblocks than open lanes.

The result of the research in Brazil gives the impression of being out of step with the international commercial reality, which hinders the fostering of a biotechnology industry that, to be robust, must be "international". There is ground-breaking research in the academic world in Brazil, some that generate interesting startups that survive for some time with public funding (such as FAPESP and FINEP), but what can be done in addition to government funding for R&D? Biotechnology companies often need not only an initial round of venture capital, but rather several rounds.

The increase in the number of researchers trained in graduate schools and scientific production is important for the scientific and technological base of Brazil. However, university/business interaction, the private sector investments in the development of new drugs, as well as public policies for the sector - such as public/private partnerships, government procurement and subsidies for innovation - are recent movements that have not yet had a direct impact, for example, on foreign dependence and the commercial trade deficit for medications.

CONCLUDING REMARKS

It is not easy to have a good overview of the life sciences/biotechnology sector in Brazil. In our point of view, this comes from a lack of an institution, such as a biotechnology association, that could consistently gather, organize and publish information, keeping a database of private and public biotechnology companies, funding sources and revenues of the sector along the years. This is not only important for foreign investors but also for policy makers.

A lot of the information on the private Brazilian life sciences is from non-peer reviewed studies, most of which were made by a private foundation, Biominas Brasil. It is unfortunate though, that these studies, which have been published since 2001, do not have a uniform methodology, not allowing for a comparison and follow up of the sector, which would provide a better understanding of the private biotechnology sector along the years.[20-23] Has it really grown? Are companies thriving? Bianchi (2010 and 2011) published work aiming at identifying the number of private companies in the country,[24-25] so did Cebrap in 2011,[26] different methodologies to define the sector have been used.

Encompassing a much broader topic, Carlos Augusto Gadelha, has authored many studies and papers,[4, 12, 13, 27] on the human health industrial complex. Zylberberg E et al published in 2012 an overview of the industry, reviewing data from Gadelha, Biominas and Cebrap.[28]

To our knowledge, the initiative to specifically study human health biotech came with Rahim R and co-workers.[14] In this 2008 paper, the group interviewed many entrepreneurs, policy makers and regulatory agencies in Brazil, and provided a good picture of what was going on in the country, including many of the problems that should be addressed for a better development of the sector. In the past 6 years, much has changed: there is a cultural change within some universities, research institutes and respective technology transfer offices, regarding a more entrepreneurial involvement, Coinfar, an interesting enterprise and interviewee, no longer exists, new companies such as Mendelics and Biozeus have been created and pharmaceutical companies are more aware that they must innovate. The latter point is in agreement with a most recent paper published in 2012, that focuses on innovative drugs and vaccines in China, India and Brazil. In the case of Brazil, most of the innovative drugs and therapeutics are in pre-clinical stage and being developed by national pharmaceutical companies, Cristália and Ache.[29]

In addition, new policies are in place and new projects have been started since 2008. We hope that all of this has been addressed in this paper, bringing an up-to date overall picture of the human health biotechnology in Brazil and a criticism of the sector through a different angle. The combination and development of multiple conditions for biotechnology in human health is necessary to contribute to a development process based on innovation in Brazil.

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Article

Importance of venture capital investors for the industrial biotechnology industry

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ABSTRACT
As in the medical biotechnology area some decades ago, the fast technological development within industrial biotechnology (IB) has caused numerous new ventures. Venture capital (VC) has become a major capital source for these companies and VC investors have particularly allocated financing to research and development (R&D) based companies. Since the early 2000s, the global net stock of VC investments in IB companies has continuously increased over the past 12 years and exceeded 3.5 billion US dollars at the end of 2013. In 2013, the gross amount of VC money was 386 million US dollars distributed to 20 companies corresponding to an average amount of 19.3 million US dollars for each company. The rising capital contribution into the IB sector indicates that it is seen as an attractive investment opportunity for VC investors. Analysing the VC investments by segments shows that there is a strong preference for biofuels and biochemicals. The regional breakdown of VC activities shows that the Americas are the leading region followed by Europe.

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EMERGENCE OF A DEDICATED IB INDUSTRY

The medical (red) biotechnology industry evolved a few decades ago. Based on scientific breakthroughs in the 1970s and 1980s the first companies arose in the United States (US), like Genentech (founded in 1976), Biogen (founded in 1978) and Amgen (founded in 1980). Meanwhile a dedicated medical biotechnology industry has emerged with significant global sales developing more new therapeutics than the traditional pharmaceutical industry based on small molecules. The same development is currently observed for industrial (white) biotechnology (IB) as, over the last years, biotechnology is being increasingly used in the production of bulk chemicals and materials, such as base chemicals and polymers as well as high value products, like consumer chemicals and specialty chemicals.[1,2]

The main reason for this development is that consumers are increasingly becoming conscious about the

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environmental impacts of their consumption and see the need for sustainable development. IB is commonly accepted as a promising approach to overcome the consequences of diminishing fossil resources, such as crude oil, coal and natural gas by progressively shifting towards renewable resources and less energy intensive methods of production.[3,4] Instead of energy intensive chemical processes using high temperatures, IB achieves the same results using enzymes, microorganisms and other biological catalysts operating at low temperatures. And IB enables the use of renewable resources as industrial raw materials. These raw materials are typically agricultural materials, such as starch and their residues. Thus, IB can play a major role in lowering the carbon footprint of products across many industry sectors, including chemicals, food and feed, pulp and paper and textiles.[5,6] In addition, IB provides tools for the development of new products which cannot be made using traditional chemical processes.

To show the diversity of molecules produced through biotechnology processes some examples are described in the following. 1,3-Propanediol, for example as bulk chemical, is a molecule mainly used as a building block in the production of polymers. It can also be formulated into a variety of industrial products including cosmetics, adhesives, coatings and paints as well as composites and laminates. 1,3-Propanediol has a production volume of more than 100,000 tonnes per year. A new biotechnology process enables the conversion from corn syrup by a genetically modified strain of bacteria by DuPont Tate & Lyle BioProducts. Another bulk chemical is succinic acid which is used as a precursor for polyesters and a component of alkyd resins. It is also applied in the food and beverage industry, primarily as an acidity regulator. Global production is estimated at 30,000 tonnes per year. This molecule is more and more produced through the fermentation of glucose from renewable feedstock and purification of raw bio-based succinic acid. Companies like BioAmber, Reverdia, Myriant, BASF and Purac are progressing from demonstration scale production to viable commercialization.

An example for a specialty chemical is the amino acid lysine which is an important additive to animal feed because it is a limiting amino acid when optimizing the growth of certain animals, such as pigs and chickens, for the production of meat. The production exceeds 600,000 tonnes per year and main producers are Archer Daniels Midland, BASF and Evonik. Lysine is usually manufactured by a microbial fermentation process using bacteria from a base mainly of sugar. Genetic engineering research is actively pursuing bacterial strains to improve the efficiency of production and allow lysine to be made from other substrates. Another high value product is the vitamin riboflavin, also known as vitamin B2, which is a micronutrient with a key role in maintaining health in humans and animals. Various biotechnological processes have been developed for industrial scale riboflavin biosynthesis using different microorganisms which are genetically modified to increase the bacteria's production of riboflavin. BASF, for example, produces riboflavin using a filamentous fungi.

IB can make an important contribution to transform the economy from petro-based to bio-based. But producing through biotechnological routes is, at least in the starting phase, more expensive compared to traditional chemical production routes, as the synthesis of existing products by chemical procedures is frequently well established.[7] In order to produce competitively compared to chemical synthesis, huge investments are needed to develop cost efficient manufacturing technologies and to scale-up biotechnological production.[8] Capital demand is high since production facilities for chemical syntheses cannot be changed to biotechnological production without substantial new investments. Despite these challenges, IB has emerged from a research and development (R&D) based field to a substantial industry.

ANALYSIS OF VC ACTIVITIES AND IB MARKETS

The same development as in the medical biotechnology area started for IB as the fast technological development has caused intensive entrepreneurial activities. In addition to established companies, an increasing number of dedicated IB companies have been founded during the last decades. The primary aim of this article is to analyse venture capital (VC) investment in the global IB industry for the past 12 years from 2002 to 2013. The data presented in this article are taken from the Zephyr database of the Bureau van Dijk. Zephyr is the most comprehensive database worldwide on corporate financing, initial public offering (IPO) and mergers & acquisition (M&A) activities including VC deals. 288 companies were identified with IB as core activity using appropriate key words and a detailed analysis of each company based on its business activities. The challenge was to separate these dedicated IB companies from medical and agro or plant biotechnology companies as well as non IB focussed companies deriving from traditional sectors, like the chemical industry. The identified companies were categorised into one or more of the following 4 business areas: biofuels, biochemicals (including biomaterials) and bioactives. For each IB company all deals in the Zephyr database, which took place in the years from 2002 to 2013, were identified and analysed. Deals relating to joint ventures and share buybacks were excluded since these deals do not represent new investments into the companies.

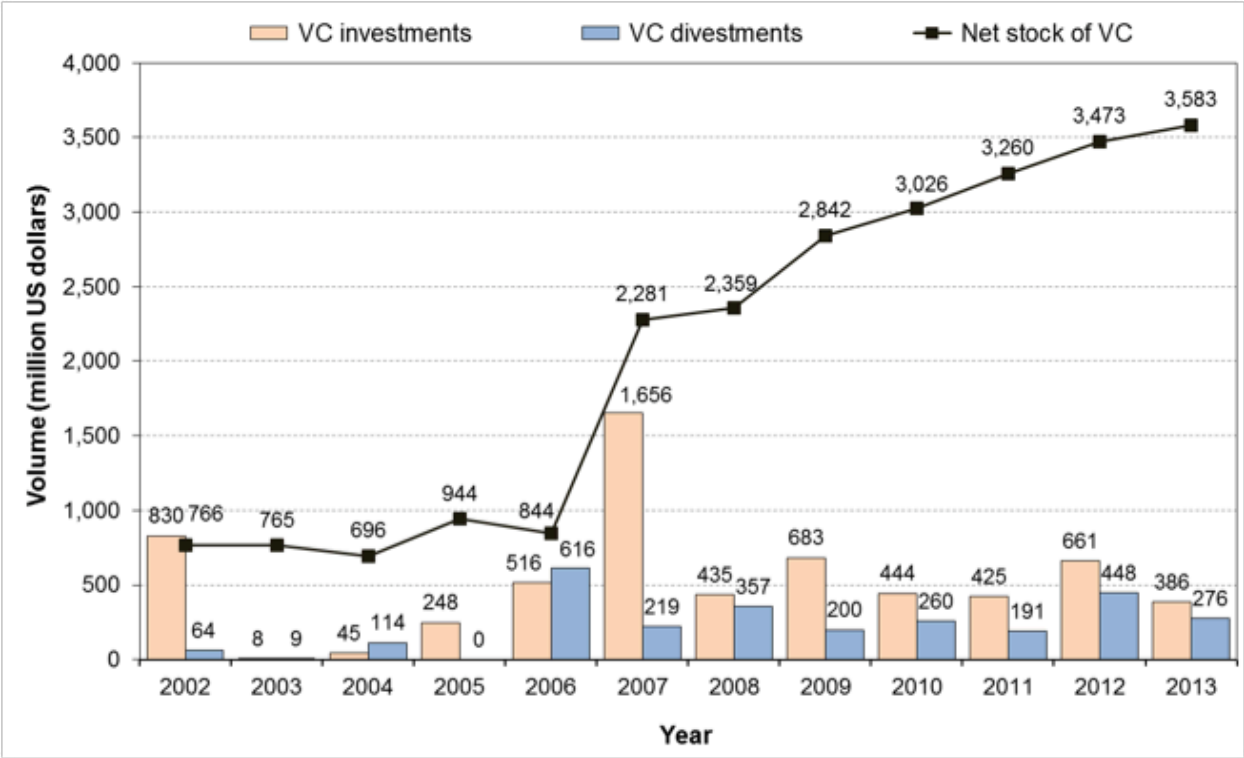

Figure 1: Volume of VC investments/divestments and net stock of VC

In addition to VC activities some market data regarding biochemical markets are presented in this article.[2,5] The market data derive from a database, built up since 2003 by Festel Capital, based on desk research using public sources like databases, articles and company disclosures as well as interviews with experts from the industry, universities and research institutions, the investment sector as well as governmental institutions. Within the database, the sales of biochemicals are estimated as rolling forecast. The sales of all biochemical products made from renewable resources using biotechnological conversion processes are considered. If single chemical process steps are involved, these products are also considered, but renewable raw materials converted only through chemical processes and non-renewable raw materials converted through biotechnological processes are not included in these market data. The sales figures in this data base only show product sales between two independent companies based on market prices, i.e. not considered are captive production or inter-company sales. Biofuels and bioactives, like active pharmaceutical ingredients and intermediates, are not included in the market data presented in this article.

EXTENT OF VC INVESTMENTS IN THE IB INDUSTRY

From 2002 to 2005, VC activity in the IB business was still rather limited. The net stock of VC grew slightly from 766 million US dollars in 2002 to 844 million US dollars in 2006, which corresponds to a compound annual growth rate (CAGR) of only 2% (Figure 1). But then VC investors discovered IB as an attractive investment opportunity and increased their engagement substantially beginning in the year 2007 with around 1.7 billion US dollars increasing the net stock of VC from 844 million to around 2.3 billion UD dollars. Especially significant investments in biofuel companies in the US had driven these numbers. During the last 6 years the volume of new VC investments is between 400 and 700 million US dollars per year and the volume of divestments between 200 and 450 US dollars. As new VC investments have exceeded divestments every year since 2007 the net stock of VC steadily increased with a CAGR of 25% from 2007 to 2013 resulting in a net stock of VC of around 3.6 billion US dollars in 88 companies by the end of 2013. During the whole examination period from 2002 to 2013, VC companies invested a total of 6.3 billion US dollars in 107 companies in relation to 2.8 billion US dollars divestments.

Taking a closer look at the number of companies with VC investments and divestments shows also the

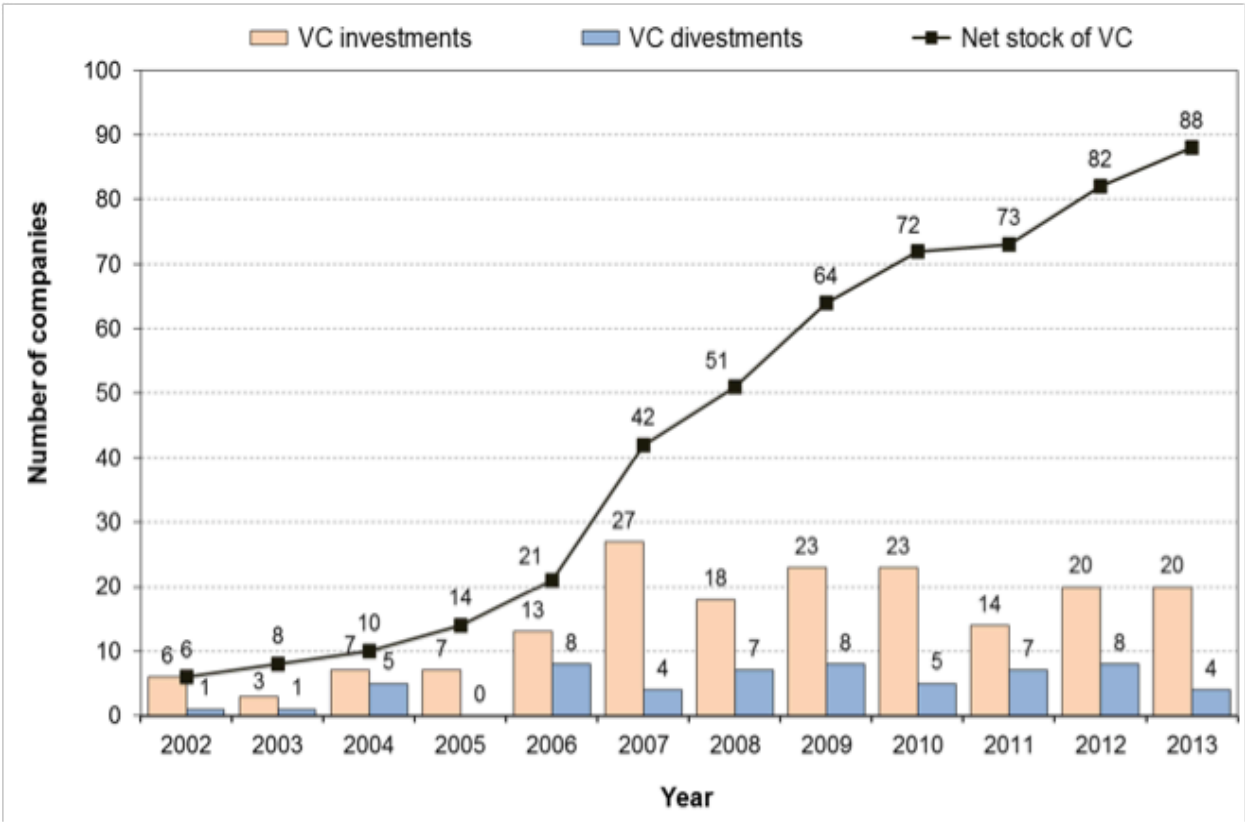

Figure 2: Number of VC investments/divestments and net stock of VC

growing interest of VC investors in IB. Starting with a number of 6 IB companies with VC investments in 2002, there was a modest increase to 14 in 2005 (Figure 2). The following years there was a sharp rise in the number of IB companies with VC investments to a net stock of 88 at the end of 2013. Since 2009 there is a slightly falling trend in the number of IB companies receiving new or additional VC investments from 23 in 2009 to 20 in 2013. The number of divestments during these years was between 4 and 8 companies per year, whereas the average volume of divestment cases was quite volatile, ranging from 69 million US dollars in 2013 to 24 million US dollars in 2009.

These numbers have to be discussed in the context of investments in the whole biotechnology area. Despite the increasing trend of VC investments IB still plays a subordinate role in the whole biotechnology industry. All biotechnology companies achieved a total VC investment amount of 5.7 billion US dollars alone in 2013 primarily in North America with 4.0 billion US dollars.[9] This means that the volume of new VC investments in medical biotechnology companies in 2013 is nearly as high as all investments between 2002 and 2013 in IB companies. It is interesting to see that the size of financing rounds in the IB and medical biotechnology area are similar. In 2013 the amount of VC money flowing to the analysed IB companies was 386 million US dollars, distributed to 20 companies. This corresponds to an average amount of 19.3 million US dollars for each target company. For comparison, most recent data on a large group of medical biotechnology companies revealed that in 2013 an amount of 4.0 billion US dollars was distributed over 276 financing rounds, which results in an average amount of 14.6 million US dollars per financing round.[10]

PREFERRED COMPANY TYPES AND REGIONS

Coming from these general numbers the question was whether there are preferred company types and regions for VC investments in IB companies. The analysis of the age of the IB companies when VC investments were made, i.e. the differentiation in companies up to 3 years old and companies more than 3 years old, shows the increasing maturity of VC investments. During the years 2002, 2004 and 2006 significant VC funding volumes were assigned to companies with an age of up to 3 years (Figure 3). This suggests that VC was a significant financial source for companies in the early stage. Since 2007 most of the annual VC investments were allocated to older companies with an age of more than 3 years.

