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Contents

Editorial

Will personalized medicine be a driver for widespread price controls?

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Keywords: personalized medicine; comparative effectiveness; orphan drugs; economics; pricing

Personalized medicine—prescription of drugs most likely to benefit and least likely to harm individual or groups of patients—promises welcome positive changes to healthcare. It may, however, also have negative sequelae originating from incompatibilities with the current healthcare delivery system and the need for regulatory and policy changes to accomodate personalized medicine.

Personalized medicine is the delivery of medical treatments to individuals or groups based on their susceptibility to disease or response to a treatment. Through the use of genomic and other biomarker technologies, personalized medicine holds the potential to identify which subsets of patients are most likely to benefit from a treatment and also which patients may be suscriptible to certain side-effects. A majority of drugs are effective only in a small proportion of people who take them. Unfortuntely, it is difficult to determine in advance which patitents will respond positively, so many patients are simply prescribed potentially-effective drugs in sequence until a suitable drug emerges. This means that resources are wasted in prescribing ineffective drugs, while patients may see their disease progress unchecked and may also experience uneccessary side-effects from the ineffective drugs. Personalized medicine has the potential to reduce this waste and to speed appropriate drugs to patients, while reducing the prevalence of unecessary side-effects.

A potential downside of the increased use of personalized medicine is that the regulatory system and healthcare policies may not be properly calibrated to accomodate it. For example, the lack of advance knowledge of which drugs may be most effective in a patient creates competition among branded drugs, in advance of generic entry. Consider the cases of top-selling biologics Enbrel, Humira, and Remicade. The three drugs, each of which has worldwide sales in excess of $6 billion, cover overlapping indications. Physicians, payers, and patients, and other prescription-decision incluencers may consider price in deciding which of these drugs to first prescribe for a given indication, increasing price elasticity and keeping prices in check. Because personalized medicine holds the potential to improve knowledge of which drugs may be most-effective and least detrimental for a subset of patients, it holds the potential to create mini-monopolies, decreasing price elasticity, and indirectly facilitating higher drug prices.

Would patients, payers, and society in general gladly pay higher prices for a more streamlined prescription system with increased drug effectiveness and advanced knowledge to avoid some side-effects? Potentially, but this is where the conflict with current regulatory and other policies comes into play.

Well before modern advanced biomarkers and targeted therapies such as Herceptin and Gleevec were developed there was another class of personalized medicines—the treatments for orphan diseases. These diseases are defined by the FDA those affecting fewer than 200,000 people in the U.S., or which affect more than 200,000 persons but not are not expected to recover the costs of developing and marketing a treatment drug. The FDA provides developers of orphan drugs with seven years of market exclusivity—independent of patents—and tax credits.

Drugs for orphan diseases are essentially personalized medicines: they target a small group of patients for whom other drugs are ineffective. Despite the small populations served, orphan drugs can be very profitable. Companies like Genzyme have built their enterprises on these drugs. Genzyme has earned billions of dollars selling orphan drugs, which prices as high as $300,000 per patient per year. They justify their high prices in three ways. Firstly, the high prices are necessary to allow them to recoup R&D investments with a relatively low sales volume (due to the small populations served). Second, the small populations means that the high prices have a relatively small impact on health payer budgets. Finally, Genzyme provides the drug for free to those without insurance or whose payers are unwilling to pay.

The orphan drug program is a valuable one, as it promotes the development for diseases that might otherwise not merit interest by biopharmaceutical developers. Genzyme's pricing system is also rational, rewarding the company for its risky R&D investments while ensuring that needy patients are not deprived access to medicines for lack of financial resources.

A conflict arises when personalized medicine enables relatively prevalent diseases to be divided into subsets of individual orphan diseases, or when personalized medicine provides sufficiently reliable predictions of drug efficacy in subsets of patients that it creates a niche-monopolies.

In the first case, where a relatively prevalent disease is divided into individual orphan diseases, the potential exists for the seven-year marketing exclusivity and tax credits to be granted for drugs that do not technically meet the orphan criteria. This unintended use of orphan drug designations could lead to higher prices for these drugs without merit. The second case, creation of a niche-monopoly by removing uncertainty regarding which of a group of similar medicines is most likely to work in a patient subpopulation, could also see drug prices rise as price elasticity decreases.