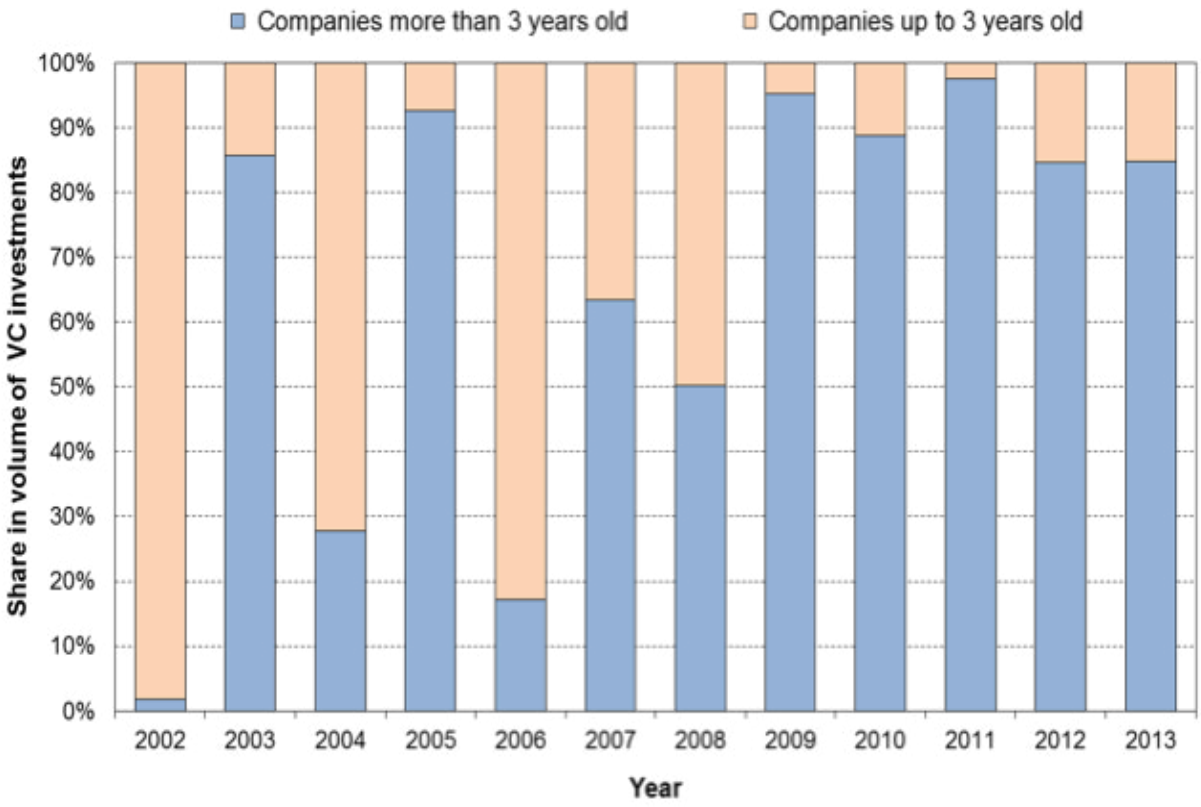

Figure 3: VC investments by age of the company at time of investment

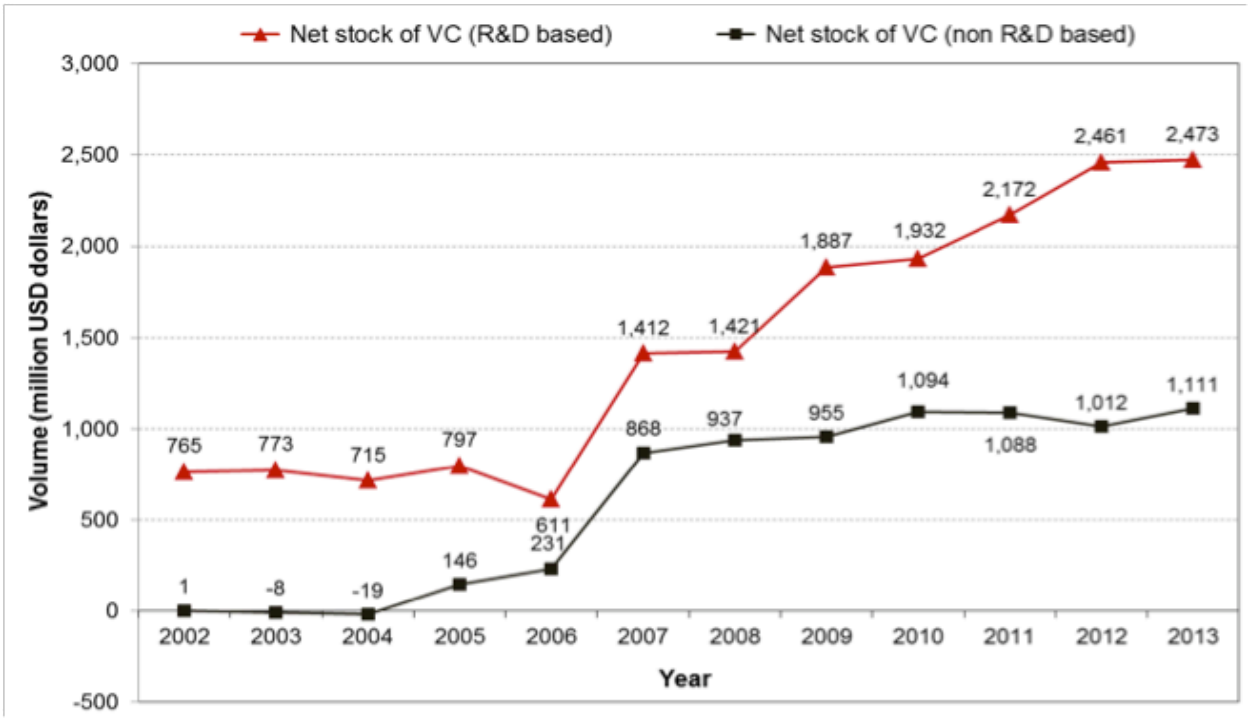

Figure 4: VC investments in R&D based and non R&D based companies

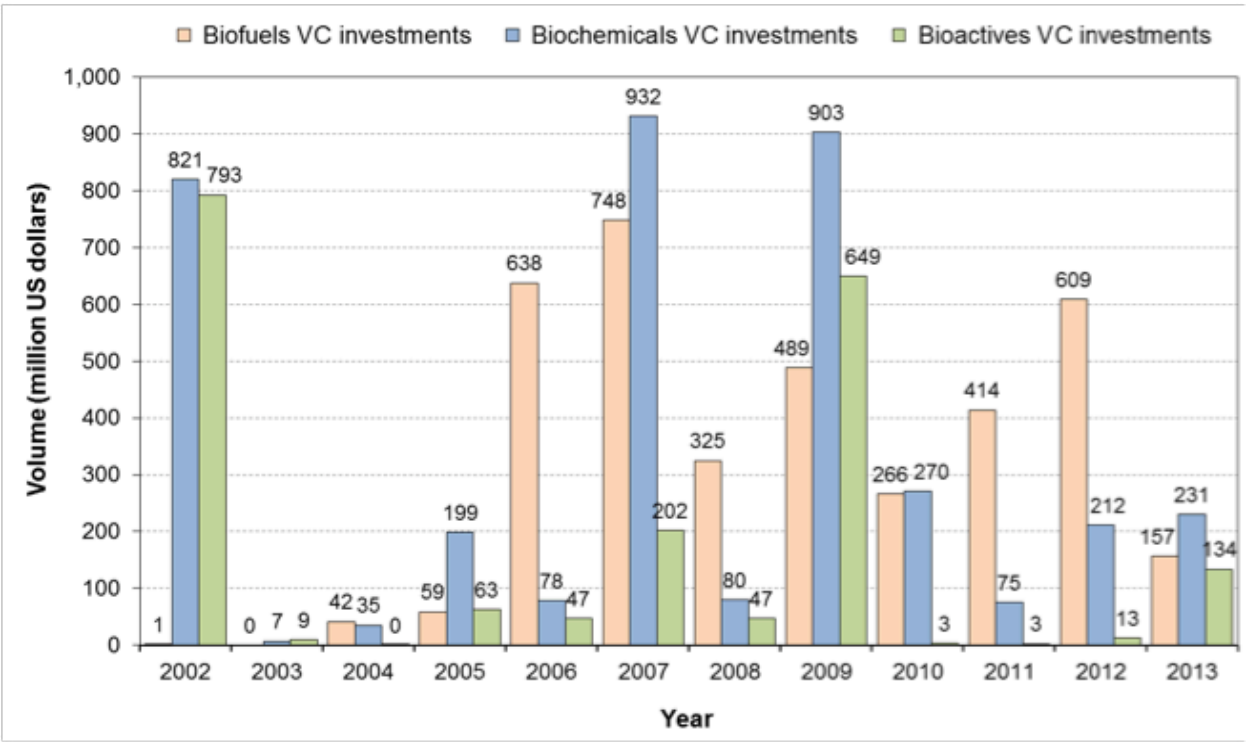

Figure 5: Volume of VC investments in IB companies

VC activities in the IB industry are focussing on R&D based companies (Figure 4). R&D based companies are defined as companies with at least one own active patent. The high percentage of VC volume allocated to companies that received a patent either before or after the VC inflow underpins the strong affinity of VC to research oriented companies. A good example is Amyris Biotechnolgies, founded in 2003, which has been working on a class of hydrocarbons called isoprenoids as a substitute for petrol. Isoprenoids have the advantage that, like alcohols, they are part of the natural biochemistry of many organisms. Amyris's hydrocarbons are engineered to have precisely the same molecular structure as their oil-based equivalents, and are therefore one-for-one replacements for fuels. Amyris raised US-Dollar 20 million in the first round of funding in 2006. Another example is Cobalt Biofuels, founded in 2005, with technologies in microbial physiology, strain development, fermentation and low-energy fuel separation. In October 2008, Cobalt Biofuels raised US-Dollar 25 million in a third round of funding to accelerate the commercialisation of biobutanol.

Non R&D based companies typically specialize on the usage of existing IB technologies e.g. by taking licenses from R&D based companies. For non R&D based companies there was a significant increase in the accumulated net VC investment in 2005 and 2006 compared to R&D based companies closing the gap. Whereas the net VC investment for R&D based IB companies continually increased until 2013, the net stock of VC in non R&D based companies remained relatively stable after 2006. In 2013, the net stock of VC in R&D based IB companies was 2.5 billion US dollars, compared to 1.1 billion US dollars in non R&D based companies.

Analysing the VC investments in IB companies by segments shows that there is a preference for biofuels and biochemicals. In 2006 and 2012, the investments in biofuels significantly increased which could be explained by the strong oil price increase in 2006 and 2011/2012 (Figure 5). Looking at the volume of VC divestments shows intensive activities in 2006 and 2012 (Figure 6). Whereas in 2006, biofuels and biochemicals show strong divestment activities, biochemicals were particularly divested also in 2008 and biofuels in 2009 and 2012.

Taking a closer look at biofuels shows that after very low investment activities during the first years there were strong investments in the years 2006, 2007 and 2012, building up a net stock of VC at the end of 2013 of more than 2 billion US dollars (Figure 7). The picture regarding biochemicals is totally different. Coming from a net stock of VC of more than 700 million US dollars in 2002 there were strong investments in 2007 and 2009 resulting in a net stock of VC at the end of 2013 of more than 2.3 billion US dollars (Figure 8). Rather similar is the situation for bioactives coming from a net stock of VC of

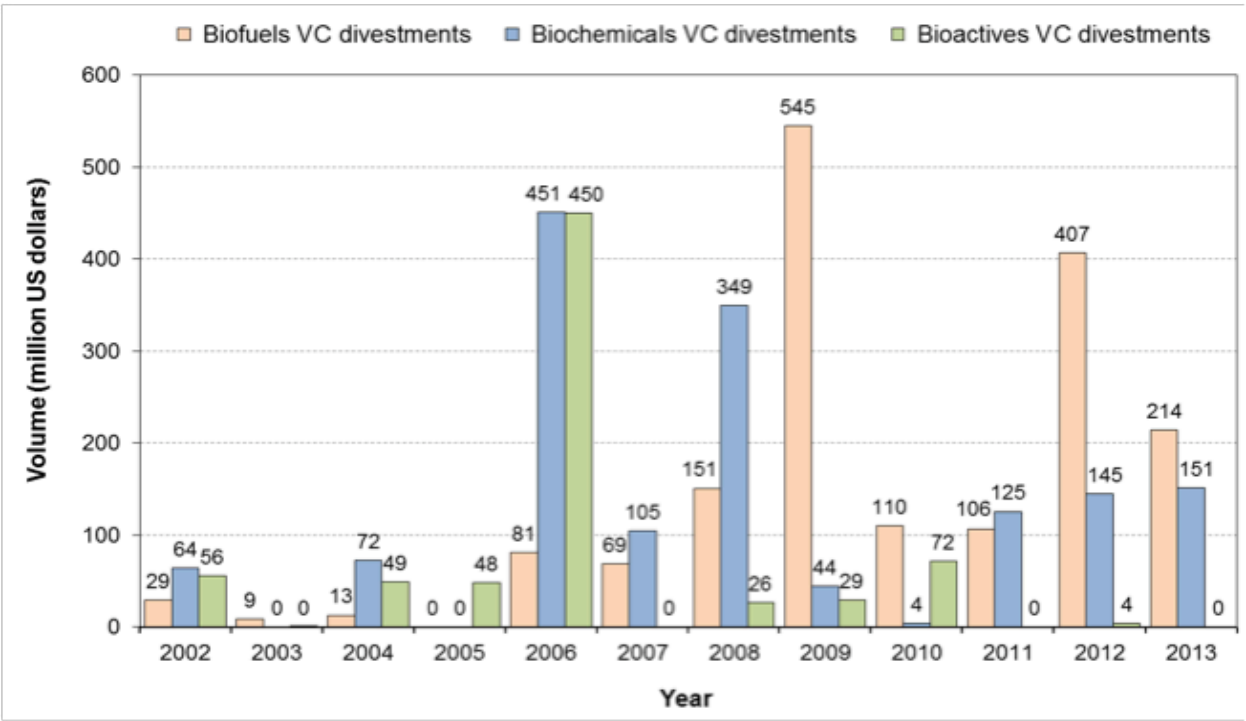

Figure 6: Volume of VC divestments of IB companies

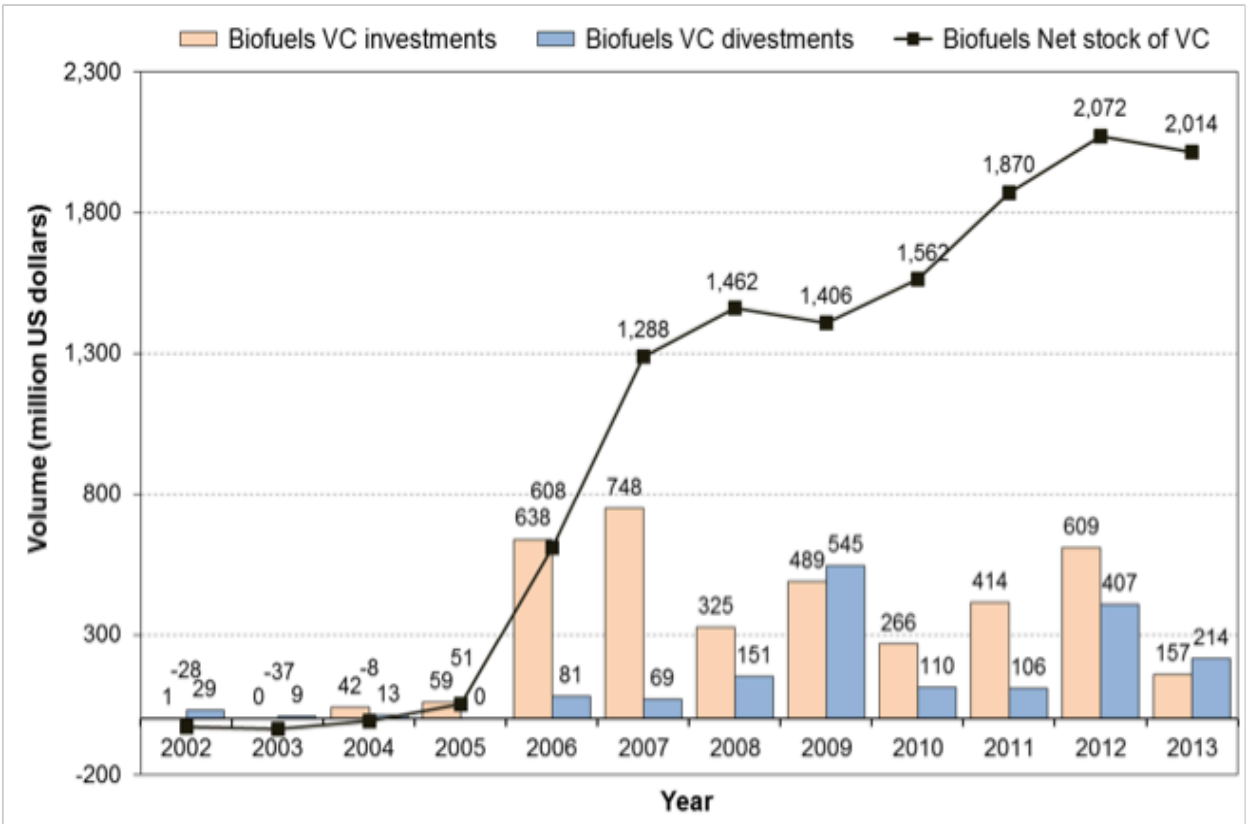

Figure 7: Volume of VC investments/divestments and net stock of VC of biofuels companies

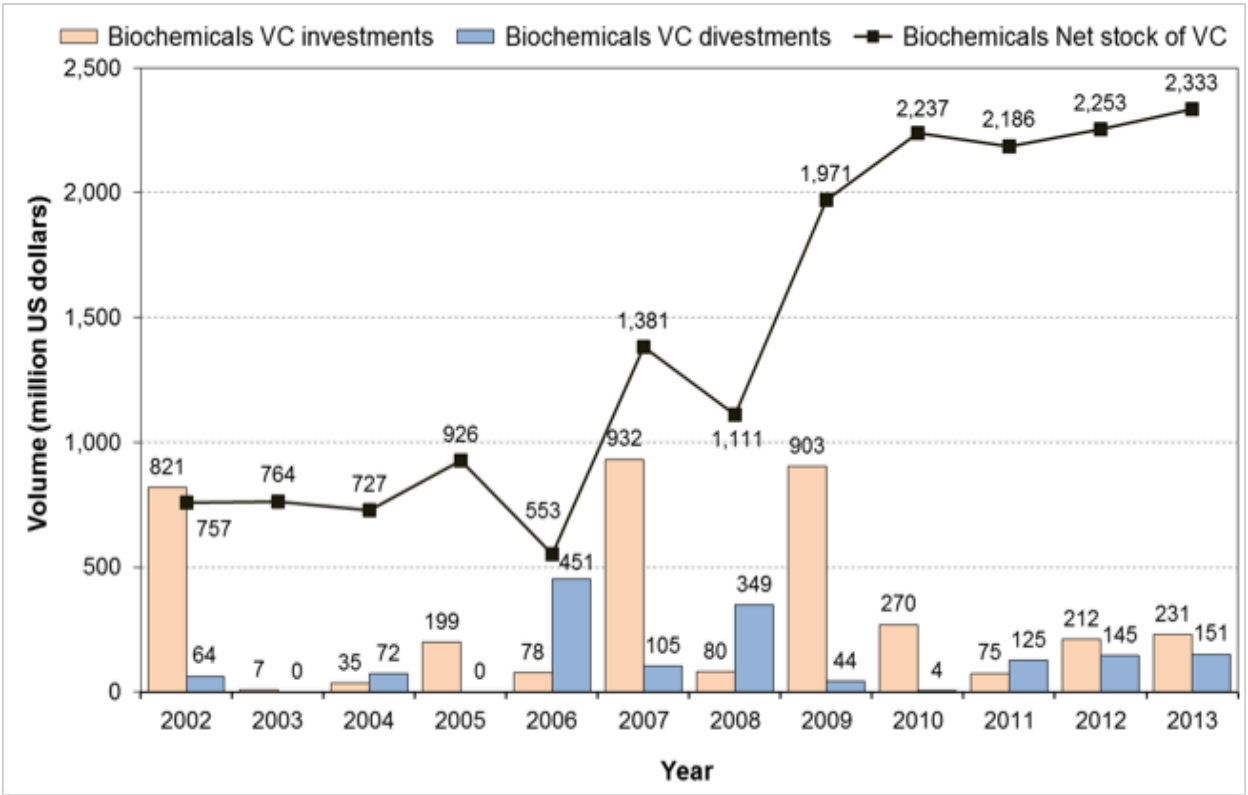

Figure 8: Volume of VC investments/divestments and net stock of VC of biochemicals companies

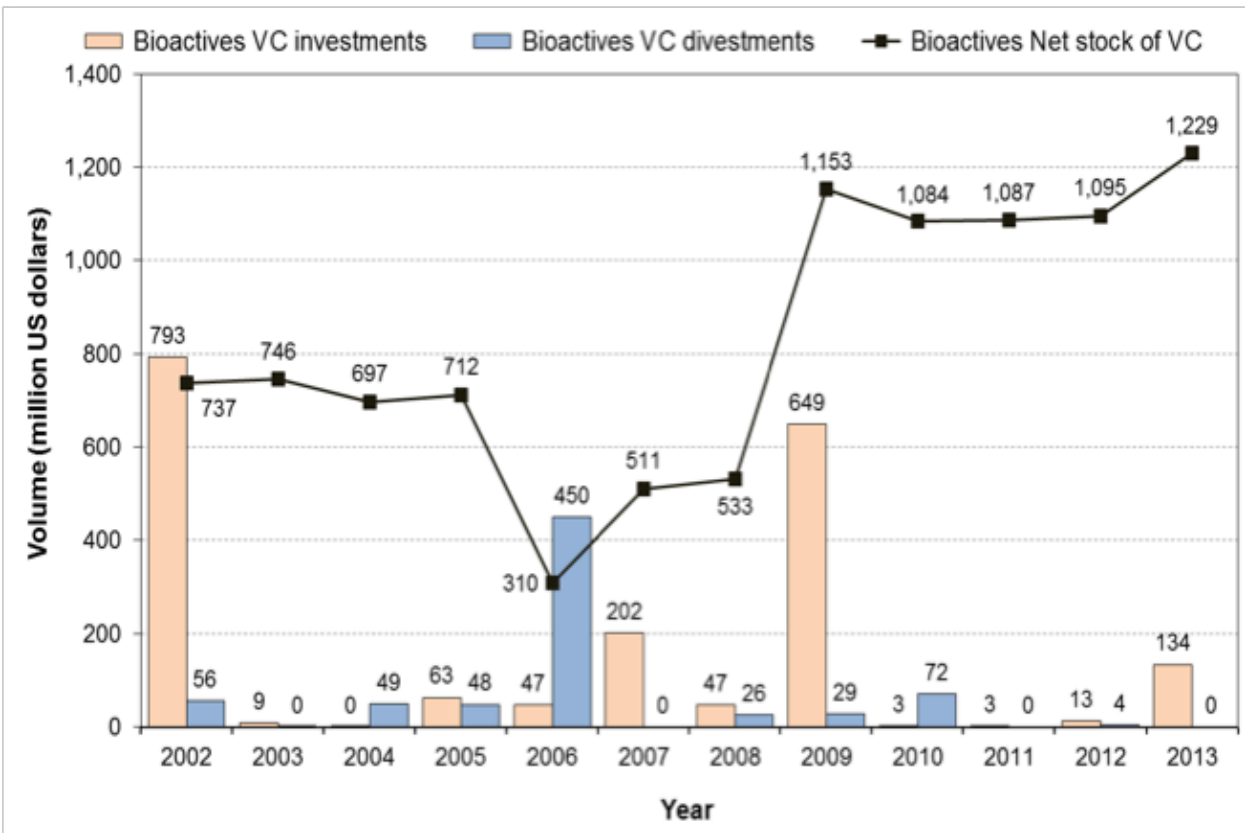

Figure 9: Volume of VC investments/divestments and net stock of VC of bioactives companies

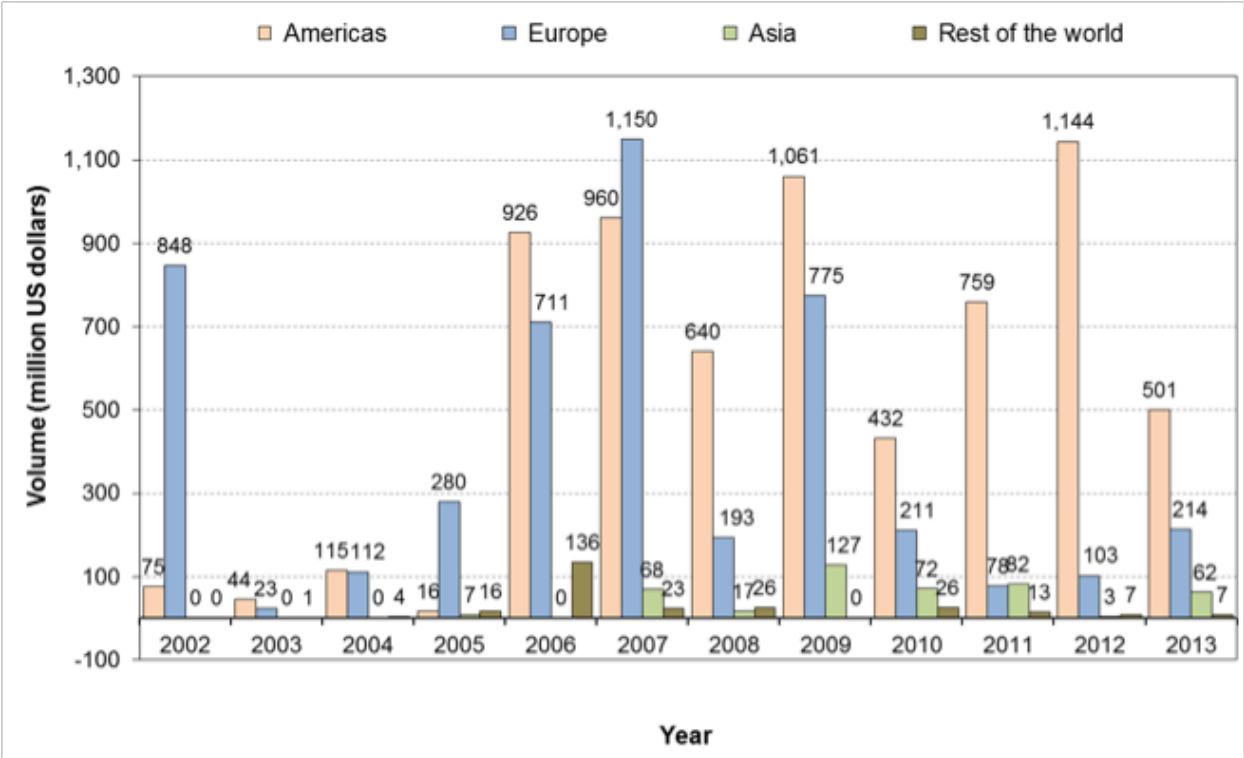

Figure 10: Volume of VC investments by region

more than 700 million US dollars in 2002. After strong investments in 2009 and significant divestments in 2006 the net stock of VC at the end of 2013 of around 1.2 billion US dollars is half of that of biochemicals (Figure 9).

The differentiation between biofuels and biochemicals is sometimes difficult as molecules, like butanol, can be used for different purposes. For example Gevo, founded in 2005, uses metabolic engineering of suitable host organisms to obtain strains which exhibit the increased yield and productivity sufficient to produce commodity chemicals and fuels, in particular butanol, on a large scale. It has developed a process technology to enhance productivity and lower product separation costs. Gevo raised US-Dollar 30 million in two rounds of funding in 2007, and US-Dollar 17 million in a third round in 2008. An example from Europe is Green Biologics, founded in 2003, which develops butanol producing microbial strains using genetic engineering and will integrate these strains into a novel fermentation process. In 2007, Green Biologics raised its first round of funding of US-Dollar 2.3 million.

The regional breakdown of VC activities in the IB industry reveals that the Americas is the leading region with a volume of VC investments of about 7.0 billion US dollars from 2002 to 2013, followed by Europe with about 4.8 billion US dollars (Figure 10). Since 2006, the volume of VC investments per year in the Americas remained on a high level always above 400 million US dollars with a maximum of 1.1 billion US dollars in 2012. In contrast, there is a downward trend in Europe since the peak of 1.2 billion US dollars in 2007. In Asia and the rest of the world there has been a modest total volume of VC investments between 2002 and 2013 of 0.7 billion US dollars for both regions. The number of VC investments per region shows the same picture with the Americas as dominating region (Figure 11).

MARKET SIZE AND GROWTH OF BIOCHEMICALS

The reasons for the increasing VC investments in the IB industry and especially biochemical companies are the huge market volumes and growth rates. Chemical sales in 2010 were in total 1,431 billion Euros with a 75.4 billion Euros share for biochemicals representing 5.3% of total chemical sales (Table 1). Although basic chemicals made up around 34.2% of total chemical sales in 2010 (= 490 billion Euros), only 3.3% of those (= 16.1 billion Euros) were biochemicals. Biochemicals had a share of 19.2 billion Euros of sales equalling 4.9% of chemical sales in the polymers & fibres segment, which was in total 392 billion Euros. Within specialty chemicals, which accounted for 333.2 billion Euros, the share of biochemicals was 6.6% of chemical sales (= 21.9 billion Euros). The highest share of biochemicals within chemical sales with

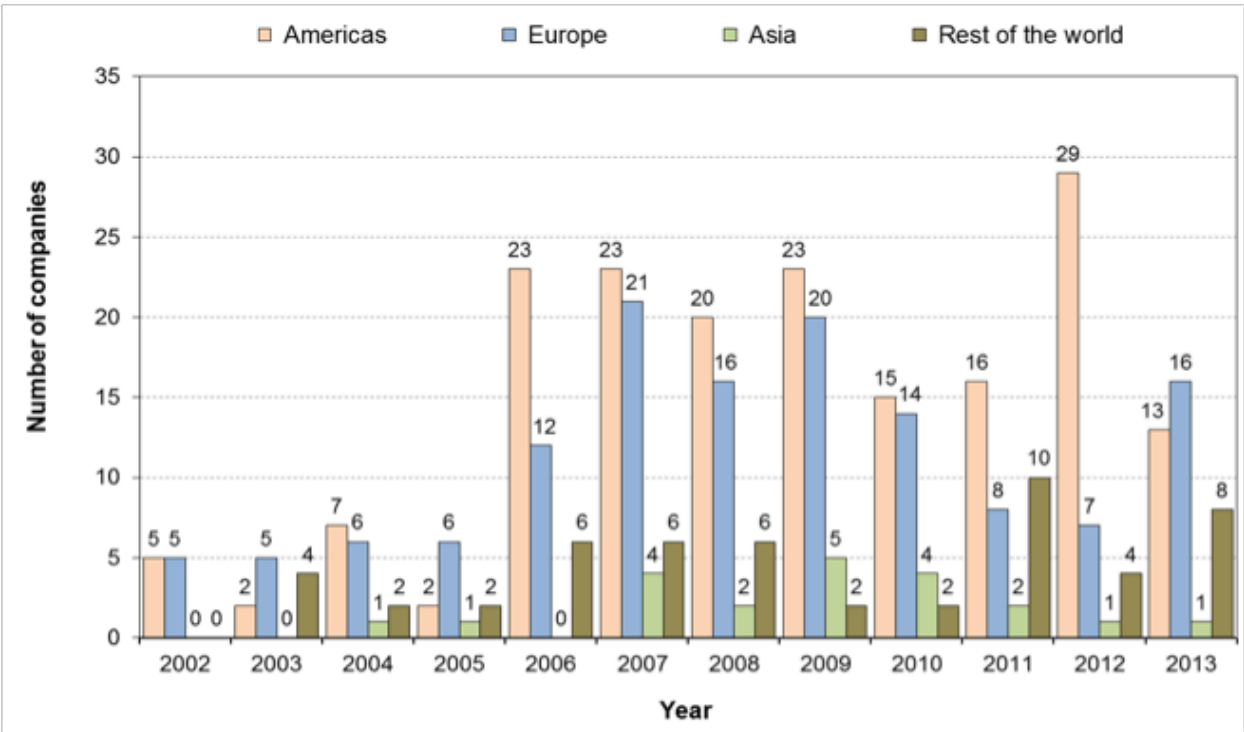

Figure 11: Number of VC investments by region

Table 1: Chemical and biochemicals sales per segment in 2010

	Chemical sales 2010		Biochemical sales 2010		
	Sales [billion Euro]	% of total sales	Sales [billion Euro]	% of total sales	% of chemical sales
Base chemicals	490.0	34.2%	16.1	21.3%	3.3%
Polymers & fibres	392.0	27.4%	19.2	25.5%	4.9%
Specialty chemicals	333.2	23.3%	21.9	29.0%	6.6%
Consumer chemicals	215.6	15.1%	18.2	24.2%	8.5%
Total	**1,430.8**	**100.0%**	**75.4**	**100.0%**	**5.3%**

Table 2: Chemical and biochemicals sales per segment in 2015

	Chemical sales 2015		Biochemical sales 2015		
	Sales [billion Euro]	% of total	Sales [billion Euro]	% of total	% of chemical sales
Base chemicals	545.1	30.5%	34.0	18.1%	6.2%
Polymers & fibres	495.9	27.8%	60.0	31.9%	12.1%
Specialty chemicals	446.3	25.0%	51.4	27.3%	11.5%
Consumer chemicals	297.5	16.7%	42.9	22.8%	14.4%
Total	**1,784.8**	**100.0%**	**188.3**	**100.0%**	**10.5%**

Table 3: Chemical and biochemicals sales per segment in 2020

	Chemical sales 2020		Biochemical sales 2020		
	Sales [billion Euro]	% of total	Sales [billion Euro]	% of total	% of chemical sales
Base chemicals	595.2	26.8%	71.4	16.5%	12.0%
Polymers & fibres	626.8	28.2%	167.4	38.8%	26.7%
Specialty chemicals	595.5	26.8%	89.3	20.7%	15.0%
Consumer chemicals	407.4	18.3%	103.7	24.0%	25.5%
Total	**2,224.9**	**100.0%**	**431.8**	**100.0%**	**19.5%**

Table 4: Biochemicals sales including growth rates for the different segments in 2010, 2015 and 2020

	Biochemical sales [billion Euro]			CAGR	
	2010	2015	2020	2010 – 2015	2015 - 2020
Base chemicals	16.1	34.0	71.4	16.1%	16.0%
Polymers & fibres	19.2	60.0	167.4	25.6%	22.8%
Specialty chemicals	21.9	51.4	89.3	18.6%	11.7%
Consumer chemicals	18.2	42.9	103.7	18.7%	19.3%
Total / average	**75.4**	**188.3**	**431.8**	**20.1%**	**18.1%**

215.6 billion Euros had consumer chemicals with 8.5% (= 18.2 billion Euros). This is remarkable, as consumer chemicals was the smallest chemical segment with only 15.1% of total chemical sales.

In 2015, it is predicted that chemical sales will reach 1,785 billion Euros (Table 2). Sales for industrial biochemicals will be around 188.3 billion Euros representing 10.5% of total chemical sales. Whereas basic chemicals will contribute 30.5% of total chemical sales (= 545.1 billion Euros), only 6.2% (= 34 billion Euros) will be biochemicals. Polymers & fibres will strongly increase to 60 billion Euros which is almost a third of total biochemical sales and 12.1% of 495.9 billion Euros as chemical sales in that segment. Specialty chemicals will show 446.3 billion Euros including 51.4 billion Euros for biochemicals, which is 27.3% of total biochemicals sales and 11.5% of chemical sales. Consumer chemicals with 297.5 billion Euros will include biochemicals sales of 42.9 billion Euros. With 14.4%, this is the largest share of biochemicals sales in a chemicals segment.

It is predicted that chemical sales will increase to 2,225 billion Euros in 2020, whereby 431.8 billion Euros, representing 19.5% of total chemical sales, will belong to industrial biochemicals (Table 3). The importance of base chemicals will further decrease with 26.8% of total chemical sales in 2020 compared with 34.2% in 2010. Predicted sales of 595.2 billion Euros include 71.4 billion Euros biochemicals, equalling a share of 12%. Polymers & fibres will achieve the highest biochemicals sales with 167.4 billion Euros. This will be almost 40% of total biochemicals sales and 26.7% of chemical sales, which will be 626.8 billion Euros. Specialty chemicals with 89.3 billion Euros will account for 15% of 595.5 billion Euros as total chemical sales in that segment. Consumer chemicals will be the second largest biochemicals segment with 103.7 billion Euros. This is 24% of total biochemicals sales and 25.5% of 407.4 billion Euros as total sales for consumer chemicals.

The growth rates are shown in Table 4. The CAGR for biochemical sales from 2010 to 2015 is 20.1%. The CAGR from 2015 to 2020 reaches, with 18.1%, almost the same level as the CAGR from 2010 to 2015. A more differentiated picture regarding growth rates is possible by looking at the sales figures for each segment of biochemicals. From 2010 to 2015, the segment polymers & fibres shows the strongest growth with 25.6% and base chemicals, with 16.1%, the smallest. The polymers & fibres segment also grows the –strongest from 2015 to 2010 with 22.8%. Specialty chemicals have the smallest growth with 11.7%.

It is important to note that all growth rates outperform by far the growth of traditional chemicals.

CONCLUSIONS AND FURTHER OUTLOOK

VC investors have continuously increased their investments over the past 12 years and have particularly allocated financing for R&D oriented companies. When looking at the regional distribution of VC transactions it becomes apparent that the Asian region is still under represented regarding VC investments. This is particularly surprising as Asia is generally considered as the region with the highest economic growth rates. The reason could be that the major VC providers are located in the US and Europe. Due to the rising economic power combined with the enormous size of the markets in Asia, it is expected that VC investments in IB companies in Asia will increase significantly during the next years. From the perspective of the supported companies, through the increasing volume invested in the IB sector as a whole and in particular for R&D oriented companies, VC can be regarded as a motor of growth in this emerging industry. But the situation is changing. In the red biotechnology segment most VC investors have shifted their focus towards more matured and thus less risky investment projects more than a decade ago and in IB a similar development has taken place during the last years. Before 2009, a significant share of the total VC investment volume was allocated to new companies with an age of up to 3 years. After the financial market crisis the vast majority of VC was directed to more matured companies with an age of more than 3 years. This more conservative investment policy of VC investors can be seen as a worrying trend with severe financial consequences for new IB ventures.

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From the Board Room

Early commercial assessments: An innovative tactic for small biotechs

Anthony Giovinazzo
is President and CEO of Cynapsus Therapeutics, Inc., which is developing the only non-injectable (sublingual) delivery of the only approved drug (apomorphine) to be used as a rescue therapy for the on-demand management of "off" motor symptoms of Parkinson's disease.

ABSTRACT

As a small biotech company embarks on a drug development program, there is a tendency for management to focus on a well-defined set of issues. Is the science behind the drug valid? Does it solve an interesting problem or unmet need? What are the prospects that the medical community and patients will embrace it as a valuable new solution? And what is the range of indications the drug is conceived as addressing? These are all valid questions, but a small biotech can do even more to prepare itself for the drug development process, which is a journey that can take many years and cost a significant amount of money.

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As a small biotech company embarks on a drug development program, there is a tendency for management to focus on a well-defined set of issues. Is the science behind the drug valid? Does it solve an interesting problem or unmet need? What are the prospects that the medical community and patients will embrace it as a valuable new solution? And what is the range of indications the drug is conceived as addressing? These are all valid questions, but a small biotech can do even more to prepare itself for the drug development process, which is a journey that can take many years and cost a significant amount of money.

One of the most important extra steps the company can take is to assess the existing commercial landscape relative to the unmet medical need, in order to analyze the eventual demand for their new drug. This analysis is based on a projected target profile and projected pipeline competition, which also requires successful clinical trials and FDA approval. The earlier in the drug development process these assessments occur, the better. Although some CEOs might question the need for an early commercial assessment—in light of the extensive time and planning that is involved—there is ample evidence that, done properly, it can be a uniquely powerful tool to demonstrate and maximize a drug's value. It can give a small biotech a major advantage as it embarks on the drug development process, especially informing clinical trial design, for example, primary and key secondary endpoints. Most importantly, the biotech can speak confidently with capital providers and potential pharma partners about what is important to these stakeholders: namely, how many patients are likely to use the drug; why would they need and accept the drug; what other drugs offer the same solution; and who will pay for it and why.

Our company, Cynapsus Therapeutics, conducted an early commercial assessment process based on our drug candidate APL-130277, for which we are now planning Phase 3 trials. The drug is a sublingual formulation of apomorphine, an on-demand medication for Parkinson's disease patients suffering from hypomobility "off" episodes. Currently, apomorphine is only available as an injectable product that is usually administered by caregivers. The existing product's delivery mode and poor tolerability profile have limited the use of this potent and effective therapy. APL-130277, in contrast, enables absorption directly into the bloodstream through the oral mucosa and can be easily self-administered in many cases.

Our first step was to establish the overall goals of the assessment. Foremost among these was to broadly analyze the commercial potential of APL-130277 for Parkinson's patients in the U.S. and Europe who experience "off" episodes. However, we established a series of related secondary goals as well: to understand the

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prevalence of "off" episodes and our drug's potential role in the treatment paradigm; to assess the competitive environment; and to clarify market access issues and the pricing and reimbursement landscape. In addition, we wanted to develop, modify and validate target product profiles for APL-130277 and determine how the potential market size would likely be influenced by its novel route of administration and potential clinical, safety and tolerability attributes.

To achieve these goals, we initiated a campaign of primary research that comprised the use of independent consultants and interviews with 775 neurologists internationally, 37 Parkinson's patients and 53 major payors across the U.S. Our primary research also included physician and patient interviews to obtain quantitative feedback. In addition to these primary sources, we consulted a wide variety of secondary sources of data, ranging from the National Parkinson Foundation to the U.S. Census Bureau, as well as our own prior primary research (i.e., surveys of neurologists and payors) to inform our analysis. A special focus of the assessment was the revenue potential of the drug in the U.S., which we analyzed across several revenue scenarios involving varying adoption levels and frequency of use.

The results we obtained from this assessment were both comprehensive and informative. For example, they provided us with:

- **An improved understanding of the potential customer base for the drug.** "Off" episodes affect around 50 percent of the approximately one million Parkinson's disease patients in the U.S.; the incidence of the episodes tends to be relatively high in moderate to severe Parkinson's patients who have a history of dopaminergic drug use.
- **An insight into the drawbacks of existing treatments.** Apokyn, currently the only medication approved to treat "off" episodes, has had limited usage in the U.S. due to critical barriers such as unfavorable route of administration and lack of convenience associated with an injection.
- **A clarification of the unique benefits of our drug formulation.** APL-130277 is a rapidly dissolving thin-film vehicle incorporating stabilizing ingredients with apomorphine in solid form, plus pH buffers to enhance stability, lower irritation and maintain optimal absorption. Rapid uptake results in efficacious concentrations quickly.
- **A better picture of the competitive landscape for our drug.** We analyzed five direct competitors to APL-130277 (compounds that either act as rescue medications or have the potential to lower the "off" time and cycle) as well as 11 indirect competitors (that reduce the "off" time and thus lower the frequency/dose of the rescue medication).
- **A good indication of necessary next steps to educate.** Prescribers, nurses, patients and caregivers all need to be informed of the potential of apomorphine to address "off" episodes, as well as the specific advantages of oral delivery. A multi-stakeholder communication program is therefore a necessary initiative for us.
- **Estimates of the potential market opportunity for our drug.** We have generated annual revenue forecasts and annual unit consumption forecasts for APL-130277 through the year 2030, assuming a "best case" (in which our drug is launched with no major competitors other than Apokyn) and a "probable case" (in which our drug is launched with other direct competitors). We also had an independent consulting group produce a similar study based on their primary and secondary research.

A prime factor shaping the course of the commercial assessment was the unmet need for a new treatment, as perceived by three distinct populations: patients, neurologists and payors. The burden of "off" episodes and the lack of practical treatment options result in a large unmet need for a rescue therapy that is effective and easy to administer for patients and their physicians. Survey responses from each of these three sectors suggest that APL-130277 has the potential to grow the limited apomorphine market in the U.S. driven primarily by increased physician adoption and greater patient acceptance.

Survey results suggest that patients would benefit from a quick-acting, easy-to-use drug such as APL-130277 to treat "off" episodes that provides relief from the quality-of-life burden without imposing a high treatment burden; currently, when presented with the opportunity to use Apokyn, most patients choose not to initiate treatment, primarily due to the injection and possible skin irritation and inflammation. And among those who do begin treatment, around 50 to 75 percent tend to drop out of therapy. Patients are enthusiastic about APL-130277 and suggest they are likely to discuss it with their neurologists. One patient commented, "I would not want to use the injectable version…I don't like injections.

The strip would definitely be very easy for me to use, and I wouldn't mind using it, and it wouldn't be as conspicuous as the needle."

Meanwhile, neurologists indicate a positive attitude toward APL-130277 and see it as a promising potential therapy, based on its quick-onset action of 10 to 15 minutes and its easy-to-use sublingual formulation. Neurologists suggest a greater likelihood to prescribe APL-130277 over the injection to their Parkinson's patients and expect a much greater patient acceptance rate for it. For many neurologists, the complex initial titration and patients' reluctance to use shots cause them to avoid adopting the injection into their practice. One neurologist commented, "I haven't used the injection because it's complicated…I think [APL-1302767] is definitely worlds better than the injectable type. It will be easier to administer… Nobody wants to inject themselves. But anyone can take six little sublingual doses." Another neurologist said, "there's a much, much lower threshold for recommending APL-130277 and for patients' acceptance."

Payor feedback suggests they would view APL-130277 similarly to other branded Parkinson's disease therapies (e.g. Apokyn) and would place it in a non-preferred branded tier without restrictions in commercial and Medicare plans.

Of the approximately 400,000 U.S. Parkinson's patients who experience "off" episodes, less than one percent is currently treated with injected apomorphine, whereas a survey of 500 neurologists indicates that up to 49 percent of all patients would be candidates for treatment with sublingual apomorphine. Furthermore, each of these patients is expected to use a more convenient sublingual product much more frequently. Most payors already list apomorphine as medically necessary, and inclusion of APL-130277 in formularies will only require the consent of providers' pharmacy and therapeutics committees, which typically meet at least quarterly. The technical challenges overcome to create this formulation provide extended patent protection, limiting the expected competition to only a few players pursuing alternative routes of administration of Levodopa Carbidopa, which is not approved to treat "off" episodes.

The early and continuous commercial assessment process conducted by my company has given us a substantially clearer picture of the challenges we face, as well as a powerful marketing tool to share with potential investors and partners. I have little doubt that any small biotech—conducting an early and continuous assessment process on a similar scale for its own drugs in development—will find the insights it can provide to be equally valuable.

Case Study

Accelerating the growth of the bioeconomy in Malaysia

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ABSTRACT

Advances in commercial application of biotechnology worldwide over the past two decades have led to the development of a bioeconomy, whereby substantial economic outputs are from the development and use of biological materials. Bioeconomy encompasses all industries and economic sectors based on the values implicit in biological materials that can be translated into new sources of income, environmental sustainability and social well-being.

Malaysia, one of the most competitive biotechnology hubs in the Asia-Pacific region, has also taken critical early steps to coordinate and intensify national efforts to harness the potential of the bioeconomy. Most significantly, the Bioeconomy Transformation Programme (BTP) was launched in October 2012, making the country only the second in Asia, after China, and the first in ASEAN, to establish its own national bioeconomy initiative.

The BTP is in line with the Government's objective to develop Malaysia into a high-income nation by the year 2020. The BTP aims to achieve this by focusing on bio-based industries in Malaysia, a sector that has been identified as having enormous potential to further develop the nation due to the abundance of natural resources available.

With the introduction of the BTP, Malaysia is now unlocking even greater opportunities in the local and regional biotechnology industry, and enhancing the participation of the private sector. Through effective execution strategies from the Government and BiotechCorp, the biotechnology sector is now directly contributing towards efforts to drive Malaysia towards a high-income and knowledge-based economy by year 2020.

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Keywords: Malaysian Biotechnology Corporation; Bioeconomy Transformation Programme; bioeconomy; BiotechCorp; Malaysia; biotechnology; biodiversity; BioNexus

INTRODUCTION

Malaysia has identified biotechnology as one of the economic engines that will drive the nation towards a high-income advanced nation by 2020. In the last nine years, Malaysia has been actively strengthening its biotechnology ecosystem, developing its local biotechnology sector and creating a niche for itself as a reputable biotechnology hub of Asia. Malaysia's strong conducive environment and growth potential presents a multitude of long-term opportunities in developing new enterprises, new industries and new market access strategies for bio-based business.

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MALAYSIA'S COMPETITIVE ADVANTAGES

In developing its biotechnology sector, Malaysia has leveraged its rich biodiversity, cost-competitive skilled labour market, excellent transportation networks, Information and Communication Technology (ICT) infrastructure, strong government support, active public-private sector participation and what still is a cost-effective base for doing business in the region.

Malaysia's competitive advantages are further enhanced by its strong legal and regulatory infrastructure. Malaysia is a signatory to both the Paris and

Berne Conventions, a member of the Trade-Related Intellectual Property Rights (TRIPs) Agreement and has also acceded to the Patent Cooperation Treaty (PCT). Additionally, Malaysia is also a member of the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Co-operation Inspection Scheme (PIC/S) and World Trade Organisation (WTO).

To ensure the country remains competitive as a research, development and manufacturing destination, Malaysia has adopted Good Clinical and Good Manufacturing Practices (GCP and GMP). Malaysia is also a provisional adherence member to the Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) Agreement for Good Laboratory Practices (GLP).

MALAYSIA AS PLATFORM TO EXPLORE NEW MARKET ACCESS OPPORTUNITIES

Through its unique and developed trade linkages, Malaysia offers immense opportunities for biotechnology and life science companies looking to expand their markets and sales presence. Through the ASEAN Free Trade Area (AFTA), Malaysia can provide access to a regional market of more than 500 million people. Malaysia is also a signatory to ASEAN's FTA with Japan, Korea, China, India and Australia. Outside of ASEAN, Malaysia has signed Free Trade Agreements (FTAs) with Japan, Pakistan and New Zealand. Malaysia also serves as an effective platform from which to access 'Halal' markets, particularly in the Middle East.

THE NATIONAL BIOTECHNOLOGY POLICY

Recognising biotechnology as one of the key strategic drivers to accelerate Malaysia transition in becoming a high-income, a knowledge-based economy and propel the nation's social and economic development to greater heights, the Malaysian Government has introduced the National Biotechnology Policy (NBP). Launched in 2005, the NBP is a comprehensive framework designed to guide the development of the local biotechnology industry through creation of a favourable R&D environment and focused industry development that leverages on the existing strengths of the country. It envisions that biotechnology will be a new economic engine for Malaysia, enhancing the nation's prosperity and well-being.

The policy encompasses nine thrusts that underline the direction and measure offered by the Government towards developing the Malaysia's biotechnology industry. The nine thrusts include the development in AgBiotech (agriculture biotechnology), BioMedical (healthcare biotechnology) and BioIndustrial (industrial biotechnology), human capital, financial infrastructure, strategy positioning, and government commitment.