Drug pricing is a growing concern among patients, payers and policy makers (it is worth noting that drug expenditures are only a small portion of healthcare expenditures, and that drugs frequently save money by preventing/postponing the need for more expensive interventions). While personalized medicine offers many benefits to patients and other stakeholders, it could also drive the implementation of widespread price controls, a policy change not welcomed by many. As more personalized medicines are developed, the potential exists for an expansion in the number of high-priced drugs. Regardless of whether these high-priced drugs actually have a significant impact on payer budgets or simply serve as fodder for special interests, they could fuel a backlash and strengthen calls for U.S. price controls. The impact would almost certainly extend beyond personalized medicines, impacting the industry as a whole. So, it is worth examining if the current regulatory and policy structure merits amendment to accomodate personalized medicine.

Yali Friedman
Publisher and Chief Editor

Commentary

Innovating in the new austerity

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Keywords: finance, venture capital, innovation, IPO

On its face, the global life sciences sector had one of its best years in terms of fundraising in 2011. The industry raised more than $93.1 billion through public and private transactions, a 25.8 percent increase over 2010. But dissect those numbers a bit and a different story beings to emerge. For openers, debt transactions to fund such things as share buybacks, pay for acquisitions, or refinance debt accounted for 60 percent of the total, or $55 billion. In reality, a relatively modest portion of the total global financings into the sector are going to fund innovation.

The nearly $9.9 billion invested in the sector through venture capital reflected an 8.7 percent increase over 2010. But there are growing concerns about the future role traditional venture investors will play in funding biotech companies. Several life sciences venture capital firms in 2011 announced plans to reduce investment in the sector or exit it completely. That reflects both frustration with regulatory barriers and the weak market for initial public offerings that have made it difficult for venture investors to capture returns on their investments.

Dig a little deeper into the 2011 numbers, and the picture grows grimmer. Early-stage companies have found raising capital increasingly difficult as many life sciences venture firms have shifted their focus to less risky investment of later stage deals. While life sciences companies in the United States raised slightly more than $1 billion in early stage venture financings in 2011, an analysis of those numbers reveals a great concentration of the funding going to just a handful of firms. In 2011, 99 companies raised a little more than $1 billion in series A financings. But just 17 percent of the total number of companies closing first funding rounds accounted for $532 million, or more than half of the total raised. Their average deal size was $31.3 million. The average first funding round for the remaining 82 companies was only $6 million.

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We are in the midst of dramatic changes in the way life sciences companies are funded. The model of funding a company with venture capital leading to an IPO is now the exception rather than the rule for life sciences companies. Venture investors are no longer willing or able to fund companies with an indefinite exit. Instead, they are waiting later to fund companies, building exits into their investments from the start, and looking to innovative technologies other than therapeutics that can address medical and healthcare system needs, but provide a more predictable path to revenue.

The pressure felt by traditional investors is significant. At one end, they have seen a rising regulatory bar that has made it harder for the companies they back to bring products to market. At the other end, payers are putting pressure on pricing and insisting that therapies are not only safe and effective, but provide value. And then there is the IPO market, which has often beaten down share prices before companies ever begin to trade. The 23 life sciences companies that went public between the start of 2011 and the end of the first quarter of 2012 collectively raised 14 percent less money than they set out to raise and had to sell 30.4 percent more shares than they planned to sell at prices that were, on average, 23.2 percent below their target price.

Venture investors are looking to new models of funding. They are partnering with pharmaceutical companies as co-investors and building in exits in which those partners agree to acquire the company should specific milestones be met, as in the case of Third Rock Ventures and Sanofi's $125 million funding of Warp Drive Bio.

In other cases, venture investors are focused on building products rather than companies, funding the development of drugs to a proof of concept stage at which point they can license them to a pharmaceutical company. The venture capital firm CMEA in 2011 established Velocity Pharmaceutical Development, a virtual company that uses a single management team to in-license molecules that have been shelved by pharmaceutical companies because they don't fit in with their changing development strategies. Velocity looks for molecules that can be brought to proof-of-concept in two to three years

for $10 to $15 million per compound and then licensed to another company.

The good news is that as with nature, finance abhors a vacuum. As traditional investment sources have migrated to later-stage opportunities, new sources of funding have moved in to address the need. A host of new initiatives focused on funding translational research and early-stage companies bringing together the public and private sector, particularly with the goal of building life sciences centers in specific locations, have been announced in recent months. In all, Burrill & Company identified more than $2.6 billion in expected funding through nine initiatives announced this year.