Through the policy, the government has established The Malaysian Biotechnology Corporation Sdn Bhd (BiotechCorp), a one-stop centre for biotechnology; and three national R&D institutes, namely the Malaysia Agro-Biotechnology Institute (ABI), Institute of Pharmaceutical and Nutraceutical Malaysia (IPHARM) and Malaysia Genome Institute (GENOM Malaysia). The policy is implemented in academic research, transfer of technology and industrial adoption and enabling the provision of various fiscal and tax incentives to qualified biotechnology companies.

The NBP is to be implemented over three phases: Phase I — Capacity Building (2005-2010), Phase II — Science to Business (2011-2015), and Phase III — Global Business (2016-2020). Each development phase outlines the milestones and strategies to be adopted, starting from capacity development to commercialisation and finally, placing Malaysia as a competitive, leading edge biotechnology hub at the global level by 2020. Each phase is tied to four performance indicators set by the Government as a measurement of the progress and impact of the NBP

Table 1: Key indicators for the biotechnology industry, based on National Biotechnology Policy

Indicators	Phase 1 2005-2010	Phase 2 2011-2015	Phase 3 2016-2020
New Investment	RM 6 billion	RM 9 billion	RM 15 billion
Employment	40,000	80,000	160,000
Annual Revenue	RM 20 billon	RM 50 billion	RM 100 billion
Contribution to GDP	2.5%	4.0%	5.0%
Global Companies	-	-	20

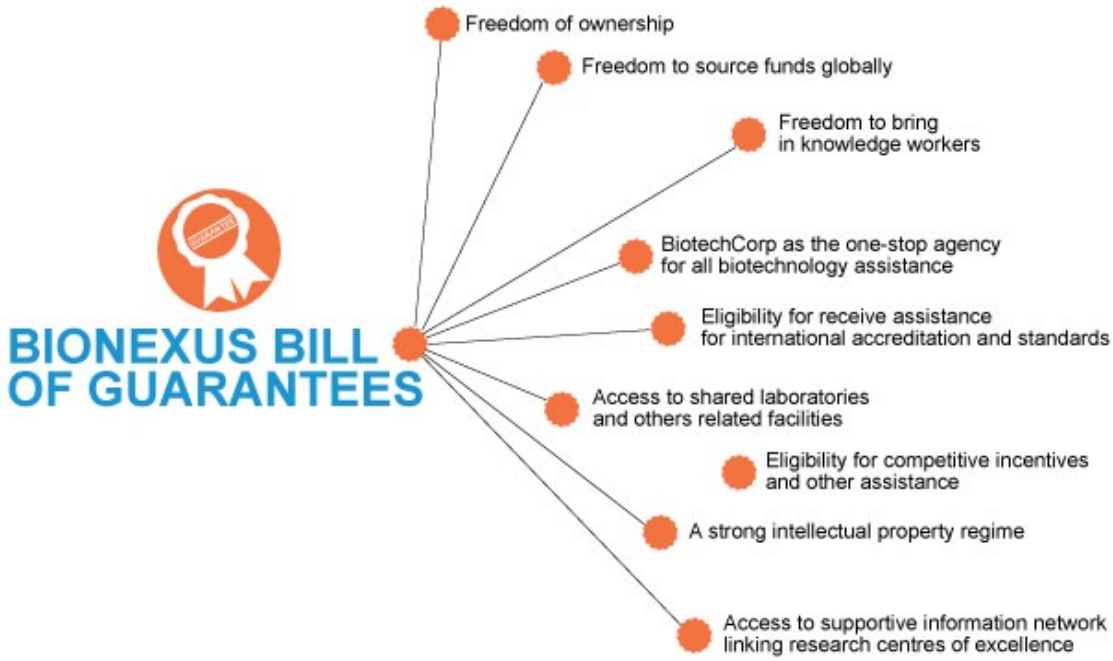

Figure 1: Overview of BioNexus Bill of Guarantees

Table 2: Malaysia's biotechnology focus areas

Sector	Focus Areas
AgBiotech	Crop, livestock, marine and aquaculture, natural products
BioMedical	Contract Research Organisation, Contract Manufacturing Organisation, Drug delivery and discovery, Medical devices and diagnostics, Biopharmaceuticals and vaccines, therapeutics, genomics, stem cell therapy
BioIndustrial	Bio-based chemicals, biofuel, biomaterials, enzyme, bioremediation

implementation, which are Investment, Employment, Revenue and Contribution to Gross Domestic Product (GDP).

The development of biotechnology targeted to contribute 2.5 percent of national GDP by 2010, 4.0 percent by 2015 and 5.0 percent by 2020. Furthermore, it is estimated that the local biotechnology industry will create a total of 280,000 new jobs both directly and indirectly by 2020.

MALAYSIAN BIOTECHNOLOGY CORPORATION

Malaysian Biotechnology Corporation (BiotechCorp) is the lead development agency for the bio-based industry in Malaysia and acts as a central contact point providing support, facilitation and advisory services for biotech and life sciences companies in Malaysia. Wholly owned by Ministry of Finance (MoF) and under the purview of Ministry of Science, Technology and Innovation (MOSTI), BiotechCorp works under the supervision of National Bioeconomy Council (formerly known as Biotechnology Implementation Council) and advice by the Bioeconomy International Advisory Panel (IAP).

BiotechCorp was established to identify value propositions in both Research & Development (R&D) and commerce and support these ventures via financial assistance and developmental services. Based on the NBP's objectives and guidelines, BiotechCorp acts as the chief driver for biotechnology development by providing strategic direction, operational assistance for businesses and developing specialised infrastructure.

Since its establishment in 2005, BiotechCorp has played a vital role in building the bio-based industry in Malaysia by providing a wide range of capacity building programs covering a variety of subjects to assist local and foreign bio-based entrepreneurs in managing their business.

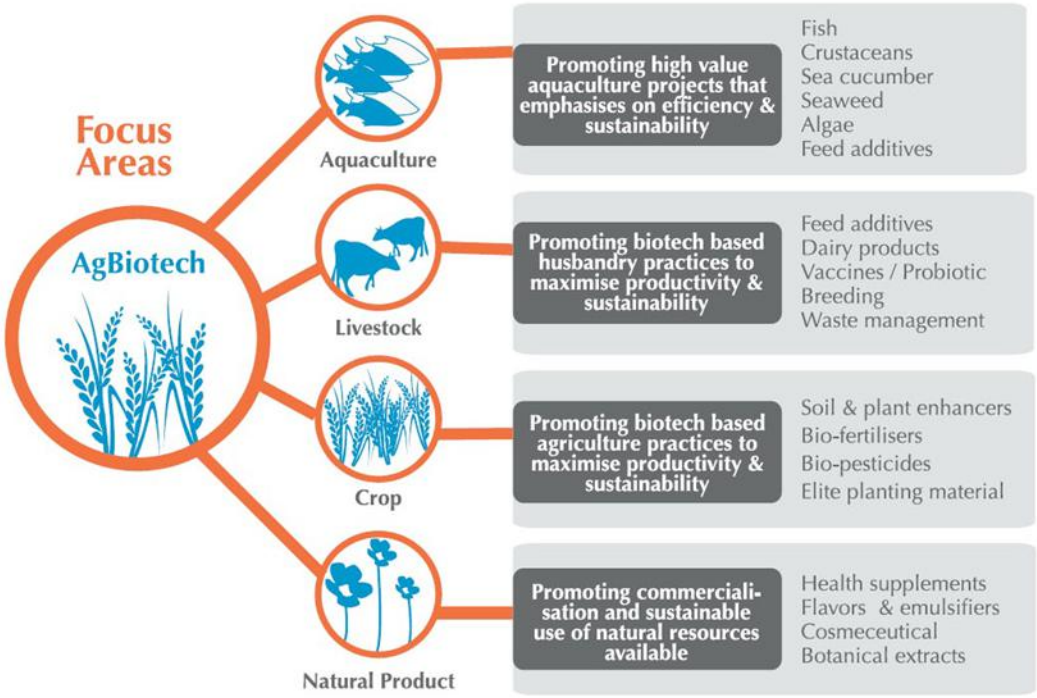

Figure 2: AgBiotech focus areas

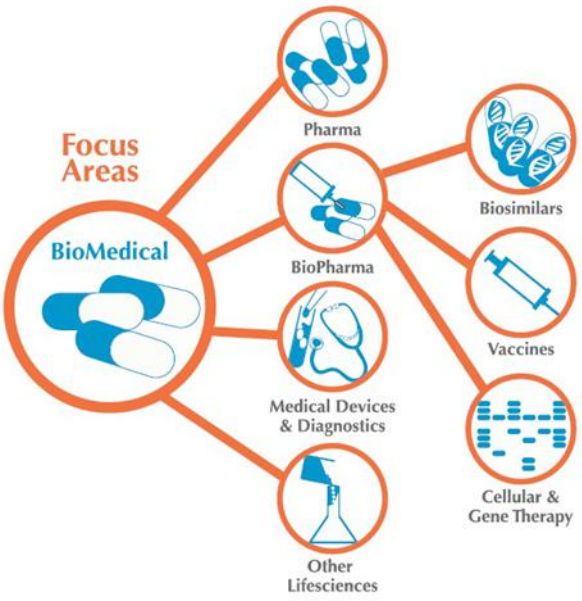

Figure 3: BioMedical focus areas

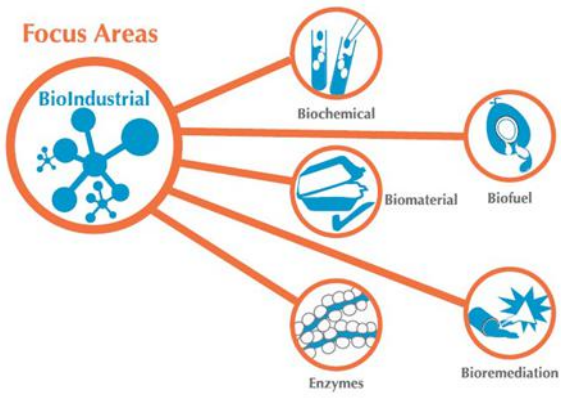

Figure 4: BioIndustrial focus areas

BIONEXUS STATUS COMPANIES

The growth of the Malaysian biotechnology sector is exemplified by the development of the BioNexus status companies. BioNexus status is a designation awarded by the Malaysian Government through BiotechCorp to qualified local and foreign biotechnology companies. The status endows fiscal incentives, funding assistance and other guarantees to assist the growth of BioNexus Status companies. Apart from the overall benefits and support, BioNexus Status companies are assured a list of privileges as stipulated in the BioNexus Bill of Guarantees.

The brand BioNexus is promoted to market Malaysia's biotechnology initiative to investors and potential partners. BioNexus leverages on the strengths of existing institutions and ecosystem. To date, BioNexus status has been awarded to a number of foreign companies that

Table 3: Summary of Phase 1 NBP achievements as at end of 2010

Indicators	Phase 1 Targets	Phase 1 Achievement
New Investment	**RM 6 billion**	**RM 5.4 billion**
- Public	RM 4 billion	RM 3.2 billion
- Private	RM 2 billion	RM 2.2 billion
Employment	**40,000**	**54,776**
- Direct	14,000	13,690
- Indirect/Induced	26,000	41,086
Annual Revenue (end of Phase)	**RM 20 billion**	**RM 13.5 billion**
- Direct	RM 9 billion	RM 6.5 billion
- Indirect/Induced	RM 11 billion	RM 7 billion
Contribution to GDP	**2.5%**	**2.2%**

has established a presence in Malaysia, including from Australia, China, Germany, India, Singapore, the UK and the US.

In 2013, there are 229 BioNexus status companies with a total approved investment of RM 3.31 billion. More than 50% these companies are already generating revenues, five of which are already listed in stock exchanges worldwide. Supported by BiotechCorp's other initiatives in building a conducive, enabling environment, the BioNexus status companies are a credible representation of Malaysia's emerging and competitive biotechnology sector.

MALAYSIA'S SECTOR FOCUS DEVELOPMENT

The policy thrust underlined by the NBP focuses on the development of three major biotechnology sectors namely AgBiotech, BioMedical and BioIndustrial sectors. Each of these sectors presents niche areas for Malaysia to explore, exploit and expand.

REALISING THE NATIONAL BIOTECHNOLOGY POLICY TARGETS

During the first five years of the NBP implementation, BiotechCorp has played a central in providing critical support and spurring activities in order to achieve the strategic goals that have been set under the Phase 1: Capacity Building Phase. By doing so, BiotechCorp has successfully laid strong foundations of infrastructure, policies and, more importantly, the creation of an environment that is conducive for the biotechnology industry in Malaysia.

Phase 1 NBP developments involved adoption of policies, plans and strategies by the Government. The main objective in Phase 1 NBP is to build a strong foundation for biotechnology, focusing on the key success factors for the industry: human resource, regulatory and institutional development.

In terms of investment, a target of RM 6 billion had been set in order to develop the necessary critical mass for the industry. The Government was envisioned as the primary driver for investment during this initial phase, with target investment of RM 4.0 billion. The private sector would play a supportive role, with a target investment of RM 2 billion.

At the end of the Phase 1, the government recorded RM 2.0 billion investments for biotechnology and another RM 1.2 billion from MOSTI Science and Technology Funds and Stimulus Packages. The private sector successfully raised RM 2.2 billion through investment from BioNexus Status companies and funds raised through venture capitals and Initial Public Offerings (IPOs). Although there is a gap of RM0.6 billion between actual and targeted investment in the Phase 1 NBP, the ratio of private vis-à-vis public investments in the Malaysian biotechnology industry remained favourable considering its early stages of evolution.

In terms of revenues generated, a total of RM 20 billion was set at the end of the Phase 1. At the end of Phase 1, the actual total revenue generated by the local biotechnology, comprising of direct, indirect and induced revenues was RM 13.5 billion. Considering the global financial crisis in 2009, which affected all sectors in Malaysia, the revenue achieved by biotech sector is considered to be relatively high.

In terms of employment that was generated between the Phase 1 period, The biotechnology industry has created around 54,776 employment opportunities, directly and indirectly. Compared against the 50,000 employment opportunities target under the Phase 1 NBP, the industry has successfully achieved 37 percent above the target.

From the total employment opportunities generated, 13,690 employees are directly engaged in biotechnology related activities. Of these, 5,640 are employed in biotechnology firms and RIs/IHLs. The remaining 8,050 employees are involved in supporting roles to the biotechnology industry, which includes, but is not limited to, administrative, management, sales, supply and distribution related activities.

Table 4: Summary of Phase 2 NBP achievements as at July 2013

Indicators	Phase 2 Targets	Phase 2 Achievement (As At July 2013)
New Investment	RM 9 billion	RM 14.6 billion
Employment	80,000	83,400
Annual Revenue (end of Phase)	RM 50 billion	RM 4.5 billion
Contribution to GDP	4%	To be determined as at end of Phase 2

Figure 5: Malaysia's strengths in research and innovation, based on international reports

In terms of contribution to GDP, the industry has achieved 2.2 percent contribution to GDP against the target of 2.5 percent. However, the industry is expected to see a significant growth in size and the contribution to GDP is likely to rise significantly, in the forthcoming years.

The significant GDP contribution of the biotechnology industry to Malaysia's economy in between the 2006-2010 periods reflects its increasingly important role in the nation's overall growth. The present industry growth is attributed to the successful implementation of Government initiatives.

MOVING FROM SCIENCE TO BUSINESS

Building on the momentum of success, strong fundamental and goodwill from the achievements of the Capacity Building Phase, the next phase will be the next test of delivery i.e. to build on this strong foundation, to create and commercialise Science to Business. Efforts are already underway to convert R&D into viable businesses based on innovative products and services, as well as opportunities for profit. BiotechCorp further aims to bring the best of global brands, as this will create the necessary rippling effect for a more dynamic domestic direct investment landscape.

Phase 2 (2011-2015): Science to Business of the NBP places an emphasis on entrepreneurial activities and commercialisation, turning scientific progress into tangible products that provide return of investment to both investors and researchers. As at July 2013, Malaysia's biotechnology industry has successfully secured a total Approved Investments of RM 14.6 billion. In terms of number of jobs opportunities created, the local biotech industry has created more than 83,000 direct and indirect employment opportunities. However, the current Revenue generation of RM 4.5 billion is still below the 5-year target of RM 50 billion. Nonetheless the revenue is expected to rise significantly with the implementation

of projects, particularly those under the Bioeconomy Transformation Programme (BTP), in the coming years.

Throughout 2011-2013, Malaysia continues to attract considerable biotechnology investments from the private sector, in spite of the recent global economic slowdown. Some of the more notable investments include investments by Biocon Ltd, to establish a biopharmaceutical manufacturing and R&D facility; a joint-venture between South Korea-based CJ CheilJedang and French chemical producer Arkema, to build the world's first bio-methionine plant.

Malaysia's status as a major investment destination and regional biotechnology hub is further solidified with the announcement of investments to establish an integrated lobster farming project by Darden Restaurants from the United States, production facility for bio-based isobutanol by Gevo Inc. from the United States, and production facility for bio-based chemicals by Verdezyne from the United States throughout the 2012-2013 period.

BIO-XCELL — ASIA'S NEW REGIONAL BIOTECHNOLOGY HUB

To further enhance Malaysia's competitiveness as a regional biotechnology hub, BiotechCorp together with UEM Land, one of Malaysia's leading property developers, has jointly developed 'Malaysian Bio-XCell', a biotechnology ecosystem located at the southern tip of Peninsula Malaysia. Bio-XCell is a platform where BiotechCorp pools soft infrastructure — financial incentives, human capital development, business and operational set-up advisory, attractive leasing models, and the physical infrastructure that will enable companies to springboard their biotechnology business and commercialisation activities. To date, four global names are present within Bio-XCell, namely Biocon Ltd, France-based Metabolic Explorer, India-based Stelis Biopharma, and US-based Glycos Biotechnologies Inc.

Table 5: Notable Malaysian research institutions and institutes of higher learning engaged in biotechnology research

Biotechnology Sector	Notable research institutes and institute of higher learning in Malaysia
AgBiotech	Malaysian Agriculture Research and Development Institute (MARDI), Malaysian Palm Oil Board (MPOB), Forest Research Institute Malaysia (FRIM), Malaysia Cocoa Board, Rubber Research Institute Malaysia, Sarawak Biodiversity Centre, Veterinary Research Institute, Universiti Malaya, Universiti Kebangsaan Malaysia, University Putra Malaysia, University Malaysia Sarawak
BioMedical	Institute for Medical Research, Malaysia Nuclear Agency, Universiti Putra Malaysia, Universiti Sains Malaysia, Universiti Kebangsaan Malaysia, Universiti Malaya
BioIndustrial	Standards and Industrial Research Institute of Malaysia (SIRIM), Malaysia Nuclear Agency, University Putra Malaysia

INTENSIFYING EFFORTS IN TECHNOLOGY DEVELOPMENT AND INNOVATION

Technology Development and Innovation is key to economic prosperity for Malaysia which focuses on bridging global technology and expertise, between bio-based companies and R&D institutions in advanced countries. Malaysia has intensified its effort to boost Research & Development (R&D) activities and continuously support the planning and implementation of programmes and activities, which centres on enhancing creativity and innovation. In addition, Malaysia is rapidly adopting and infusing elements of emerging, knowledge-intensive sciences, like biotechnology, to expand the economic base.

Malaysia's efforts in intensifying and enhancing R&D have been acknowledged internationally. In the recent World Economic Forum Global Competitiveness 2013-2014 report, Malaysia is ranked as second in Asia Pacific and 15th in the world for "Capacity for Innovation". In terms of "University-Industry collaboration in R&D", Malaysia is ranked fourth in Asia Pacific and 16th worldwide.

In the IMD World Competitiveness 2014 report, Malaysia ranks second in Asia Pacific and 10th worldwide in "Attractiveness for Researchers and Scientists" category. In the same report, Malaysia is ranked fourth in Asia Pacific and 15th worldwide for Standards of Scientific Research.

Meanwhile, the Global Innovation Index ranked Malaysia at 32 out of 142 countries in 2012 and 2013. The report identified Malaysia's major strength in market and business sophistication, although there is a room for improvement in human capital and research areas as well as institutional framework.

Moving forward, innovation will remain as main focus in Malaysia's development agenda, of which "Building the knowledge base infrastructure" is the sixth

Strategic Reform Initiative in the New Economic Model (NEM). The focus is to promote and environment for innovation for Malaysia

Thrust 4 of the NBP i.e. R&D and Technology Acquisition Development addresses the vital role of R&D in the development and sustainability of the biotechnology industry. The establishment of appropriate infrastructure to support and strengthen core Research, Development and Commercialisation (R&D&C) activities ensures that basic and applied R&D is continuous, from zero-base fundamentals up to commercialisation. Conducive research and business environment will also attract and retain both foreign and local investors, researchers and entrepreneurs.

R&D efforts in the biotechnology are mainly anchored by MOSTI, and supported by a strong network of research institutes and institutes of higher learning.

These research institutes and institutes of higher learning has undertaken several key notable biotechnology research projects, primarily in the AgBiotech sector, namely the Oil Palm Genome Project by Malaysian Palm Oil Board and the Rubber Genome Project by Universiti Sains Malaysia.

Apart from conducting research, these institutions are also actively engaging their international peers and foster collaborations, particularly in the BioMedical sector. Notable collaborations throughout NBP Phase 1 and Phase 2 include a R&D collaboration between Baylor College of Medicine, United States and University of Malaya on neglected tropical diseases vaccines in Malaysia and Southeast Asian countries; collaboration between Swiss-based pharmaceutical company Novartis and Sarawak Biodiversity Centre to explore bioactive compounds from natural resource, develop bio prospecting activities and identify novel bioactive compounds sourced from Sarawak; collaboration between Quintiles from United States and University Malaya Medical Centre (UMMC) to establish Quintiles' First Prime Site in Asia, to enhance the infrastructure for conducting clinical trials and accelerate clinical development; and collaboration between India's Council of Scientific and Industrial Research — Institute of Genomics and Integrative Biology (CSIR-IGIB) and Pharmacogenomics Centre (PROMISE), Universiti Teknologi Mara to map the Malay genome.

In the area of BioIndustrial, a local institute of higher learning, Universiti Teknologi Malaysia, through collaboration with the Massachusetts Institute of Technology (MIT), United States, has established the Malaysia-MIT Biotechnology Partnership Program (MMBPP), to develop technologies that focuses on advanced industrial biotechnology, establishment of microbial consortium for carbon dioxide in the waste water biodegradation and treatment, microbial bioreactor for self-sufficient electricity generation from waste biodegradation, and design and modelling of micro bioreactors.

In creating a conducive environment for the development of biotechnology in the country, three dedicated Centres of Excellence for Biotechnology had been established, as stipulated in the NBP, namely the Agro-Biotechnology Institute (ABI), Malaysia Genome Institute (MGI) and Malaysia Institute of Pharmaceuticals and Nutraceuticals (IPHARM). Collectively known as the National Institutes of Biotechnology (NIBM), the three institutes focuses on high quality and market driven R&D and innovations, to support and spearhead the commercialisation of the R&D activities at the institutes based on industry requirements, particularly in the AgBiotech and BioMedical sector. In the area of BioIndustrial, SIRIM has been designated as the Centre of Excellence.

Throughout Phase 1 and Phase 2 NBP, NIBM has also fostered notable international partnerships and collaborations to enhance Malaysia's global position

Table 6: Research areas of Biotechnology Centres of Excellence in Malaysia

Agro-Biotechnology Institute	Malaysia Genome Institute	Malaysia Institute of Pharmaceuticals and Nutraceuticals
Development of high quality crops and livestock based on agriculture biotechnology application	Discovery and development of genes, enzymes and cells for application in industrial biotechnology and bioinformatics	Discovery of functional food and drug from natural tropical resources for healthcare biotechnology development
• Agricultural Genomics and • Gene Discovery • Genetic Engineering • Biopharming • Animal Biotechnology • Food Biotechnology	• Comparative Genomics and Genetics • Structural Biology Systems and Computational Biotechnology • Metabolic Engineering • Protein Expression Systems	• Identification and Development of Bioactive Compounds • Bioprocessing • Pre-formulation for Product Development • Screening of Bioactive Compounds • Advance Drug Delivery Systems

in biotechnology R&D. The most prominent is the collaboration with the California Institute for Quantitative Biosciences (QB3) to develop the biotechnology ecosystem in Malaysia, particularly in drug discovery and development of natural product based therapeutics. The collaboration has produced a spin-off company, Neopeutics Sdn Bhd, an early-stage drug discovery Clinical Research Organisation, with offices and facilities in both Malaysia and the United States.

Other NIBM research collaboration partners include Stanford University from the United States (establishment of *Caenorhabditis elegans* Research Facility, a platform for gene discovery in infectious diseases), L'institut National de la Recherche Agronomique (INRA) from France, North Carolina State University from the United States, University of Sheffield from United Kingdom, Monash University from Australia, ViaLactia from New Zealand and Genome Canada from Canada, as well as participation in Drugs for Neglected Diseases Initiative (DNDi) and the Pan Asian Natural Products Drug Discovery Consortium (a collaborative research network to foster strong ties between the various research organizations within the Asian region in order to further the cause of natural products drug discovery, with an emphasis on neglected diseases).

In line with the current international biotechnology industry climate, Malaysia is now aligning its R&D efforts in biotechnology to move in parallel with bioeconomy, Leveraging on strong fundamental research expertise, internationally recognized R&D initiatives and strong public research funding, efforts are being made to consolidate, prioritise and accelerate niche R&D areas in biotechnology that are not only market-driven, but also have direct societal benefits.

Funding of research programmes in biotechnology will be more strategic, revolving around focused, networked trans-disciplinary Flagship Research Projects.

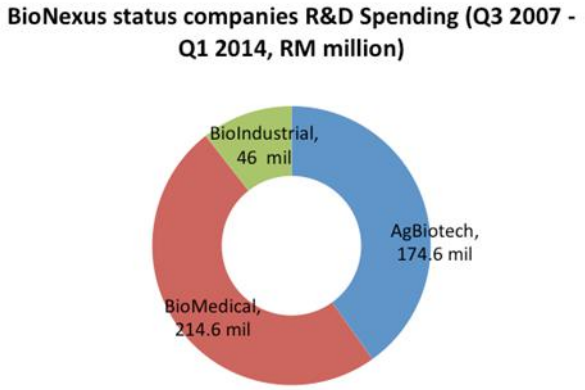

Figure 6: R&D spending of BioNexus status companies from Q3 2007 – Q1 2014

Flagship Research Projects are being established with the intention to accelerate linkages with international markets, foster international collaborations between local universities / research institutes and foreign companies, provide focused and sustained funding for bioeconomy research and innovation and contribute to human capital development, to ensure the sustainability of Malaysia's bioeconomy.

Flagship Projects that are currently on-going includes the Empurau/Mahseer/Kelah Aquaculture Research and Development Project, MyGenome Project, Proboscis Conservation Sequencing Project and the Siraj Hybrid Paddy Project. Between years 2013-2015, the Flagship Research Projects is expected to continue to expand to include algae biofuel, cellulosic sugars, tropical infectious and non-infectious diseases, biocatalyst, synthetic biology and next generation biotech/ pharma crops research.

Through strong and continuous support for bioeconomy research from the public sector, Malaysia is now well underway to be the leading hub for Bioeconomy Research and Innovation in Asia and the preferred entry point for bio-based companies to penetrate the Asian market.

CATALYSING INNOVATIONS THROUGH COMMERCIAL R&D

In terms of commercial and applied R&D in biotechnology in Malaysia, the BioNexus status companies are seen as major indicators of overall R&D expenditure. Between Q3 2007 — Q1 2014, the total R&D spending of BioNexus status companies was recorded at RM 435.2 million. During Phase 1 NBP, between Q3 2007-Q4 2010, the BioNexus status companies spent RM 132.8 million on R&D, while in Phase 2 NBP, between Q1 2011 and Q1 2014, the BioNexus status companies spent RM 302.4 million.

Strategic partnerships in biotechnology within Malaysia often involve a strong R&D component. The aim is primarily aimed on fostering R&D in biotechnology and increasing Malaysia's knowledge base. BiotechCorp has played an active role in fostering smart and strategic biotechnology partnerships not only between businesses, but also between RIs, Centres of Excellence and governments. In recent years, there had been many significant R&D collaborations that have been successfully established.

Leveraging on local basic and applied research baseline for biotechnology that has been progressively been developed, Malaysia has also adopted technology acquisition strategy. National Biotechnology Acquisition Programme was introduced is to ensure that the

Table 7: Significant Strategic R&D Partnerships in Biotechnology in Malaysia (2006-2012)

Strategic Partnership	Focus Area
AgBiotech	
Orchid Life and Genetwister Technologies, Holland	Marker Assisted Techniques for floriculture and horticulture products
Biolina and Dongtai Bioengineering, Nanjing, China	Production of microalgae in open pond systems
Standards and Industrial Research Institute of Malaysia with Vinetech	The development of specialty vinegars such as pineapple, rambutan and Bario rice vinegar
Malaysian Agricultural Research and Development Institute with Innovax	Value added virgin coconut oil with Antimicrobial Properties
Universiti Sains Malaysia and Holista CollTech	Research on plant-based collagen enzyme and extraction of bio-products
Forest Research Institute of Malaysia (FRIM) and IOI Palm Biotech Sdn Bhd	R&D in gaharu oil extraction, setting up of karas plantation, inoculation of karas trees and product development
MARDI, BiotechCorp and JEFI Aquatech	Utilize the services of the Marker Assisted Selection platform technology in the breeding of shrimps and other aquaculture products.
BioMedical	
Sarawak Biodiversity Centre and Novartis Institutes for BioMedical Research Basel (NIBR Basel) of Novartis Pharma AG	Explore novel bioactive compounds with medicinal potential
GeneNews (Malaysia) and Ministry of Health Malaysia	Diagnostic tests for liver cancer, Hepatitis B and nasopharyngeal cancer
Universiti Malaya and Dr Reddy's Laboratoy's subsidiary Aurigene Discovery Technologies (M) Sdn Bhd	Five-drug discovery programme and capacity-building post-graduate training programmes.
BioIndustrial	
Standards and Industrial Research Institute of Malaysia and Korean Research Institute of Bioscience and Biotechnology	Perform joint research activities and enhance cooperation in biotechnological research and related training
Asiatic Centre for Genome Technology and Synthetic Genomics, U.S.	Genomic approach to discover DNA-based biomarkers in the selection of superior traits in oil palm
Jawhara Bioenergie uses technology developed by Industrial Technology Research Institute, Taiwan	Bioremediation to convert municipal solid wastes treatment into biogas and biofertiliser
Forest Research Institute of Malaysia and Halagel	Develop food and pharmaceutical grade gelatine
Sarawak Biodiversity Centre and Mitsubishi Corp	Explore Sarawak's algal biodiversity as a potential source of renewable energy
University Putra Malaysia (UPM), Felda, IOI and Sime Darby	Facilitates the collaboration with globally leading technology developers and industry interested to accelerate technology development, testing and demonstration for utilisation of oil palm biomass.

technology acquired serves national interest by granting Malaysia entry into foreign markets, access to selective skills and the freedom to operate with proprietary technology. The platform technologies will also enable commercial scale up of specific initiatives in the agricultural and industrial biotechnology sectors.

BiotechCorp has spearheaded the efforts in technology acquisition under the National Biotechnology Acquisition Programme. The platform technologies

Table 8: Overview of technology acquired under the National Biotechnology Acquisition Programme

Technology Platform	Technology Provider	Application
Nanotechnology platform	Nanobiotix S.A. from France	Enables high level nanotechnology applications for non- cancer areas, including medicine, agriculture, nanomaterials and energy production
Dotscan antibody microarray diagnostic platform technology	Medsaic from Australia	Enables development of diagnostic applications for solid tumors, haematological diseases, infectious disease and autoimmune diseases
Marker Assisted Selection (MAS) technology in Plant and Animal Breeding	DNA Landmarks from Canada	Enables applications in plant and livestock breeding, by enhancing the speed and efficacy of breeding programmes through utilisation of genetic markers
Supercritical Fluid (SCF) extraction technology	Feyecon Development & Implementation B.V. from Netherlands	Enables extraction and fractionation of nutraceutical and bioactive compounds from natural sources using CO2 technology

acquired for healthcare are the nanotechnology platform from Nanobiotix S.A. in 2007 and the DotScan™ antibody microarray diagnostic platform technology from Medsaic in 2009; the Marker Assisted Selection platform technology from DNA LandMarks for agricultural; and the Supercritical Fluid technology with applications for extraction and particle formation from FeyeCon for the industrial biotechnology sector. These acquisitions provide Malaysian researchers with access to world class proprietary technology and the freedom to carry out their development work based on proven platform technologies. The acquisitions have positioned Malaysia to be in the forefront of biotechnology in the region, facilitating the transfer of knowledge and technology, and the development of new applications for commercialisation.

HUMAN CAPITAL DEVELOPMENT PROGRAMMES

Recognising that the capacity and capability of Malaysian talent in biotechnology will determine the growth of this sector, BiotechCorp implemented its Biotechnology Entrepreneurship Special Training (BeST) Programme to build critical mass of knowledge-based workers, improve hands-on technical skills, and cultivate entrepreneurship. BiotechCorp has also established the Biotechnology Entrepreneur Programme (BEP) to provide biotechnology entrepreneurs with the necessary knowledge to commence and manage biotechnology ventures, encourage the establishment of start-ups and development of small-to-medium enterprises, as well as to enhance the competitiveness of entrepreneurs and their businesses. Moving forward, BiotechCorp will continue to reinforce its human capital development initiatives through international collaborations with leading biotechnology centres such as LARTA Institute (LARTA) and California Institute for Quantitative Biosciences (QB3) under the Bio-Entrepreneurship Programme, as part of the Bioeconomy Malaysia Accelerator Programme, to develop world-class programmes capable of meeting the global industry's requirements.

BIOECONOMY TRANSFORMATION PROGRAMME (BTP)

Advances in commercial application of biotechnology worldwide over the past two decades have led to the development of a bioeconomy, whereby substantial economic outputs are from the development and use of biological materials. Bioeconomy encompasses all industries and economic sectors based on the values implicit in biological materials that can be translated into new sources of income, environmental sustainability and social well-being.

The Organisation for Economic Cooperation and Development (OECD) has estimated that by 2030, the global bioeconomy will contribute an average of 2.7% to the world's Gross Domestic Product (GDP). Recognising the significance of the bioeconomy to national growth and strength, major world economies such as the United States, the European Union, Canada, China, Australia, Finland and Russia have embarked on national bioeconomy strategies and policies that offer attractive incentives along with programmes and significant investments to boost the sector.

Malaysia, one of the most competitive biotechnology hubs in the Asia-Pacific region, has also taken critical early steps to coordinate and intensify national efforts to harness the potential of the bioeconomy. Most significantly, the Bioeconomy Transformation Programme

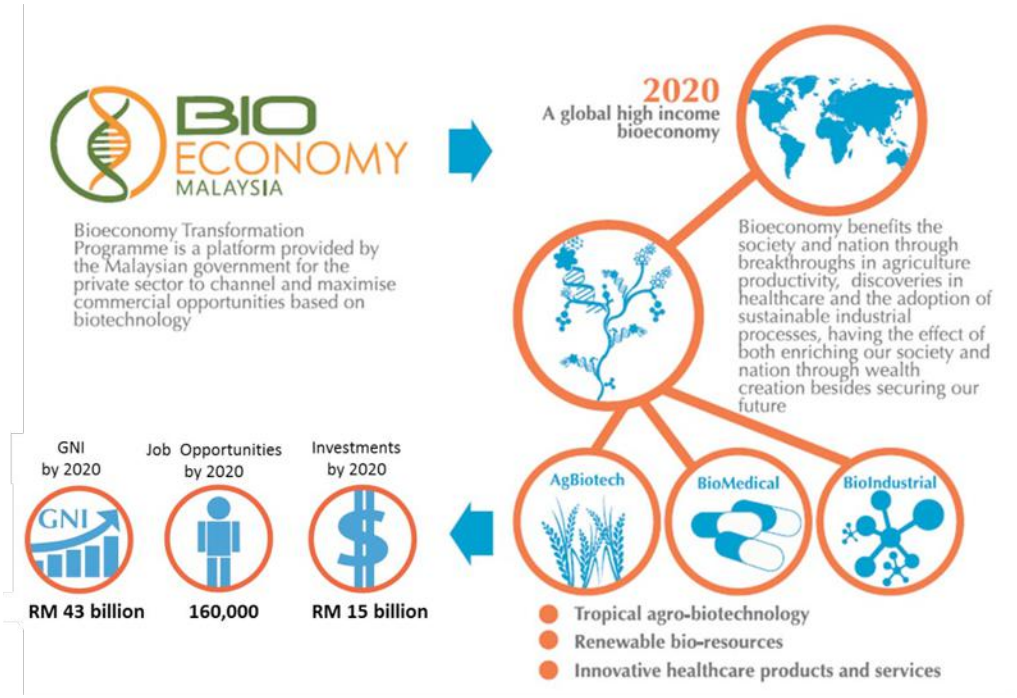

Figure 7: Overview of the Bioeconomy Transformation Programme (BTP)

(BTP) was launched in October 2012, making the country only the second in Asia, after China, and the first in ASEAN, to establish its own national bioeconomy initiative.

The Bioeconomy Transformation Programme (BTP) is a progression of the strategies outlined in the NBP and serves as a platform for the private sector to maximise commercial opportunities based on biotechnology to drive this sector. Through the BTP, the government and leading industry players will work in tandem to set national goals for the application of biotechnology, put in place the structural conditions required and develop necessary mechanisms to ensure that policy can flexibly adapt to new opportunities. The objective is to create a conducive ecosystem that can be driven by the private sector.

The BTP was launched by Prime Minister Dato' Sri Najib bin Tun Abdul Razak at the National Bioeconomy Council on 30 October 2012 to further develop the bio-based industry in Malaysia. It is in line with the Government's objective to develop Malaysia into a high-income nation by the year 2020. The BTP aims to achieve this by focusing on bio-based industries in Malaysia, a sector that has been identified as having enormous potential to further develop the nation due to the abundance of natural resources available.

The BTP is expected to promote a knowledge-based bioeconomy through the establishment of a sustainable ecosystem of R&D, commercialisation in the areas of AgBiotech, BioMedical and BioIndustrial and fostering public-private interactions in developing and exploring high impact opportunities. MOSTI is the lead Ministry while BiotechCorp has been appointed as the implementation agency for the BTP. Accordingly, BiotechCorp has been instrumental in driving the BTP by collaborating with various government agencies, the private sector, institutions of higher learning and research institutes to identify Entry Point Projects (EPPs) to be included in the programme. This has been achieved via a series of Workshops and Lab Sessions, which are ongoing.

As a base, the BTP has identified 10 Entry Point Projects (EPPs) to kick-start the growth of Malaysia's bioeconomy in the AgBiotech, BioMedical and Bio-Industrial sectors. The 10 EPPs include industrial bio-inputs, biochemicals, biomaterials, bio-based farm inputs, high value bio-ingredients, high value food varieties, biosimilars, drug discovery and pre-clinical services, molecular screening and diagnostics (MSD), as well as stem cells and regenerative medicine. Within these 10 EPPs, 20 private sector-driven Trigger Projects constitute the initial tranche of ventures launched.

The 20 Trigger Projects have been comprehensively assessed for potential benefit to the nation from the perspective of Gross National Income (GNI) generated, employment created and investment attracted. It was

projected that the BTP projects will create RM 3.6 billion of GNI, attract RM 10 billion in investments and create 16,300 jobs by the year 2020.

In addition to these significant economic impacts, the BTP will also benefit society and the nation in the following ways:

- Improve the income of the people, and especially rural communities, through projects and programmes with high inclusiveness factors — This can be achieved through the implementation of Trigger Projects involving contract farming mechanisms.
- Promotion of a green economy, contributing to long-term economic and environmental sustainability — BioIndustrial Trigger Projects such as energy crop plantation, the production of renewable biomaterials and bio-based chemicals, and production of compressed biomethane gas are expected to contribute to Malaysia's target of reducing its carbon footprint and emissions by 40% by 2020.
- Improve the health and well-being of the people — Biosimilars (as opposed to innovator biologic drugs) will drive down treatment costs by 30-40%, while MSD will make early disease detection and mitigation possible, significantly reducing healthcare costs to the Government and people.

Since BTP's launch in October 2012, BiotechCorp has continued to identify and evaluate high potential proposed Trigger Projects to be added under the programme. Through recent BTP Workshops and Labs conducted in Sabah, Sarawak, the Northern Region (encompassing Perak, Perlis, Kedah and Penang) and Johor, as well as on-going engagement with the private sector, the pipeline projects under the BTP will further supplement the bioeconomy landscape by contributing to GNI, attracting investment and new jobs. Over the period 2013-2020, the BTP is projected to identify projects contributing up to RM 48 billion in GNI, attracting a targeted RM 50 billion in investment, and creating 170,000 new jobs.

In the effort to establish greater collaborative ties between Malaysia and other countries with Bioeconomy initiatives, BiotechCorp actively seeks strategic partnerships and collaborations to share knowledge and foster international collaboration on policy strategies, actions and joint activities to promote innovation in Bioeconomy. The first of these is BiotechCorp's collaboration with Michigan State University (MSU) announced on 24 September 2013 to develop Bioeconomy Technology Roadmap and Technology Readiness Level Adoption

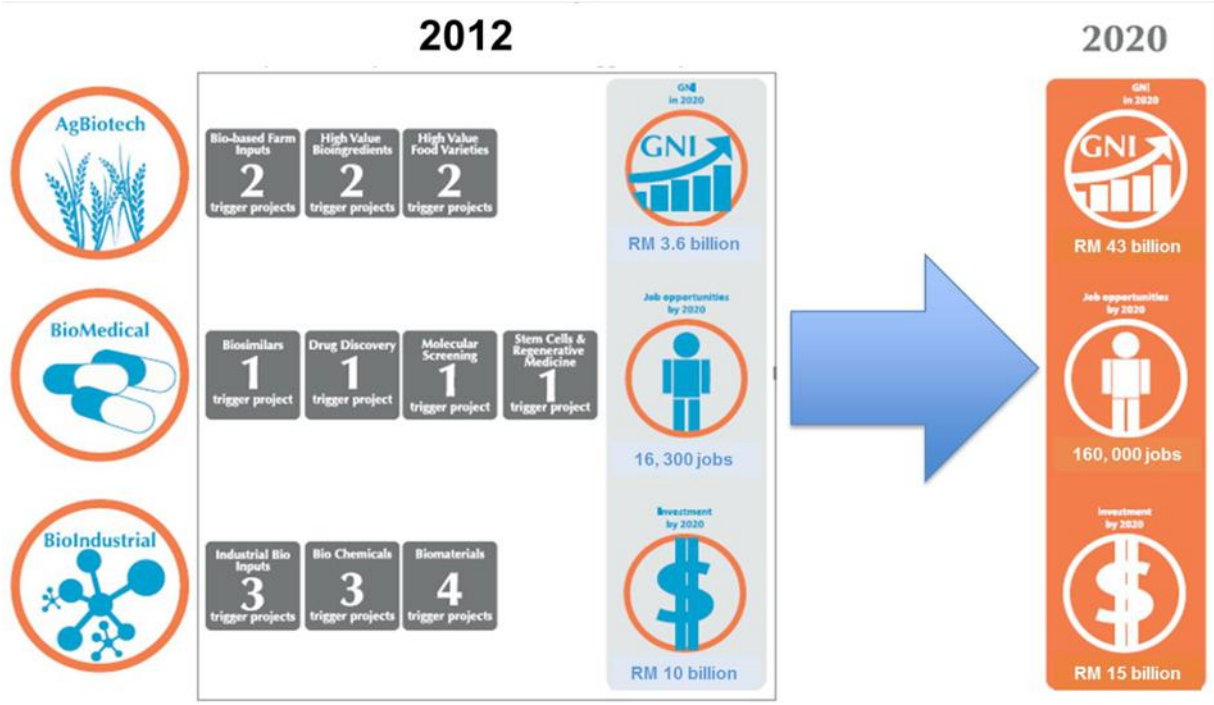

Figure 8: Achievements and Targets Bioeconomy Transformation Programme (BTP)

protocols, to bridge technology and expertise between Malaysia-United States. BiotechCorp is also in the midst of establishing other regional cooperative forum/platform, including the World Islamic Economic Forum and the Bay Area Bioeconomy Initiative in the United States.

To support the implementation of Trigger Projects under the BTP, the Malaysian government has approved the allocation of almost RM 85 million for a dedicated BTP Fund. The BTP Fund is envisioned as a "tipping point" or "bridging" mechanism to mitigate and de-risk a project from the point of view of conventional financing institutions. It is being made available in the form of soft loans to eligible BTP-approved companies over a three-year period for up to RM 10 million.

CONCLUSION

By optimising the nation's competitive edge through private and public participation, Malaysia will continue to further strengthen its local biotechnology ecosystem for the growth and development a sustainable bioeconomy that will drive the country's socio-economic position to greater heights. Malaysia's highly synergistic biotechnology sector, as well as its favourable business environment, substantial government support, well-defined framework and action policies as well as promising market access opportunities proven successful in attracting innovative biotechnology companies worldwide that are seeking ways to increase their resilience in facing turbulent economic climates.

With the introduction of the BTP, Malaysia is now unlocking even greater opportunities in the local and regional biotechnology industry, and enhancing the participation of the private sector. Through effective execution strategies from the Government and BiotechCorp, the biotechnology sector is now directly contributing towards efforts to drive Malaysia towards a high-income and knowledge-based economy by year 2020.

ABOUT MALAYSIAN BIOTECHNOLOGY CORPORATION (BIOTECHCORP)

BiotechCorp is the lead development agency under the purview of Ministry of Science, Technology and Innovation (MOSTI), acts as a central contact point providing support, facilitation and advisory services for biotech and life sciences companies in Malaysia.

BioNexus Status companies are international and Malaysian biotech companies that qualify for fiscal incentives, grants and guarantees administered by BiotechCorp. For further details, visit www.biotechcorp.com.my.

Bioeconomy Transformation Programme (BTP) is a platform provided by the Malaysian government for the private sector to channel and maximise commercial opportunities in bio-based industries.

The BTP is designed as a Transformation Programme based on biotechnology's potential to cut across various industries and transform Malaysia into a high income, inclusive and sustainable nation.

Through the BTP, Bioeconomy will benefit the society and nation through breakthroughs in agricultural productivity, discoveries in healthcare and the adoption of sustainable industrial processes, having the effect of both enriching our society and nation through wealth creation besides securing our future.

Case Study

Lean start-up: A case study in the establishment of affordable laboratory infrastructure and emerging biotechnology business models

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ABSTRACT

Historically, innovation in the biotechnology sector has relied to a large extent on the expensive infrastructure provided by universities or large pharmaceutical companies. This prohibitive start-up expense is the basis of why garage-style biotechnology entrepreneurs are exceedingly rare as compared to their software and high-tech counterparts. Recent consolidation among pharmaceutical companies and the release of next generation research equipment has produced an affordable surplus in the secondary equipment markets, reducing the barrier to entry posed by equipment expenses. We examine the biotechnology start-up Ichor Therapeutics, Inc., and review strategies that the founding team has successfully employed to establish an affordable laboratory and reduce research expenses. Corporate structuring strategies to reduce risk and provide stability are also discussed.