The largest of these efforts, a $760 million partnership between Russia's Rusnano and the U.S. venture capital firm Domain Associates, will invest in emerging life sciences technology companies, foster the transfer of technology into Russia, and establish manufacturing facilities in Russia for production of advanced therapeutic products. As part of the effort, Rusnano and Domain expect to co-invest in about 20 U.S.-based healthcare technology companies.

Other initiatives include an effort by the Welsh government to create a biotech hub through an $80 million commitment to what is targeted to be a $375 million fund; a $100 million R&D fund backed by Merck Canada, Lumira Capital, and other venture capital firms to attract pharmaceutical companies to Quebec; and a Wellcome Trust project to invest $317 million in emerging healthcare and life sciences businesses and technologies in Europe in early-stage development with significant potential to grow.

Among the most unusual efforts is a $250 million initiative from Cleveland's University Hospital, which is establishing a non-profit entity to fund and advise physician-scientists on translational research and a related for-profit accelerator that will develop selected compounds to proof of concept. Other efforts, such as the Thiel Foundation's Breakout Labs, provide grants of up to $350,000 to nascent companies with disruptive technology. The grants contain a provision requiring successful recipients to return funds to the organization to help fund future technologies.

Together these efforts reflect broad attempts to forge creative new models for funding translational research and spur development of important new therapies. They also demonstrate that governments across the globe, despite facing fiscal pressure, see the importance of investing in the life sciences to build innovation-based economies that can provide high quality jobs.

We are in a time of austerity. As healthcare costs rise and aging populations and the growing incidence of chronic disease fuel demand, governments and payers are feeling pressure to rein in spending. This is leading to price controls, the increased use of generic drugs, and demands for proof that therapies produce a value that is commensurate with their prices. Whether by governments, payers, or investors, capital today is treated as a finite resource.

For venture investors in the life sciences, that means building investments with a clear path to return in a predictable timeframe. For some, that will mean investing in later-stage deals, investing alongside pharmaceutical companies interested in the technology, or looking beyond traditional diagnostics and therapeutics to new digital health technologies that can address problems such as healthcare access and delivery, changing unhealthy behaviors, and increasing patient compliance.

But austerity can be a friend to innovation. The financial pressures of today are leading to creative efforts to forge new business and financing models. They are driving capital efficiency and putting a proper emphasis on value creation. The discipline austerity imposes is welcome. The result is that companies that fail to pursue true innovation and products that create value will find funding difficult to obtain and markets unwilling to pay premiums.

For those of us who invest in the sector, the good news is that valuations are historically attractive and power at the negotiating table lies with those who have capital. The opportunities before us have never been greater. The need for innovation that can bend the cost curve of healthcare through new ways of access and delivery, improved therapeutic efficacy, or the meeting unmet medical need is being felt around the world. The life sciences provide not only a solution, but also a way for countries across the globe to build innovation-based economies.

Original Article

Innovative biotechnology industry strategies in the U.S.' rapidly evolving payer environment

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ABSTRACT

In 2010 healthcare represented 17.9% of GDP[1]; its cost is growing significantly faster (~5%)[2] than economic growth (~2%)[3]. This growth presents a challenge to all payers, whether they are governments, employers, or individuals. Within healthcare, one of the most rapidly growing areas is "specialty drugs"[4,5] which are frequently biotechnology agents, or drugs for cancer or orphan conditions. This article starts by discussing the issues of specialty drug cost and the challenges payers face in managing specialty drugs. It then presents market structure and firm strategy theories that provide insight into firm behavior in specialty drug categories. Lastly, it discusses possible events and actions that could dramatically change the biotechnology industry and lead to increased value within the U.S. health care system.

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Keywords: payer: cost; market behavior; competitive strategy

INTRODUCTION

Express Scripts (ESI) and Medco are the two largest pharmacy benefit managers (PBMs). Both companies provide annual industry reports,[6,7] which highlight the issue of rapidly growing specialty drug costs.