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Keywords: entrepreneurship, start-up company, stem cells, automation, biotechnology, DIY bio

INTRODUCTION

Historically, innovation in the biotechnology sector has relied to a large extent on the expensive infrastructure provided by universities or large pharmaceutical companies.

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This prohibitive start-up expense is the basis of why garage-style biotechnology entrepreneurs are exceedingly rare as compared to their software and high-tech counterparts. Biotechnology entrepreneurs also face the additional challenge of inflated reagent and consumable pricing. This stems from the proprietary nature of many research products, and as a result of most research being ultimately supported by public funds.

In recent years, consolidations among pharmaceutical companies and the release of next generation research equipment has led to a surplus of pre-owned equipment in the secondary market. The equipment surplus has substantially reduced the barrier to entry imposed by limited equipment access. In the present case study, we examine the biotechnology start-up company Ichor Therapeutics, Inc., and review strategies that the founding team has successfully employed to establish an affordable laboratory, promote information sharing among team members, reduce research expenses, and guide scientific discovery. We then discuss corporate structuring strategies used by the company to reduce risk and provide stability.

BACKGROUND

Ichor Therapeutics, Inc. was founded in May 2013 with a grant from the Life Extension Foundation, a private entity that supports scientific and medical research related to the prevention of degenerative disease. The primary focus of the company is to address a known bottleneck in the field of regenerative medicine:[1] deriving hematopoietic stem cells (HSC) from human pluripotent stem cells. Briefly, HSC are a type of adult stem cell that resides in the bone marrow and maintains the hematopoietic system, which includes all immune and blood cells, throughout life. Bone marrow and cord blood transplants are useful in clinical practice to treat a wide range of diseases because of the presence of HSC within grafts. After transplantation, HSC migrate into and repopulate the hematopoietic system of the host. Unfortunately HSC are extremely rare, representing only 0.05% of bone marrow cells, so a chronic supply shortage persists.[2] Developing a scalable manufacturing process to produce HSC from pluripotent stem cells would address this unmet medical need.

A start-up company focused on stem cell research is an excellent case study because the infrastructure requirements are extensive. While many labs require basic laboratory equipment for mammalian cell culture (incubators, laminar flow hood, inverted microscope), molecular biology (shaker incubator, electrophoresis equipment, refrigerated centrifuge), and analytics (flow cytometer, microplate reader, fluorescence microscopy), Ichor also required liquid handling robotics for medium-throughput screening of differentiation protocols and a vivarium (suitable for housing severe combined immunodeficient mice) to assess the function of its cellular products *in vivo*.

BASIC EQUIPMENT AND CONSUMABLES PROCUREMENT

One of the highest barriers to entry for a biotechnology start-up is the significant cost of establishing a basic laboratory, as the acquisition and maintenance cost of equipment has historically been prohibitive. The last decade has been marked by consolidation of large pharmaceutical companies and the closure of many early stage biotech companies. However, this market volatility has nurtured a healthy secondary equipment market that can help to overcome this barrier.[3] Secondary markets include offerings at online auctions and through used equipment vendors. Regardless of where equipment is obtained, buyers should confirm the availability of user manuals, technical schematics, replacement parts, and free software before making a purchase. Failure to do so may result in unexpected post-acquisition expenses. For example, a used Molecular Devices Vmax absorbance reader can be purchased online for as little as a few hundred dollars. However, these instruments rarely include software, which must be purchased from the manufacturer at a cost of $4,119.00 (Molecular Devices, 2013, personal communication).

Reagents used during the normal operations of a biotech company present another major cost to potential entrepreneurs. Commonly used supply companies have universities and government funded labs as their primary market, and as a result of those labs buying in bulk to negotiate discounts on consumables, the list price of those same consumables have increased. The authors highly recommend comparing prices between small specialist supply companies, as the list prices from these sources can be significantly lower than the list price of larger suppliers.

Purchasing at auction

Online auction websites generally provide the largest savings when buying equipment, but offer no guarantee of item quality or customer support. The variable nature of online bidding means that item cost can be extremely dynamic at different times, even on the same website. For example, purchasers at Ichor observed that winning bids for an identical product at auction ranged from $50.00 to $3,750.00. Therefore, groups that purchase through auction should study winning bids for similar items over time to set a realistic bid ceiling and identify the

best deals. Using this information for proxy bidding — a process by which a maximum bid for an item is set by the bidder, and then the auction website automatically increases the bid up to this limit in response to other bidders — is particularly useful to help bidders avoid overpaying for highly competitive items.

The inability to purchase essential items on-demand, uncertainty about equipment quality, and lack of warranty, make auction purchasing better suited for teams with flexible timelines for equipment procurement and the expertise to repair and service equipment in-house. Groups attempting this strategy must accept that some items will inevitably need to be thrown away. However, the cost savings over time should more than justify the losses, provided a responsible bidding strategy is adopted throughout.[4]

Importantly, some universities have policies that prohibit investigators from purchasing equipment at auction, either directly or indirectly. This issue can be further complicated when the equipment purchased qualifies as a fixed asset. SUNY Research Foundation defines a capital asset as, "A single item with an acquisition cost of $5,000 or more and has a useful life beyond one year."[5] An investigator may purchase three damaged units for $5,000 each at auction, and re-use parts from two of the units to repair one unit with a refurbished value of $30,000. However, it may be difficult for the investigator to throw away the two units that were scrapped for parts because of Foundation policy. Even donated assets present a potential problem because they are assigned the fair market value at the time of acquisition. Finally, most institutions require investigators to obtain quotes from a minimum of three vendors for equipment purchases. Collectively, it is advisable for academic investigators to contact their purchasing department for specific policy information relating to auction purchasing and other forms of equipment procurement before bidding.

Purchasing through used equipment vendors

Equipment resellers are a faster, more reliable, but generally more expensive means of acquiring equipment as compared to purchasing at auction.[6] Some used equipment vendors employ in-house technicians to refurbish used laboratory equipment to factory specifications before putting the product up for sale, while others simply acquire cheap equipment at auction then directly resell to customers without servicing or recertification. Because of this, the quality of goods purchased through resale vendors can be superior to those found at auction, but ultimately each vendor must be assessed on a case-by-case basis. One major advantage over auction purchasing is that many used equipment vendors offer extended warranties on refurbished equipment, reducing purchasing risk for the buyer. Further, fewer institutional policies exist that prohibit academic investigators from purchasing from used equipment vendors as compared to purchasing at auction (SUNY Upstate Medical University Purchasing Department, 2013, personal communication).

As with other retail companies, stagnation of inventory for used equipment vendors is often undesirable because of the real cost associated with equipment storage.[7,8] Because of this, these vendors are generally motivated to move inventory quickly and may be willing to part with items for far less than the advertised price, especially if an offer is made on an unpopular product. Vendors will often accept low offers when several items are purchased at once for the same reason. Previous price reductions on equipment are generally a good indicator that the interest in the item is low, and the vendor may be willing to sell at a reduced price to move inventory.

By default, purchasers at Ichor make starting offers of not more than 50% of the asking price when purchasing from the website of a used equipment vendor. Even these offers are only made after carefully studying pricing trends and product availability through auction and other vendors. Approximately half of these "low ball" offers are accepted immediately, which supports the usefulness of haggling for start-up companies looking to stretch limited seed capital.

Information technology and specialty equipment

Computer workstations

Integrating personnel into a cohesive team is a persistent challenge at any company, and this challenge can be exacerbated during periods of rapid growth in a start-up environment. Streamlining information sharing and communication between researchers and administrative staff is essential; not only to promote efficiency within the team, but also to reduce growing pains as the company expands over time. For early stage start-up companies, hiring information technology support staff or project managers to improve laboratory efficiency can be prohibitively expensive. Fortunately, there are several free off-the-shelf solutions available, depending on the specific needs of the team. Ichor uses several of these platforms to manage its workflow, including Dropbox, Evernote, Zotero, and Quartzy. Although these tools may not be appropriate for some applications, such as those involving sensitive patient data, they can suit the

needs of many laboratories. Of note, it is generally advisable to implement these solutions early while the team is small, rather than later, when the adoption of change may be more difficult to encourage.

Dropbox is a free cloud-based storage service that automatically syncs data between computers and devices.[9] Ichor created a company Dropbox account (free up to 2 GB storage space, $9.99 per month for up to 100 GB) and installed Dropbox on all workplace computers. All team members are given their own folder to organize as they see fit. A team folder was also created that contains pertinent information, such as spreadsheet templates for common calculations and data acquisition, user manuals for equipment, and company documents, such as expense reports. Syncing data across all workplace computers increases the availability of core infrastructure because data can often be obtained on the computer attached to the instrument, but analyzed later on a general-use workstation. Because Dropbox is cloud-based, physical backups of files are generally not as necessary. Dropbox and similar services are ideal for labs with modest or low hard drive requirements, but may not be suitable with computationally intensive projects involving large data storage.

Evernote is a free cloud-based notebook client that automatically syncs data between computers and devices.[10] Evernote is customizable and is capable of handling a variety of different file types and sizes. Users are able to annotate imported spreadsheets and images, and can also attach raw data to each annotation. This helps to streamline management within the laboratory. Supervisors may review the notes and results of a team member, but can readily access the raw data for their own interpretation as needed. A personal Evernote account is free, and integrated business accounts can be added for a $10/user per month fee. Each team member at Ichor has personal and business notebooks, the latter of which is shared with other company employees. Notebooks are synced automatically across all devices. An employee's information can be maintained in the business notebooks, but company policy permits team members to make copies of non-confidential information, such as basic protocols, in their personal notebooks for later use. This policy is particularly helpful for temporary employees, such as interns or collaborators, who come to the company for technical training. When any employee leaves the company, their business account is archived and can no longer be viewed by them, but the account remains accessible for current employees to reference.

Zotero is a free cloud-based tool that organizes peer-reviewed journal articles using a searchable interface.[11] It automatically syncs data between computers and devices. Content may be collected and organized by each individual user. Zotero also supports a group feature where users can share information with one another through a central repository. Ichor uses a Zotero group to streamline document sharing among its team members. Training new employees is simplified through the use of a "new hires" folder, which contains literature reviews and protocol collections of relevance to the company workflow. New hires are able to copy this literature into their individual libraries and annotate documents all within the software. Importantly, Zotero can also integrate with common word processing applications like OpenOffice and Microsoft Word, automating bibliography and in-text citation formatting during the preparation of manuscripts for publication or grant submission.

As the needs of a laboratory become more sophisticated, management software like Quartzy, a cloud-based platform, can be used to centralize order requests, track inventory, store laboratory records, and schedule equipment use. Vendor supplied programs can also be useful to augment workflow by centralizing service requests. LabLinker, for example, allows researchers to schedule services such as DNA sequencing and primer synthesis.

Collectively, there is a wide selection of affordable information technology solutions to promote laboratory efficiency and improve communication. Ichor regularly surveys its team members at laboratory meetings to identify workflow bottlenecks, and then uses this information to seek out technology solutions to address them. Team members then provide critical feedback of new solutions during trial periods before a decision is made to rollout the software company-wide. This cycle has helped Ichor to establish a company culture where efficiency is valued and promoted.

Laboratory Automation

Laboratory automation solutions may represent one of the most underutilized and cost-effective benefits of engaging in used equipment purchases. Liquid handling robots in particular have broad applications in the laboratory. They are adept at performing repetitive tasks, and generally have less random error than human technicians.[12]

Ichor utilizes traditional embryoid body formation as a preferred method of inducing pluripotent stem cell differentiation, and purchased a used Biomek 2000 (Beckman Coulter, USA) at auction (GoIndustry, DoveBid, USA) to automate the process. Briefly, embryoid body formation involves detaching pluripotent stem cells from their growth surface, and transferring them to culture dishes with low adherence in the presence of media containing factors that promote differentiation into desired cell types. Because the new growth surface has low adherence, the pluripotent stem cells

self-aggregate to each other rather than the plate surface, forming spheres termed embryoid bodies. The size of the embryoid body influences the differentiation process, so it is important to control this variable when optimizing differentiation conditions.[13,14]

To enable sterile work including cell culture, a customized semi-sterile enclosure was constructed for the Biomek 2000 using basic materials from a home improvement store at a cost of less than $550.00. The functionality of the robot was greatly enhanced by the development of several custom 3D printed tools, which cost less than $5.00 each to print. To validate the system and demonstrate proof-of-concept for its utility in embryoid body formation, production of CD14+CD45+ monocytes from pluripotent stem cells using an embryoid body method was successfully automated on the Biomek 2000 (Eric Zluhan, 2014, manuscript in preparation).

Collectively, liquid handling robots have the potential to dramatically improve workflow and reduce labor expense in a lean start-up environment. They can be substantially augmented to support unique applications with a little creativity and minimal capital. If planned carefully, automated methods can be designed in a modular format that provides short-term value by performing basic processes, yet enables convenient module integration for more complex applications in the medium or long term.

Vivarium

Assessing the function of human pluripotent stem cell derived products *in vivo* represented the most demanding infrastructure requirement for the company. Human cells cannot be evaluated in standard laboratory mice because they will be rejected by the host immune system. Instead, severe combined immunodeficient (SCID) mice need to be used. These genetically engineered mice have deficient immune systems that permit engraftment of human cells; but by extension, they are also hypersensitive to otherwise benign pathogens and must be housed in specialized clean rooms to avoid death from opportunistic infection.[15]

To accommodate this need, Ichor built a customized 11' x 9' clean room that utilized a two-tiered positive pressure system. Vinyl flooring[16] was installed and the room was then subdivided with standard 2" x 4" studs[17] into three smaller rooms, including a viewing room, a gowning room, and a clean room. The rooms were electrically wired on two circuits, one controlling LED lights installed for basic lighting, the other controlling germicidal fluorescent light bulbs[18] installed in under cabinet light fixtures[19] for disinfection. The walls were constructed with reflective insulated sheets[20] and an observation window, sliding glass door, and interior door were also installed. Air was filtered with HEPA allergen removers containing carbon filters[21] and piped into the rooms through galvanized heating duct. Three units were installed for the clean room, and one for the changing room to create a tiered positive pressure gradient. A blow-off was also installed in the clean room. The clean room and gowning room were sealed with silver foil tape[22] to maintain pressure and control air flow.

To promote a pathogen free environment, each room (walls, floor, and ceiling) is disinfected with 70% isopropyl alcohol and UV light every two weeks. To assess relative air sterility, LB agar petri dishes are placed uncovered inside and outside each room for 45 minutes then covered and grown overnight at 37 °C. Colonies are then scored and recorded.

Although the clean room design may not be appropriate for all applications, available data suggest it is effective at protecting the company's SCID mice from infection. In over 9 months of operation, clean room LB plates have not grown a single bacterial colony, and no detectable or discernable infection has been observed in laboratory mice. The cost to construct the vivarium was $2,259.52($879.52 materials + $1,380.00 labor) and up to 15 cages can be conveniently housed in the clean room. This is in stark contrast to an estimated $43,164 – $45,144 a commercial-grade vivarium of similar size.[23]

BUSINESS MODEL

It is well known that most biotechnology companies inevitably fail because of the high risk associated with clinical research and development programs. Surprisingly, few founding teams take this fact into consideration when developing their business plans.[24] For small start-up companies, cash flow may be detrimentally turbulent. When an early stage start-up company runs out of operating capital, its assets are often liquidated and the resulting capital is returned to investors. Losing basic laboratory functionality can prematurely terminate an otherwise viable venture and it can take many months to rebuild necessary infrastructure, even after raising new capital. At Ichor, the preservation of laboratory access has been prioritized. To accomplish this, Ichor uses multiple corporate entities to manage its business and research programs. These entities reflect a mixture of traditional high-risk biotechnology research and development, but are stabilized by more conservative business structures.

Ichor Therapeutics, Inc. functions as a contract research organization. Research and development activities, including employee payroll, are performed through this entity. Ichor Therapeutics, Inc. operates the online store WeCellStuff.com through a DBA to obtain

wholesale pricing on reagents and consumables. As a contract research organization, Ichor Therapeutics, Inc. can perform work for hire in addition to its intramural research, which helps to offset overhead. This strategy has a long history of use by biotechnology companies at all stages of development.[25]

In 2014, Ichor Therapeutics, Inc. diverged its capital assets to a separate corporate entity, Ichor Laboratory Solutions, Inc., which leases laboratory equipment. As a leasing company, Ichor Laboratory Solutions, Inc. is able to utilize more conservative financing, such as low interest debt financing, and is not dependent on grants, research contracts, or dilutive investment to support its operations. Because the Ichor team is skilled in asset procurement, equipment leasing can be used to increase revenues or support other companies and entrepreneurs of strategic value.

Real estate in Central New York is inexpensive as compared to other regions in the United States. Ichor Therapeutics, Inc. has partnered with Kelsey Moody & Associates, LLC, which is owned and operated by Ichor's CEO. Through this agreement, Kelsey Moody & Associates, LLC can issue convertible notes instead of collecting rent, allowing Ichor Therapeutics, Inc. not only to persist, but remain operational during periods of insolvency. Through this partnership, Ichor Therapeutics, Inc. also provides various tenants shared access to its research facilities. Although indirect, including a real estate component to the broader company structure has stabilized Ichor Therapeutics, Inc. and allows the founding team to make strategic decisions that focus more on the medium and long term, rather than short term, success of the company. In recent years, graduate students have become more focused on entrepreneurial ventures and careers in industry, rather than the pursuit of traditional academic appointments.[26] A strategy involving real estate acquisition may be particularly well suited for young graduate students who expect to complete many years of study in one location, and lend necessary stability as they build out their own biotechnology start-ups.

In an effort to reduce the burden of high consumable and reagent pricing for its research and development activities, Ichor has established an online store WeCellStuff.com, which is a distributor for several manufacturers. Although online sales provide a small basal level of revenue for the company, functionally, it permits Ichor to receive wholesale pricing on these items for its own intramural research programs at considerable savings.

One consideration of using a multiple company approach is that investment deals are complicated. A company with active contract research activities, leasing, and real estate may actually deter investors who want the flexibility of investing only at the level of a specific research program. To overcome this obstacle, Ichor has designed its business structure to support the incorporation of subsidiary intellectual property holding companies. Investment funding is received at the level of the subsidiary, and Ichor Therapeutics, Inc. (the contract research entity) is contracted by the subsidiary to perform the research, while the subsidiary retains resulting intellectual property. This structure provides numerous advantages to all parties. The investor benefits because start-up expenses are reduced, they can invest at the level of a specific research program, and they are not subject to any liabilities or other risks associated with other ongoing activities (equipment leasing, real estate, etc.). Forced liquidation of company assets is not a factor, so the company achieves its goal of preserving access to a functioning laboratory. Employees can be repurposed to work on other contract projects during periods of turbulent cash flow, enabling the founding team to maintain a competent workforce.

It is important that entrepreneurs understand that a multiple company structure should be planned for early, but should be executed slowly over time. The cost to maintain a corporation can range from approximately $250 – $5,000 per year (depending on corporation type, state fees, and the extent to which accounting and legal services are sourced). When dealing with several corporate entities, a new entrepreneur should be careful to balance corporate needs with financial realities. For example, capital assets and research intellectual property were contained within Ichor Therapeutics, Inc. during the early stages until the business was sufficiently mature to benefit from diverging these components into distinct companies. Making this sort of move too early can put a new venture at risk of being "nickel-and-dimed" to death. Spin-off companies should contribute to growth and reduce risk, not contribute to either.

For entrepreneurs who want to focus exclusively on technology development or lack sufficient capital or assets to benefit from the aforementioned strategies, community laboratories are an attractive alternative. These laboratories can range from small do-it-yourself (DIY) hobbyist labs, the so-called biotechnology "hacker spaces",[27] to large institutional biotechnology incubators.[28] DIY-shared spaces can be rented for low monthly membership fees, whereas institutional incubators rent out dedicated suites that contain both office and wet laboratory space. To subsidize the expense of maintaining expensive core facilities, many academic universities offer per run or per hour pricing for equipment use, so even the most expensive equipment is often readily available for use. Collectively, the savvy entrepreneur can creatively utilize these and similar solutions to overcome the accessibility barrier, despite significant financial constraints.

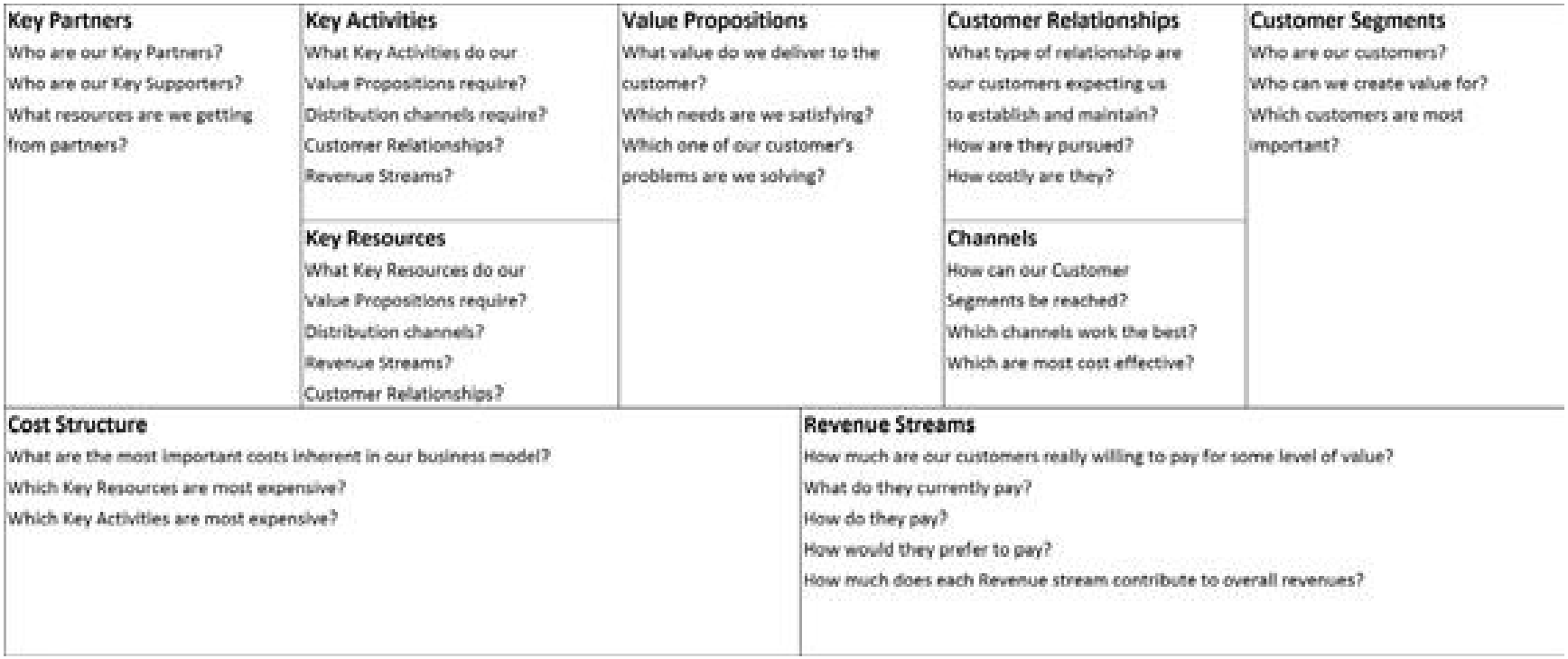

Figure 1: The Osterwalder business canvas

Emerging business models

At the most basic level, the focus of Ichor has been to create a network of companies that can sustain a pre-clinical research and development pipeline. Other companies, at all stages, have found opportunities to establish sustainable infrastructure. Functionally, this is a balance of reducing operational expenses and increasing revenue. One of the more interesting and increasingly popular emerging motifs is to apply laboratory automation technologies to improve experiment reliability, drive down costs, and offer early-stage revenue. This strategy is distinct from most life science ventures, which typically do not have cash flow in the early stages of development.

Emerald Therapeutics and Transcriptic are two biotech start-up companies with a focus centered on automation. Both of these companies offer automated lab services, which run customized protocols designed by researchers through the company website. A large variety of tasks have already been automated, including common techniques like PCR, transfection, chromatographic tests, DNA preparation, and RNA extraction among others, with more manually intricate techniques such as x-ray crystallography and patch clamp recording being developed. The value of the automated laboratory model not only comes from the ability to perform experiments more quickly and accurately than a human technician could for the same price, but also adds a valuable revenue component to the company. Founders of Transcript claim that a task requiring a technician to perform liquid handing for a months' time could be compressed into a week. Relevant information is also recorded at each step of the process, making replicating the experimental conditions far easier and making the end results more reliable.[29]

Laboratory automation is a powerful tool, but it is still limited by logistics and issues with customer relations. Interestingly, some of the most common technical issues relate to tasks that would be simple when performed by a human technician. For example, the need to move samples in and out of cold storage and incubation chambers, or the uncapping and recapping of different containers can be challenging for a robotic arm. Another challenge is managing the storage and maintenance of many different test specimens and special materials shipped to the worksite from users. Advertising services to potential customers is difficult, and often requires proactive outreaching to university labs. As with any emerging service, researchers may be cautious to risk large sums of limited funds. Transcriptic and Emerald Therapeutics attempt to address these flaws through custom engineering devices to handle logistical tasks, and by using modular workstations to allow their operations to adjust to a sporadic workflow.

The end product of automated laboratory services is simply a compilation of user experimental data, which could eventually support a broader market base than previous service models. This could have a transformative effect internationally, as areas with poor infrastructure could use these services to perform experiments that would otherwise be unfeasible.

ASSET IDENTIFICATION FOR CORPORATE STRUCTURING

Because every start-up is unique, providing a comprehensive "how to" guide for creating a successful company is not feasible. However, the ability to effectively identify and capitalize on corporate assets is perhaps the most important trait shared by each company discussed previously. The business model canvas is a tool the authors of this manuscript recommend to entrepreneurs at all stages to identify and focus on critical business activities. The original Osterwalder Business model canvas contains 9 components (Fig. 1) that show how a company intends to generate revenue. These include, 1) value propositions, 2) customer segments, 3) channels, 4) customer relationships, 5) revenue streams, 6) key activities, 7) key resources, 8) key partners, and 9) cost structures. Several variants of have been made based on the open source Osterwalder Canvas, but most still focus on these original 9 blocks. The business model canvas is an excellent tool for designing a new venture, illustrating your business model, and for refocusing an existing business model to be more efficient.

CONCLUSION

Traditional sources of seed capital for high-tech and software startups, such as friends and family, have historically been insufficient to support the financial demands of biotechnology ventures. But as barriers to entry are eroded, biotechnology as an industry is beginning to move from centralized institutions to the garage. Ichor began in the living room of its founder, who at that time was a medical student. The company has since grown and expanded into a string of companies that balance the risk of research and development with conservative, sustainable enterprises. It is the hope of the authors that this manuscript provides some guidance for aspiring entrepreneurs and shows, by example, that garage-style biotechnology startups are not only possible, but also viable.

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DISCLOSURES

KJM holds equity positions in the following for-profit stem cell therapy companies; Ichor Therapeutics, Inc., ImmunePath, Inc., and Advanced Cell Technologies, Inc. EZ and DW hold equity positions in Ichor Therapeutics, Inc. GF holds equity positions in Humurine Technologies, Inc. and Ichor Therapeutics, Inc. The authors declare no further conflicts.

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From the Classroom

The University of Colorado certificate program in bioinnovation and entrepreneurship: An update and current status

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ABSTRACT

The purpose of this paper is to provide an update and report the current status of the cross-campus University of Colorado Denver program in bioinnovation and entrepreneurship, details of which were first reported in the *Journal of Commercial Biotechnology* in 2012[5]. The paper outlines the joys and challenges of implementing an inter-campus program that attempts to marry cutting-edge biotechnology innovation with a solid business foundation. The tremendous value offered by such a program, particularly to biotechnology and life-science researchers, is outlined. Operationalization and process issues such as differential tuition rates, distance between campuses, and class timing issues are considered, and solutions are offered. Finally, recommendations are provided for other business schools considering a similar program.

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The past decade has seen a tremendous growth and interest in new forms of collaborative education. Especially relevant is the need to provide fundamental business education to entrepreneurially focused disciplines, particularly in the STEM (science, technology, engineering and mathematics), medical and biotechnology fields, where the demands of pure research often lead researchers to be product focused as opposed to market focused. Indeed scholars have argued that as the STEM and biotechnology disciplines grow,[1] so will the need for well-targeted business education[2] tailored to aiding these researchers in converting concepts and prototypes into successful new products and startups. Technical skills are critical to creating innovations that add value; however without social, business, or emotional intelligence these innovations may not gain market acceptance.[3] Indeed past research has suggested that bioentrepreneurs need fundamental business knowledge and related skills that go beyond the development of concepts or the creation of unique products.[4]

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BACKGROUND AND VISION

The vision behind the University of Colorado Certificate Program in Bioinnovation and Entrepreneurship was to provide bioscience students access to these requisite business skills and ways of thinking. This vision, along with the initial processes involved in the formation of the certificate program, was reported in the *Journal of Commercial Biotechnology* in 2012.[5] The program was one of the first where several individuals from cross-campus

entities (a Business School, a Graduate School, and a Medical School) collaborated to bring value-added business education to bioentrepreneurs. Due to its pioneering nature, little prior research existed on how to structure such a program; therefore, many decisions were taken "blind" with a "do what seems right and make changes later" philosophy. It is now four years since the program was launched and, as with any startup, it has gone through peaks and valleys. In the process, much learning has accrued in terms of how best to structure such a program, and, perhaps more importantly, pitfalls to avoid. It is our hope that this update will provide guidance to those considering similar cross-campus collaborative endeavors at other Universities.

Program Rationale and Goals

The science student appears to lack a basic understanding of what makes a biotechnology offering successful, beyond developing what he or she considers to be an innovative product that can surmount the appropriate regulatory hurdles. To explore this assumption, the authors have augmented the six one-on-one interviews conducted with prospective bio-entrepreneurs as reported in the previous paper,[5] with an additional 36 such interviews. The findings reveal significant deficiencies in these students' knowledge of core business concepts, most importantly marketing, finance and legal issues. For instance, many of those interviewed did not grasp the salience of the cost and risk imposed by the regulatory process or the importance of securing funding able to cover both these costs and support the student for an extended period of time. Further, there was little appreciation that at the end of the development process, having cleared the regulatory hurdles, the product might not be viable, as the students did not see sufficient value in performing a thorough market analysis prior to beginning the development process.

Likely because the science issues are complex and consuming, these students generally assumed amicable industry relations and a warm market reception for their innovations. However, competitive reality teaches that "better" is in the eye of the beholder, meaning that a new product must have enough relative advantage to cause potential adopters to discontinue their current product.[6] More concerning is that new products with sufficient relative advantage are seen as threats and existing firms will fight to maintain their products' market share and profits, even if this means blocking the bioentrepreneur's superior solution. In essence, we found that science students develop a "product" orientation, not a "market" orientation, a difference that can greatly alter their innovations' future outcomes.

The business student appears to lack a meaningful understanding of biotechnology concepts, the time frames involved in developing new products and the unique legal and regulatory environments in which the bio-scientist is compelled to operate. If business students are to partner with scientists to reduce the risk of startup failure, it is imperative that they understand the *reasons* for the innovation and the *time commitments* imposed by various regulations. This knowledge will highlight the protracted nature of the process, the requirement of extended and flexible financing, and the need for a clear market application at the beginning of the project.

Thus, it was construed that two-way learning was essential for either student to succeed in the biotechnology space and the most practical way to provide this opportunity was through a truly cross-disciplinary and cross-campus educational program that involved a two-way flow of ideas, training, and people. Given the idiosyncrasies of universities, it became clear that to facilitate this level of intra-organizational cooperation required the assistance of a liaison, one capable of coordinating the efforts of willing faculty and students.

The University and the JABS Center

The University of Colorado-Denver is a large state university, with 13 schools and colleges serving over 28,000 students in two campuses – a downtown Denver campus where the Business Schools and many non-medical disciplines are housed and the Anschutz campus where the medical school and most biotech-related departments are located. Additionally, situated adjacent to the Anschutz medical campus is the Fitzsimons Life Science Park, a large biotechnology center that is part of the incredible eco-system dedicated to life sciences in Colorado. The distance between the two campuses is about 15 miles and driving time varies from 30 minutes to over an hour, depending on weather and traffic conditions.

Prior to the merger of the two campuses into one large University in 2004, the campuses were independent, with different governing bodies, philosophies and administrative systems. As expected, some of these differences persisted post merger, which has made it difficult for joint programs to work seamlessly, even when the primary parties agree that an initiative is consistent with their respective goals and of benefit to their students. Addressing this issue required what we call a "boundary spanner," an existing entity with enough standing and credibility to interface between the campuses. For the purposes of bioentrepreneurship collaborations, such an

entity already existed in the form of the Business School's Center for Entrepreneurship.

The Center for Entrepreneurship (now called the *Jake Jabs Center for Entrepreneurship*, after a $10million gift from Colorado-based furniture baron Jake Jabs in 2013, henceforth referred to as the Jabs Center) is one of the largest university-based entrepreneurial centers in the country, offering 18 dedicated graduate courses in entrepreneurship and an ever-increasing number of undergraduate courses. These courses are primarily taught in the evening, consistent with the business school's positioning as a professional institution dedicated to educating older individuals who have business experience. The core faculty of the Jabs Center has always supported curriculum initiatives that prioritized cross-campus education as evidenced by current relationships with several non-business departments such as nursing, arts and media, and bioengineering.

It is important to note that the Center for Entrepreneurship, and the now Jabs Center, is a strictly cash funded program relying on student tuition dollars for survival. Further and like any business, it pays "rent" and its share of other overhead costs to the University, and reimburses the Business School for specific services rendered. Survival and sustainability, therefore, depend on generating adequate enrollments to cover operational costs, a fact that applies to all of its programs or initiatives.

The Bioentrepreneurship Program and Certificate

Considering Colorado's interest in biotechnology, which is supported by a burgeoning eco system and world-renowned scientists in the medical school, we saw a clear opportunity for developing a cross-campus educational program that integrated science and business. The Jabs Center director, in consultation with the core faculty, one of whom is a leading bioentrepreneurship expert at the medical campus, recognized this and worked to create what has become known as the certificate in Bioinnovation and Entrepreneurship.

The bioentrepreneurship certificate was designed to enhance collaborative learning. The vision was that all prospective students would take a "core" class (i.e., Fundamentals Of Life Science Innovation), taught by a renowned physician, bioentrepreneur and life-science expert. This class would be taught at the Anschutz medical campus, adjacent to the Fitzsimmons Life Science Park, thereby enhancing interaction between students and bioentrepreneurs and lending an experiential flavor to the program. After completing the requirements for this class, students were expected to take two additional classes from the Jabs Center. Upon completion, students would receive a Certificate in Bioentrepreneurship from the Business School, along with a notation on their official University transcript.

While the Fundamentals Of Life Science Innovation class was required of all students seeking the certificate, the complementary business-school-taught classes were electives. For guidance, students were expected to consult with an advisor who would channel them to classes that made the most sense given their background, experience and aspirations. Thus, the cross-campus certificate program would provide business students with background knowledge in the life sciences and exposure to the medical campus, while life-science students would gain skills and perspective on issues relevant to businesses.

In addition, efforts were taken to ensure that the "core" bioentrepreneurship class was acceptable to the school's MBA program as a general elective, and that students had enough leeway in their curriculum to be able to take the three-course certificate as part of their general MBA degree. Further, students were allowed to choose whether they wanted a certificate in "bioentreprneurship" or in "entrepreneurship" should they have decided after taking the core class that the biotechnology field was not for them.

This simple program, whereby students take only 3 courses to get a certificate, combined with AACSB accreditation and modest tuition fees ($4000), is unique. Further, by allowing anyone with a Bachelor's degree to take the classes as a non-degree student a pathway was created for anyone in the biotechnology community to benefit from these classes and the certificate program.

Process Issues

All this sounded wonderful in theory, but execution was more challenging than anyone could have imagined.

The Graduate School

While the Jabs Center had the mechanisms in place to pay both full-time and adjunct faculty, a significant problem arose when we learned that the certificate's most important faculty member, the renowned bioentrepreneurship researcher teaching the "core" class at the medical campus, could not be paid. The issue was that the medical campus followed a different administrative system than the downtown campus, resulting in bureaucratic hurdles that made it impossible to compensate the faculty member. While the concerned faculty member was kind enough to offer to teach the class without being

compensated, this was not considered to be a long-term, sustainable solution.

Addressing this issue required the aid of another "boundary spanner," an entity with associations on both campuses known as the Graduate School. Surprisingly, following a meeting with the faculty member teaching the bioentrepreneurship course, the Jabs Center director, and the dean of the Graduate School, an arrangement was crafted. The Graduate School dean agreed to pay the professor as long as the tuition revenue from that course was retained. The faculty member was pleased with the outcome, but both the dean and director were left feeling a bit uneasy. The graduate school dean was a little wary that the tuition would not cover the faculty member's cost and the Jabs Center director was wary that tuition revenue would be forfeited if the course became popular. Enrollment uncertainties aside, this unexpected, and very novel, arrangement appears to be sustainable.

Time and distance

As with culturally based customs that go unnoticed until confronted by a different culture, so was the case with the location and times of our classes. Classes at the medical campus are typically held in the daytime, while those in the business school primarily take place in the evenings. The "core" class was taught at the medical school in the daytime, consistent with typical class timings on that campus. However, this daytime class was inconvenient for a majority of business school students who are working professionals with daytime jobs. Many of these students go to work early to be able to take classes that start at 5 pm or 6:30 pm at the business school.

A related issue is the distance between the downtown campus and the Anschutz medical campus. As previously mentioned this is approximately 15 miles and typically takes 30-plus minutes to drive in light traffic and fair weather conditions. However, adding up the commuting time between campuses, the time needed for the class and any class-related activities such as group projects, suggests that a business professional working in downtown Denver would lose a half-day of work to take this one course. Given these time and distance issue, the flow of business school students to the medical campus was modest, far lower than originally expected.

For biotech and medical students, taking classes at night, especially at the downtown location, was equally inconvenient. The majority of them had accommodations in the proximity of the medical campus. Driving downtown, taking long classes (typically 2.75 hours), interacting with group members and then driving back to their homes left little time for homework and recreation. Furthermore, the few who braved these inconveniences found that graduate business education was accretive; meaning instructors typically assume their students have basic knowledge of business concepts. This required additional studying, which also increased the amount of time needed to complete these classes.

Tuition and fees

Realizing the inconvenience to students to take classes at a sister campus 15 miles away, the Jabs Center offered business students a $500 discount for taking the "core" class at the Anschutz medical campus. This incentive had a positive effect in that it increased the *interest level* among business school students in the biotechnology field, and while the scholarship did increase the flow of business students taking the core class, its effect was less than predicted. On an average, this has incented four to five students per year to take the class, about one-half the projected number.

When addressing the tuition issue for business students, a bigger problem arose because our target students in the medical school are charged about half the tuition per course than are business school students. These students could take the "core" class at their normal lower tuition rate (since it was a medical campus class), but had to pay double the tuition to take the two entrepreneurial classes needed to complete the certificate. Further, depending on their home department's degree requirements, there often wasn't enough leeway in their degree plans to accommodate the two business classes required for the bioentrepreneurship certificate. In other words, these students had to pay double the tuition rate for their business classes and often these classes did not fulfill any of their degree requirements.

Realizing the problem, the Jabs Center worked with some medical campus departments (e.g., bioengineering) to create special exceptions that allowed their students to get the certificate by taking the core class, one entrepreneurship class, and an independent study conducted at their home department. Further, the center opened up its general scholarship fund to medical students, resulting in a $500 discount for medical students to take entrepreneurship classes. However, despite all these efforts, the flow of medical or bioengineering students to the business school did not significantly increase.

While the number of business students taking the core class at the medical campus exceeded the number of medical students who took entrepreneurship classes at the Business School, the numbers in both directions were very modest and far less than what was envisioned when the certificate program was created. This has

resulted in non-trivial negative cash flows for the Jabs Center, which as mentioned earlier, relies on a cash-funded business model.

GOALS ACHIEVED

Despite the barriers indicated above, the program's curriculum itself was extremely well received and successful in enabling medical researchers to a) grasp basic business concepts, b) gain useful contacts in the entrepreneurial eco system including venture capitalists and marketing specialists, and c) develop a better understanding of the legal barriers unique to their product and industry. Several of these students participated in the Jabs Center's annual business plan competition, and a few even received prizes. Thus one of the main goals of the certificate, to get medical researchers to understand and appreciate the business lens of innovation, was achieved.

Business students greatly appreciated the opportunity to team up with scientists and understand their environment and eco-system. This helped them to appreciate some of the specific nuances of the biotechnology and bioengineering environment, which in turn led them to dispassionately evaluate opportunities as they teamed-up with scientists on class projects. Reports from business faculty whose pedagogy requires comprehensive business development projects were encouraging as "integrated" teams (i.e., those comprised of business and science students) produced sound business plans with meaningful social implications. These results suggest that the second main goal of giving business students an opportunity to understand the unique world of life-science business creation was also achieved.

Continuous Improvements

The results suggest that the educational vision is being realized, and that the problems encountered are structural in nature, reflecting cultural and administrative dissimilarities between the two campuses and respective colleges. These problems are being addressed as they directly impact enrollment, which affects both the number of students who can benefit from the certificate program and its financial viability. Inspired by the certificate program's positive impact in the most crucial areas of student education, the entire bioentrepreneurship team consisting of the Jabs Center director and faculty, the Graduate School dean, and Dr. Meyers, are committed to improving the biotechnology initiatives across both campuses. Following is a series of activities, either planned or underway, intended to address some of these structural issues as well as enhance the student experience.

- Dr. Inge Wefus, associate dean of the Graduate School, applied for and received an NIH BEST grant to supplement bioinnovation and entrepreneurship offerings to graduate students. As a result, Dr. Meyers, in collaboration with other domain experts, is able to provide at no cost to the students, a series of four mini-seminars in bioentrepreneurship tailored to postdoctorate students at the medical campus.
- The Digital Health Group was created as part of the CITI Digital Health Consortium at the Business School to collaborate with those interested in designing, developing, testing and deploying digital health products and services.[7] This is an excellent opportunity for both science and business students to collaborate on real world projects.
- The 3rd meeting of the Society for International Bioentrepreneurship Education and Research (SIBER) was hosted at the medical campus this past June.
- The core *Fundamentals of Life Science Innovation* class has been "internationalized" by offering a module on International Bio-business and promoting an international trip offered in summer to Ireland. Collaboration with CU Denver CIBER (Center for International Business Education and Research) promises to open more doors in the next few years.
- To meet the time and place needs of students on both campuses, the core class is now offered in a hybrid format. Most of the class is conducted online, but supplemented by a weekly, 1.5 hour long, in-person presentation that is facilitated by a prominent guest faculty who speaks to the week's focal topic. Dr. Meyers is also working on making these interactive sessions available on the Business School campus using real time videoconferencing. Additionally, a number of business faculty have created online courses to meet the growing need for greater time and place flexibility among students who are working professionals. Two classes of

interest to bioentrepreneurship students address entrepreneurial issues in finance and marketing.

- Collaborations are being sought to allow law students to take the core class and have it provide course credit toward their JD degrees. Given the legal issues associated with life science innovations, having laws school students in the certificate program will have a synergistic effect on all students' bioentrepreneurship education.
- The Graduate School is planning to offer a new masters program in Biomedical Sciences and Biotechnology. Three entrepreneurship courses are likely to be part of the curriculum.

DISCUSSION

The certificate program in bioentrepreneurship is fundamentally successful, but continues to face operational challenges as previously noted in areas like administrative inconsistencies, incompatible degree requirements, distance barriers, differential tuition rates and different class timings. These process issues turned out to be far more important than originally thought and have prevented the certificate from benefiting the anticipated number of students. To fully reach the potential market and gain the enrollments needed for the program to be financially self-sustaining, each of these process issues is being addressed as indicated below:

1. While the hybrid format and live videoconferencing innovations are a great aid to accessibility, the core class should be taught at both campuses, in the daytime in Anschutz medical campus, as it is currently scheduled, and in the evenings in the Business School. This will enable students to take the core class at a familiar time without having to travel. The class should be heavily experiential in nature featuring group projects and great bioentrepreneuers as guest speakers. Additional accommodations should be made for law school students if the current attempts to involve these students are successful.
2. Compensation should be made by Jabs Center directly to the faculty. If this can be achieved, it will streamline the agreement with the Graduate School, allowing that relationship to focus on student issues, like expanding the program to other colleges.
3. Since one of the main goals of the certificate program is to provide business knowledge to scientists, two business classes should be offered by the Jabs Center at the medical campus every year. These classes should be provided at tuition rates comparable to other courses taught at the Anschutz campus.
4. All students should be required to attend a daylong capstone class that would include a networking session, and a pitch night. The networking session would enable scientists to meet business students as well as marketers, accountants, and lawyers. The pitch night would involve "elevator pitches" to real venture capitalists and biotech firm executives, with the best concepts being awarded special prizes.
5. To fund this array of classes and tuition discounts, a donor (either individual or corporate) should be secured. Given the student-driven nature of the financial needs, it should not be too difficult to secure a suitable donor, especially if naming rights are provided (e.g., The John and Mary Doe Certificate in Bioinnovation and Entrepreneurship).
6. Science and business students should be strongly encouraged to team up for the purpose of writing an actionable business plan that is submitted to a new biotechnology track (sponsored by a donor) at the Jake Jabs Business Plan Competition. The annual competition is currently open to the students and alumni of universities from Montana to New Mexico. The competition is a high-visibility event attended to by angel investors, venture capitalists, and leading members of the business community.
7. The Jabs Center should seriously consider offering the bioentrepreneurship certificate fully online, and to allow interested people from around the world to take the three classes and receive the certificate. This would open the certificate to a new global audience, making the aforementioned internationalization of the core course more meaningful and relevant.
8. Should there be enough interest, the Jabs Center should set up an office in the medical campus and also offer select courses on site. Clearly several other programs including dentistry, sports medicine, and physician practices can benefit from an integration of business knowledge.

The way forward

The purpose of this article was to discuss the implementation and current status of the University of Colorado Certificate Program in Bioinnovation and Entrepreneurship. Being a new, innovative program, it experienced several significant startup challenges including those that were culturally, structurally and financially based. While all of these issues are being addressed, the program's primary goals of helping: 1) scientists understand and appreciate basic business concepts and form appropriate relationships with business professionals, and 2) business students understand the fundamental nuances of the biotechnology industry, were both achieved.