Within specialty drugs, a few therapeutic classes, which are comprised primarily of biotechnology agents, account for the majority of spending. Additionally, despite low prevalence of these conditions, the growth of spending is also high.[8] Figure 2 shows data from Express Scripts for its beneficiary population—notably four therapeutic categories account for ~60% of specialty drug spending.[9]

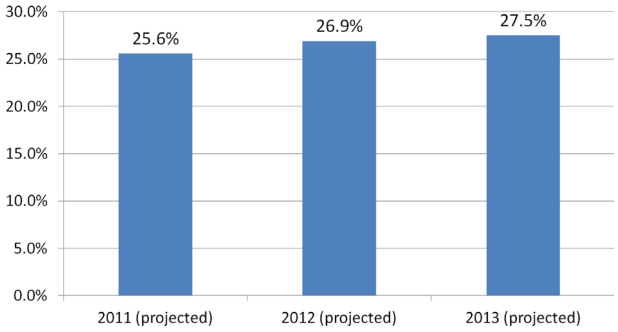

Figure 1: Specialty drug trend
Source: Express Scripts 2010 Drug Trend Report

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Condition	Total Specialty Spend (%)	2012 Trend (%)	Branded Agents
Rheumatoid Arthritis (RA)/Crohn's Disease	28.6%	22.0%	Enbrel, Humira, Simponi, Cimzia, Remicade, Rituxan, Orencia , Actemra
Psioriasis			Enbrel, Humira, Amevive, Stelara
Multiple Sclerosis (MS)	22.9%	31.1%	Avonex, Betaseron, Copaxone, Rebif, Extravia, Ampyra, Gilenya
Pulmonary Arterial Hypertension (PAH)	4.6%	28.8%	Adcirca, Letaris, Retavio, Tracleer, Tyvaso, Venvatis,, Flolan, Remodulin
Growth Hormone Disorders	3.4%	15.4%	Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Tev-Tropin

Figure 2: Leading conditions and branded agents
Sources: EMD Serono Specialty Digest, 7th edition, Express Scripts 2010 Drug Trend Report

Two biotechnology agents for inflammatory conditions, Enbrel® and Humira®, are typically among clients' drugs in terms of total cost.[10] Dr. Gary Owens, Chairman of the Towers Watson RX Collaborative Pharmacy & Therapeutics (P&T) Committee, reported that in his experience, an MS agent, such as Copaxone® or Avonex®, may well also be in clients' top ten highest total cost drugs.[11]

The majority of drugs in the FDA pipeline are specialty agents. In analyzing 150 drugs in the FDA pipeline, Medco estimated that 25 (~17%) are either monoclonal antibodies (MAbs) or therapeutic proteins.[12] A separate but increasingly important driver of specialty drug costs in the U.S. are drugs for orphan conditions. According to a PhRMA 2011 report[13], there are about 460 drugs for orphan conditions in clinical trials or under FDA review. Of these, approximately 40 are MAbs.[14]

These are most frequently new molecular entities (NMEs) or less frequently, new indications for currently marketed drugs. Accordingly, even though on a separate basis, orphan conditions are rare and not costly on managed care's typical measure of cost, a per member per year (PMPY) basis, with all the drugs currently available and in development for orphan conditions, costs are growing, and collectively will be substantial cost drivers. As shown above, pulmonary arterial hypertension is a current example of this.

PAYER MANAGEMENT OF SPECIALTY AGENTS

This article defines payers broadly, with a focus on large third party payers, including managed care organizations (MCOs), the Medicare program, state Medicaid programs, pharmacy benefit managers (PBMs), employee benefits managers, employers and other large payers. In discussions over the last several years with numerous senior decision makers across the spectrum of payers, even though many "blockbuster" oral agents have and are becoming available generically, because of the rapid increase in specialty drug spending, pharmacy costs are approaching 20% of total healthcare costs. Currently, payers' primary methods of controlling specialty pharmaceutical costs are via prior authorization (PA), selection of preferred agents in categories where there are multiple options, use of specialty preferred providers (SPPs), and fourth tiers for non-preferred specialty agents.[15] These 4th tiers may have either a flat copay or coinsurance; commercial plans tend to employ flat ($) copays, whereas Medicare Advantage plans employ coinsurance (%).[16] Express Scripts' report also highlights the financial challenges that biotechnology and other specialty agents place on payers—for "traditional" drugs, including both branded agents and generics, the average 2010 member copayment represented 22% of the total costs; for specialty agents the average copayment represented only 2.6% of cost.[17]

A notable trend is that when products for a particular condition are covered under the pharmacy and medical benefits [for example subcutaneous (RX benefit) and infused agents (medical benefit) as occurs in RA], payers are working to more closely align these benefits in terms of coverage and patient cost-sharing. Typically for products under *both* benefits, managed care pharmacy directors play an active role in making formulary decisions and other policies, as well as projecting and tracking costs. In our experience, pharmacy directors are more cost sensitive than medical directors, not surprisingly given their focus on a specific component of healthcare spending.