The main lesson we learned is that execution is as important as inspiration. For those at other Business Schools considering a similar program, the authors would first like to offer their congratulations; the concept itself is worthy and such types of cross-disciplinary educational opportunities are indeed likely to become the wave of the future. However, the authors would also like to encourage the leaders at other Business Schools to learn from our mistakes and consider the following process issues as they develop similar programs:

1. Determine the flexibility each target student group has in its degree plan to accommodate a number of certificate-specific courses;
2. Ensure that all students will have access to all required classes, either by offering them at all relevant locations (in person or by live video conferencing) or by teaching them online;
3. Carefully design the curriculum with consideration of the best faculty;
4. Standardize the tuition for all students to the lowest rates, or have sufficient scholarship funds available to accomplish the same objective;
5. If needed, secure one or more donors prior to program launch;
6. Allocate sufficient funds to cover expected program losses during the first three years; and
7. Plan for future program expansion. Consider options to enhance the courses and consider different formats (e.g., online) as the program expands.

Once you have a sound program, our final forward-looking thought, and one we currently are focusing on, involves integrating the program with the biotech community. It is likely prudent to begin developing relationships with appropriate technology oriented firms early in the process. The objective would be to identify those firms that are able and willing to support your programs and their objectives by: a) being on advisory boards, b) acting as student mentors, c) offering meaningful internships, d) providing scholarships, and e) sponsoring specific program initiatives. With the right vision, students and pedagogy, we believe that this element will bring your program, and ours as well, full circle and make it fully sustainable.

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Legal & Regulatory Update

Which types of bioinformatics inventions are eligible for patent protection?

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ABSTRACT

The field of bioinformatics is flourishing, and strong growth is only projected to continue. Like any cutting edge technology, bioinformatics requires an integrated IP strategy involving patent, trade secret, and copyright laws. The patent system in particular can be a powerful protection for commercializing bioinformatics inventions as long as a corresponding patent application meets certain patent law standards. Recently, the most rapidly evolving of these patent law standards—patent eligibility—came to a crescendo last year when the Supreme Court in *Alice v. CLS Bank* introduced a two-step test for determining whether computer-implemented inventions are patent-eligible. Since then, other courts and the USPTO have applied the test on inventions implemented on a computer and/or using the Internet with fact-dependent results. Here, we discuss how these decisions relate to bioinformatics inventions. We then analyze bioinformatics patents that have recently issued post-*Alice*. While the law remains relatively underdeveloped, it becomes clear that relying on a general purpose computer to perform routine or conventional steps in a claim will not infuse patent-eligibility into a claim. However, bioinformatics inventions remain patentable, especially when the patent prosecution team properly and persuasively presents the technical improvements and commercial embodiments.

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INTRODUCTION

The field of bioinformatics is flourishing, and strong growth is only projected to continue.[1] Like any cutting edge technology, bioinformatics requires an integrated IP strategy involving patent, trade secret, and copyright laws.[2] The patent system in particular can be a powerful protection for commercializing bioinformatics inventions as long as a corresponding patent application meets certain patent law standards. Here, we discuss how the most rapidly evolving of these patent law standards—patent-eligibility—applies to bioinformatics applications.

1 Over the next several years, the global bioinformatics market is projected to grow at over 20% from $4.1B in 2014 to $12.5B in 2020. http://www.finances.com/analyses-and-opinions/analysis-opinions/49771-global-bioinformatics-market-will-reach-usd-12542-4-million-2020.htm.

2 Michael A. Gollin, *Protecting Bioinformatics' Value*, American Chemical Society, October 2004, at 19, available at http://pubs.acs.org/subscribe/archive/mdd/v07/i10/pdf/1004business3.pdf.

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Statutorily, patent-eligibility is broad: "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" is eligible for patent protection.[3] However, the Supreme Court has defined certain exceptions, such as abstract ideas, that are not patent-eligible. The U.S. Patent & Trademark Office (USPTO) assesses the patent-eligibility of bioinformatics and computational biology applications the same as other computer software.[4] When the Supreme Court recently agreed to hear a case regarding the patent-eligibility of a software patent in *Alice v. CLS Bank*,[5] one group had proposed that all software inventions are ineligible abstract ideas. Another group urged the Supreme Court to rule that the abstract idea exception is a coarse filter only rarely to be applied.

In deciding *Alice* in June 2014, the Supreme Court excited neither group. On the one hand, the Supreme Court did find that the challenged software patent was a patent-ineligible abstract idea, but it declined to categorically associate computer software inventions as ineligible abstract ideas. In reaching this outcome, the Court set forth—and subsequent lower court decisions have applied—a test for determining whether patent claims are patent-ineligible abstract ideas.

We outline patent-eligibility of inventions implemented on a computer and/or using the Internet in light of the recent decisions applying this test. We also explain how this relates to bioinformatics inventions. We then analyze bioinformatics patents that have recently issued post-*Alice*. While the law remains relatively underdeveloped, bioinformatics inventions appear to be very much protectable through the patent system. Importantly, some key points can help ensure that an application meets the patent-ineligibility standards.

STEP 1: ARE CLAIMS DIRECTED TO AN ABSTRACT IDEA?

The first step of the Supreme Court's *Alice* test asks, are the claims directed to an abstract idea? The Supreme Court declined to define the term "abstract idea," and even acknowledged that at some level, all inventions are directed to an abstract idea. For this step, the Court focused on preemption: whether the invention seeks to improperly patent building blocks of human ingenuity. If a patent claims broad building blocks, it is directed to an abstract idea.

Supreme Court

In its analysis of preemption, the Supreme Court first generalized the claims at issue—even when the claims recite more than its generalization:[6]

> *[A] method of exchanging financial obligations between two parties using a third-party intermediary to mitigate settlement risk. The intermediary creates and updates "shadow" records to reflect the value of each party's actual accounts held at "exchange institutions," thereby permitting only those transactions for which the parties have sufficient resources.*[7]

After generalizing the claims, the Supreme Court found that the claims were directed to an abstract idea for covering fundamental economic principles.

Federal Circuit

The Federal Circuit—the court that decides patent cases directly below the Supreme Court—has applied *Alice* six times with mixed results. Some decisions have found that the claimed invention is directed to an abstract idea while others have found that the claimed invention is not directed to an abstract idea.[8] For those decisions finding abstract ideas, the Federal Circuit—similar to the Supreme Court—has generalized the following claimed inventions before finding them to be directed to abstract ideas:

- "A process of organizing information through mathematical correlations [that is] not tied to a specific structure or machine."[9]
- "Managing a bingo game while allowing a player to repeatedly play the same sets of numbers in multiple sessions."[10]

3 35 U.S.C. § 101.

4 http://www.uspto.gov/web/offices/pac/mpep/s2106.html.

5 *Alice v. CLS Bank*, 134 S. Ct. 2347 (U.S. 2014).

6 To illustrate this point, the Supreme Court's generalization word count compared to the actual claim language is 49 to 198.

7 *Id.* at 2348.

8 In addition to *DDR Holdings* finding the claims patent-eligible, a majority opinion in I/P Engine, Inc. v. AOL Inc. 576 Fed App'x 982, 995 (Fed. Cir. 2014) did not address subject matter eligibility even though the dissent would have held the claims patent-ineligible as being directed to an abstract idea.

9 Digitech Image Techs. v. Elecs. for Imaging, Inc., 758 F.3d 1344, 1350 (Fed. Cir. 2014).

10 Planet Bingo, LLC v. VKGS LLC, 576 Fed App'x 1005, 1007 (Fed. Cir. 2014).

- "Creating a contractual relationship—a 'transaction performance guaranty'—that is of ancient lineage" even if narrowed to particular types of relationships.[11]
- "The process of receiving copyrighted media, selecting an ad, offering the media in exchange for watching the selected ad, displaying the ad, allowing the consumer access to the media, and receiving payment from the sponsor of the ad."[12]
- "Collecting data, recognizing certain data within the collected data set, and storing that recognized data in a memory."[13]

Different from the above cases, in another case finding patent-eligibility, the Federal Circuit refused to simplify the claimed invention as being directed to an abstract idea.[14] The claims cover an e-commerce outsourcing system that serves a web page to a user with a look and feel of the host web page when a link on the host web page has been clicked by the user. Rather than finding that the claims were directed to an abstract idea, the court reasoned that the claims do not recite a mathematical algorithm, a fundamental economic or longstanding commercial practice. The court found that the claimed solution is necessarily rooted in computer technology to overcome a problem arising in the realm of computer networks. Thus, the court concluded that the case was not as straightforward as *Alice* or other abstract idea cases.

Takeaway for step 1

In the step 1 analysis, courts have generalized an entire invention (even if it involves multiple steps) down to a sentence. And if the invention can be so generalized, the court is likely to find that the claims are directed to an abstract idea. However, distinguishing the claimed invention from mere mathematical algorithms, fundamental economic principles or longstanding commercial practice saved one patent from this finding.

To avoid having the patent generalized to an abstract idea, it is important to frame the invention in a way that is not interpreted as overly broad. Seeking to patent applications of building blocks of human ingenuity, rather than seeking to patent the building blocks themselves, should be a goal. It is also important to avoid a characterization of the invention as a mathematical algorithm. Even if a significant component of the invention is an algorithm, real-world tie-ins applications of the algorithm may be able to avoid a characterization that the invention seeks to patent the mathematical algorithm.

STEP 2: SOMETHING MORE TRANSFORMS NATURE OF THE CLAIMS?

The second step of *Alice* asks, in looking at the individual claim elements and the combination of claim elements, is the nature of the claim transformed into a patent-eligible application (inventive concept)? That is, for patent-eligibility, a sufficient element or combination of elements must ensure that the patent in practice amounts to significantly more than a patent upon the abstract idea itself.

The Supreme Court in *Alice* notably (and maddeningly) did not define what the "more" standard consists of. But the Supreme Court shed some light on what meets this threshold by way of example in *Alice*. The Supreme Court, by analyzing certain previously decided Supreme Court cases, provided reasoning for how its previous cases fit within the new step 2 framework. Subsequent Federal Circuit decisions also shed light on what meets this threshold.

Meets the sufficiently more threshold

- The patent in *Diehr* was "a computer-implemented process for curing rubber that employed a well-known mathematical equation," using the equation in a process designed to solve a technological problem in conventional industry practice.[15] *Alice* explained that the Diehr patent met step 2 because "the curing rubber process used a thermocouple to record constant temperature measurements inside the rubber mold—something the industry had not been able to obtain. The temperature measurements were then fed into a computer, which repeatedly calculated the remaining cure time by using the mathematical equation. These additional

11 Buysafe, Inc. v. Google, Inc., 765 F.3d 1350, 1355 (Fed. Cir. 2014).

12 Ultramercial, Inc. v. Hulu, LLC, 772 F.3d 709, 715 (Fed. Cir. 2014).

13 Content Extraction and Transmission LLC v. Wells Fargo Bank, National Association, 2013-1588, -1589, -2014-1112, -1687, at 7 (Fed. Cir. 2014).

14 DDR Holdings, LLC v. Hotels.com, L.P., 773 F.3d 1245 (Fed. Cir. 2014).

15 *Alice*, at 2358 (citing Diamond v. Diehr, 450 U.S. 175, 177 (1981)).

steps … transformed the process into an inventive application."[16]

- The patent in *DDR Holdings* focuses on the problem of losing visitors to a third-party's website. The patent relates to a host website that sends its visitors to a web page on the outsource provider's server that 1) incorporates "look and feel" elements from the host website, and 2) provides visitors with the opportunity to purchase products from the third-party merchant without actually entering the merchant's website. The Federal Circuit explained, "The claimed solution is necessarily rooted in computer technology in order to overcome a problem specifically arising in the realm of computer networks."[17]

Does not meet the sufficiently more threshold

General Computer Claim

- A general-purpose computer does not supply the inventive concept,[18] especially when the recited computer functionality is generic and limited.[19]
- Instructing the practitioner to implement an abstract idea with routine, conventional activity at a high level of generality.[20]
- Use of a generic scanner and computer to perform well-understood, routine, and conventional activities commonly used in industry.[21]

Purely Conventional

- The computer implementation was purely conventional.[22]
- Each step of the claims was conventional (i.e., using a computer for electronic record-keeping, obtain data, adjust account balances and issue automated instructions). Further, as an ordered combination, the method elements added nothing not present in separately considered claims.[23]

No Real-World Tie-Ins

- A process of gathering and combining data that does not require input from a physical device. A process that employs mathematical algorithms to manipulate existing information to generate additional information without additional limitations to something more than a patent-ineligible data profile.[24]

16 *Id.*

17 *DDR Holdings*, at 1257.

18 In this Supreme Court case, the patent was directed to an algorithm implemented on a general-purpose computer. The computer implementations did not supply the inventive concept because the process could be carried out in existing computers long in use. Gottschalk v. Benson, 409 U.S. 63, 64, 67 (1972).

19 In this recent Federal Circuit case, the patent invoked computers without adding an inventive concept because the computer functionality was "generic and quite limited": a computer receives a request for a guarantee and transmits an offer of guarantee in return. Limiting the use of the abstract guarantee idea to a particular technological environment was held to be insufficient. *Buysafe*, at 1355.

20 In this Federal Circuit case, the patent claims recited data-gathering steps that "added nothing of practical significance to the underlying abstract idea." The steps of consulting and updating an activity log represent "insignificant data-gathering steps and thus add nothing of practical significance to the underlying abstract idea." Nor did having the system actively restrict public access because it was considered "insignificant pre-solution activity." *Ultramercial*, at 715-716.

21 The Federal Circuit ruled that at most, the claims attempt to limit the abstract idea of recognizing and storing information from hard copy documents using a scanner and a computer to a particular technological environment. *Content Extraction*, at 9.

22 In one Supreme Court case, the patent claimed a computerized method for using a mathematical formula to adjust alarm limits for certain operating conditions (e.g., temperature and pressure) that could signal inefficiency or danger in a catalytic conversion process. However, the computer implementation was purely conventional. Parker v. Flook, 437 U.S. 584, 593, 594 (1978). In a recent Federal Circuit case, the patent was directed to a program that is used for the generic functions of storing, retrieving and verifying a chosen set of bingo numbers against a winning set of bingo numbers. The function performed by the computer at each step of the process is purely conventional. *Planet Bingo*, at 1009.

23 *Alice*, at 2359.

24 *Digitech*, at 1351.

Takeaway for Step 2

The "something more" standard will continue to be developed, but some things are clear. First, it helps if any of the elements of the claim or the combination of elements recite novel steps or non-routine components. But reciting a novel implementation of an abstract idea by itself does not turn the abstraction into something concrete. Novel implementations of abstract ideas are especially irrelevant in this analysis if the novel implementation is pre- or post-solution activity. An example of pre- or post-solution activity is if the claim recites a token non-abstract claim limitation, which is not directly related to the invention's solution. Second, it helps if the combination of elements adds something not present in the individual elements. For example, the combination could improve the functioning of a computer or effect an improvement in another technology or technical field. Finally, it helps to limit the claimed invention in a meaningful way so as to not cover building blocks of human ingenuity. For example, it helps to recite a physical device that is at the heart of the invention, especially if a claim is directed to a data structure or data profile.

To achieve the "something more" threshold for computer-related applications, the patent should focus on technological improvements. For example, an application could save CPU processing resources, save time and/or improve memory management. Further, the patent should focus on any improvements that the invention has in another technology. Finally, claiming physical, real-world limitations as a necessary part of the claimed invention may decrease the likelihood that the claim will be interpreted as seeking to improperly patent an abstract idea.

BIOINFORMATICS PATENTS POST-*ALICE*

Since *Alice* was decided, several hundred bioinformatics patents have issued,[25] showing that bioinformatics subject matter is very much patent-eligible. From the issued patents to date, we get a glimpse of the subject matter that the USPTO considers to be patent-eligible in this area.

Example 1

As discussed above, it is important to frame the invention in a way that is not interpreted as overly broad or easily characterizable as an abstract idea. For example, in one patent the claim recites a method for classifying a hepatocellular carcinoma (HCC).[26] The independent claim recites four method elements:

(i) measuring, *in vitro*, nucleic acid expression level of a [specific] group of selected genes,
(ii) determining from said measurement an expression profile of said selected genes,
(iii) calculating ... a distance between said expression profile and a center point in n-dimensional space of six subgroups, each being defined by the presence or absence of clinical and genetic features, and
(iv) classifying said HCC tumor in the subgroup for which the value of the distance is minimal.

This claim is directed to a specific application rather than being directed to an abstract idea, according to the Examiner. In the Reasons for Allowance section of this patent's Notice of Allowance, the Examiner indicated that "the narrowness and specificity of the claims as a whole, which is limited to a very specific group (HCC liver samples from patients with HCC), a very specific set of genes, and six specific classification sub-group features, weighs in favor of patent eligibility."[27]

Thus, specific claim features make it difficult to interpret a claim as overly broad or abstract. Seeking to patent *applications* of building blocks of human ingenuity, rather than seeking to patent the building blocks themselves, should be a goal. Even if a significant component of the invention is an algorithm, it is important to avoid a characterization that the invention is a mathematical algorithm. Real-world tie-ins or biological applications of the algorithm can avoid a characterization that the invention seeks to patent the mathematical algorithm.

Example 2

The next example involves a patent that appears to be directed to an abstract idea, but that whose claims

25 Much like the definition of bioinformatics itself, the classification of bioinformatics patent applications is imprecise. Nonetheless, for purposes of this paper, a bioinformatics patent is defined as a patent either issued in the group art unit at the USPTO that has been charged with bioinformatics applications, 1631, or a patent that references the term "bioinformatics." Thus, the reference to several hundred bioinformatics post-*Alice* could very well be an underestimation because not all bioinformatics patents will be classified in art unit 1631 or reference the term "bioinformatics."

26 U.S. Patent No. 8,935,102.

27 See Notice of Allowance of U.S. Patent No. 8,935,102, page 5, mailed September 5, 2014.

purportedly are transformed into something more, according to the USPTO. One way to transform is to recite non-routine and/or non-conventional steps performed on a computer. This patent is directed to providing glycemic control. The representative claim in part recites:

(v) determining, using the one or more processors, a rate of glycation of the patient based at least in part on the determined correlation between the received mean glucose value information and the received current HbA1C level;
…
(vii) updating, using the one or more processors, the target HbA1C level based on the determined rate of glycation of the patient and the application of the received one or more patient specific parameters to the determined correlation; and
(viii) determining, using one or more processors, one or more parameters associated with the physiological condition of the patient based on the updated HbA1C level, wherein determining the one or more parameters associated with the physiological condition of the patient includes one or more of modifying a current alarm setting, modifying a current target threshold setting related to monitored analyte levels, or modifying a medication intake level.[28]

Immediately before this patent was allowed, the Examiner raised a potential patent-ineligible rejection during an interview.[29] The Applicant subsequently amended the above step (viii) to recite the underlined feature and the application was allowed. Thus, while the Examiner's Reasons for Allowance do not explicitly state the reasons for patent-eligibility, a logical inference is that the Examiner deemed the above claim patent-eligible because of the added feature. The Reasons for Allowance indicates that no prior art shows the above three steps, each of which requires use of a processor.[30] Assuming that this Examiner followed the *Alice* framework (which recent guidelines have required[31]), the Examiner likely considered that the use of a computer processor to determine the above parameters of a patient was unconventional or non-routine because of the novelty of the method steps. Thus, using a computer to perform unconventional steps can transform an abstract idea into an inventive concept.

Example 3

Another patent is directed to a method of identifying, assessing and/or treating cancer growth for a patient.[32] In allowing the claims, the Examiner included an Examiner's Amendment that amended the claims for patent-eligibility purposes.[33] The representative claim (with Examiner's amendments in underlined) recites:

(i) constructing one or more improved quantitative metrics ~~the~~ for metastasis in a selected population of other patients by developing a graphical representation based on a histogram that characterizes a relationship between occurrences of the metastasis and microvessel density information measured for the selected population of other patients, wherein the developed graphical representation includes either a Receiver Operator Characteristic (ROC) curve or at least one of a true positive fraction (TPF) curve, a false positive fraction (FPF) curve, and a Specificity curve, and one or more data points of the graphical representation is associated with at least one threshold microvessel value or at least one threshold biomarker surrogate value;
(ii) acquiring a first set of numeric biomarker data for the patient before having placed a biomarker in the patient;
(iii) acquiring a second set of numeric biomarker data for the patient after having placed the biomarker in the patient;
(iv) determining a set of mean numeric biomarker differences associated with one or more occurrences of the metastasis based on the first set of numeric biomarker data and the second set of numeric biomarker data, wherein the set of mean numeric biomarker differences correspond to biomarker surrogate values for microvessel density information; ~~and~~
(v) predicting quantitative and objective risk for the patient's metastasis based on the biomarker surrogate values and at least one of the one or more improved quantitative metrics for the

28 U.S. Patent No. 8,924,159.
29 See Interview Summary of U.S. Patent No. 8,924,159, September 30, 2014.
30 See Notice of Allowance of U.S. Patent No. 8,924,159, pages 2 and 3, mailed October 24, 2014.
31 http://patentlyo.com/media/2014/12/FR-for-101-guidance.pdf.
32 U.S. Patent No. 8,935,099.
33 See Notice of Allowance of U.S. Patent No. 8,935,099, pages 2 and 3 (November 17, 2014).

metastasis in the selected population of other patients,

(vi) developing a treatment plan for the cancer growth of the patient based on the predicted quantitative and objective risk for the patient's metastasis; and

(vii) administering the treatment plan to the patient to target the specific nodules of the patient.

The Reasons for Allowance explains the Examiner's reasoning for the patent-eligibility of this claim. The Examiner analogizes these claims to the Supreme Court decision *Diehr* (explained above) in which a rubber curing process was held to be patent-eligible:

> *The [amendment] emphasizes the physically realizable aspect of applicant's invention ... by application of an improved treatment to a patient. The practical application of the construction and use of an improved metric in cancer growth and metastasis is realized at the level where the patient receives a new and improved treatment. This ... cannot be achieved absent the reliance of improved quantitative metric as specified in the ... claims. Further, the improvement is expressly coupled to the detailed procedure for constructing an improved quantitative metric.*[34]

This case illustrates two important points. First, in the past 50 years, the Supreme Court has only explicitly affirmed the patent-eligibility of one patent's method claims. And that was in *Diehr*. Any similarities to *Diehr* (i.e., solving a problem that the industry had not been able to solve, and using an algorithm to improve an existing technological process) can help persuade an Examiner of patent-eligibility. After all, next to the patent statute itself, the Supreme Court is the most binding and authoritative source for the USPTO. And because *Diehr* has been good law for over 30 years, Examiners are much more likely to find patent-eligibility when it is persuasively shown that they are on the Supreme Court's side.

Second, this case highlights the importance of real-world tie-ins. The claimed graphical representation includes at least one data point associated with at least one threshold microvessel value or at least one threshold biomarker surrogate value. It appears that the Examiner gave patent-eligible weight to the manipulation of the claimed microvessel and biomarker data because they impacted real-world treatment of a patient. Thus, real-world tie-ins that can show practical application of an idea can supply the inventive concept. Notably, the above claim does not explicitly recite a computer, even though the specification discloses computer use. Instead, the claim appears to inherently rely on a computer through the claimed manipulation of data and graphical representation. Thus, while computer recitations are important in showing patent-eligibility of computer-implemented inventions, it is not the only way.

CONCLUSION

With the forecasted growth of an already hot industry, the patent system will likely remain an important vehicle for protecting commercialization of bioinformatics applications. Even though the patent-eligibility of these inventions is somewhat unsettled, the courts have not precluded computer-implemented inventions from patent eligible subject matter—especially when the inventions include technological improvements. However, relying on a general purpose computer to perform routine or conventional steps in a claim will not infuse patent-eligibility into a claim. This technology requires a more sophisticated approach.

34 See Notice of Allowance of U.S. Patent No. 8,935,099, page 4.

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