In our years of discussions with managed care decision-makers, including at MCOs, PBMs, and employee benefit management firms (EBMs) only very rarely do they perceive differences between agents in established biotechnology classes to be *clinically significant*, e.g. lead to observable differences in outcomes (as opposed to differences that are solely statistically significant, which, by itself, is a much lower bar). Payer industry sources have noted that, even when they perceive that multiple products in a therapeutic class are very comparable in terms of efficacy and safety (and thus in their minds substitutable), biotechnology and other specialty manufacturers have not been willing to offer substantial discounts (≥20%) to gain share. This relative lack of price differentiation is what in fact theories of company behavior given a particular market structure would suggest.

MARKET STRUCTURE AND MARKET BEHAVIOR INSIGHTS

In fact, well-established and documented market structure and firm strategy theories provide insight into how

and why pricing is how it is in the multiple specialty drug therapeutic categories.

A first mover or "innovator" biotechnology agent develops; at this point in time, the market structure may be considered a monopoly, simply as a matter of terminology. This may either continue, for example in smaller markets, or where it is very difficult to develop additional agents in the therapeutic class. Alternately, specialty drug categories typically transform into oligopolies, e.g., where there are several agents competing within a given "space," in this case therapeutic class, such as agents to treat inflammatory conditions and MS. This may even be true of orphan conditions, as it is with PAH.

Several leading market structure theorists provide insight into market structure of oligopolies, and the implications for the biotechnology industry.

In *Competitive Strategy*[18], Dr. Michael Porter identifies market structure factors that contribute to the biotechnology industry's typical oligopolistic structure on a therapeutic class basis; tumor necrosis factors (TNF) for inflammatory conditions are an example of this. There are major barriers to entry into the biotechnology industry, which protect competitors that are in the market. These factors include economies of scale, capital requirements, cost disadvantages independent of scale (such as superior research and development expertise) and government policy (such as FDA approval requirements). Additionally, firms typically file a number of patents, to protect anything that may be proprietary, as well as presumably to block competition. One estimate of patent protection as a competitive strategy for the pharmaceutical industry is that it increases costs by 30%[19]; for biotechnology agents, the cost increase is likely to be significantly higher, given the complexities related to research, development, and manufacturing of these agents.

In *Industrial Market Structure and Performance*[20], Drs. F. M. Scherer and David Ross discusses the structure and behavior of oligopolies, industries in which there are relatively few firms, with, in their terminology, over 40% of share held by ≤ 4 firms[21], as is typically the case for therapeutic classes in which biotechnology agents compete. Scherer comments that "when market concentration is high, the pricing decisions of sellers are interdependent… perceptive managers will recognize that their profits will be higher when cooperative policies are pursued than when each firm looks after its own narrow self-interest… even in the absence of any formal collusion among firms, we should expect tightly oligopolistic industries to exhibit a tendency toward the maximization of collective profits, perhaps even approaching the pricing outcome associated with pure monopoly."[22] Coordinated behavior can still occur such as via price leadership, which may either be led by a dominant firm, or be barometric, based on market conditions.[23] Scherer notes that "the U.S. law is more permissive with respect to subtler forms of conduct that could have the same effect as explicit agreements."[24]

Table 1: Institute of Medicine comparative effectiveness research priorities

Quartile	IOM comparative effectiveness priorities
1	Compare the effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory diseases, including Crohn's disease, ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis.
2	Compare the effectiveness (including effects on quality of life) of treatment strategies (e.g., topical steroids, ultraviolet light, methotrexate, biologic response modifiers) for psoriasis.
3	Compare the effectiveness of different treatment options (e.g., laser therapy, intravitreal steroids, anti-vascular endothelial growth factor (anti-VEGF) for diabetic retinopathy, macular degeneration, and retinal vein occlusion.

The entry of "generic" competition, which has transformed and greatly lowered the costs to payers of pharmaceuticals with the patent expirations of "blockbuster" agents, may well not be as powerful a force for lowering costs in the biologics industry. The Patient Protection and Affordable Care Act (ACA) of 2010 grants biotechnology agents a 12 year period of market exclusivity, rather than the shorter exclusivity period for which the Administration advocated. Another challenge is that the U.S. regulatory pathway for "biosimilars" is unclear, potentially delaying the entry of biosimilars until 2014.[25] According to Express Scripts, "Most biosimilars will not be A-rated so automatic substitution will not occur."[26] Also, under the Biosimilars Act, the period of exclusivity for the first marketed follow-on biologic (FOB) depends on a number of factors, and can range from 12 to 47 months, further constraining competition.[27]

However, as Professor Scherer discusses, there is long-term substitutability between different alternatives. For example, in travelling between Washington DC and New York, there are the options of car, train, plane and now even buses. In beverage packaging, manufacturers have the alternatives of plastic, metal, glass and even laminated cardboard. In treating hypertension, beta blockers, ace inhibitors, calcium channel blockers, and diuretics—for which each class has multiple agents, including generics—are used. There may even be alternative therapeutic modalities; as shown in Table 1, several Institute of Medicine (IOM) Comparative Effectiveness Research (CER) priorities include biologic agents.[28]

THE NEW WORLD: POSSIBLE OR IN FACT LIKELY?

Payer-driven changes

There are environmental changes occurring in the payer world, which will give payers more power. For employers, one is the high rate of unemployment ~8-9% (and also underemployment (~15% total).[29] Slack in the employment market provides companies with more power in determining wages and benefits. Notably, workers' income is also relatively stagnant; in 2010 the average wage index was $41,674.[30] As Figure 3 shows, workers' income has remained relatively stagnant, while costs of healthcare (and this healthcare benefits) have risen sharply. In the words of Helen Darling, President and CEO of the National Business Group on Health, "workers have been giving their (pay) raises to the healthcare system for years."[31]

Thus, the high cost of healthcare has a dramatic impact on employees in its impact on worker income, and potentially may lead to an impetus toward beneficiaries selecting lower cost alternatives or forgoing treatment they perceive as not absolutely necessary. Ultimately individual Americans, not just large third party payers, will face the rising costs related to the increasing number of biotechnology agents.

In 2014, the Patient Protection and Affordable Care ACT (ACA) expands health insurance to people and small businesses that may either not have health insurance currently, or for whom it is very costly. If the individual mandate and the expansion of Medicaid to 400% of the Federal Poverty Level (FPL, $43,560 for an individual, $89,400 for a family of four[32]) are not overturned by the Supreme Court, which heard cases related to the ACA in March, Medicaid managed care, and managed care through the Health Insurance Exchanges (HIEs) will grow substantially in 2014 and thereafter. Notably, the Institute of Medicine (IOM) stressed that "affordability" should drive how the essential health benefits for these new HIE plans should be defined. Drugs are defined is one of the essential benefits; if this includes biotechnology, and how specifically this is defined, will be another issue.[33] Payer industry experts[34], note that state Medicaid programs and Medicaid managed care plans are already "more aggressive" than are commercial plans. They expect this to continue with the expansion of Medicaid managed care and that the MCOs in the HIEs will also be more aggressive in managing costs, due to the need to maintain affordability and increased pressure on margins.

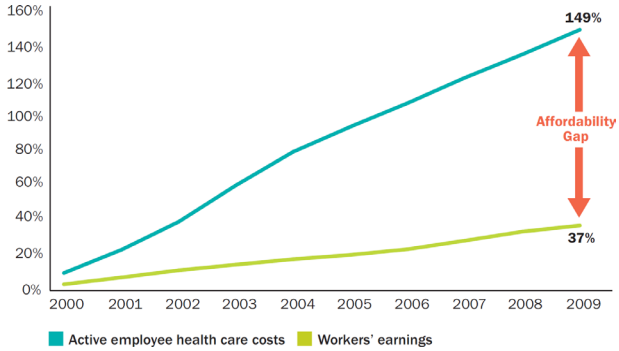

Figure 3: The growing affordability gap

Sources: Towers Watson Health Care Cost Survey 2010 (active employee data) and Bureau of Labor Statistics, seasonally adjusted data from the Current Employment Statistics Survey August to August, 2000 – 2009
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Opportunities for industry

So we expect a much more challenging payer environment, as shown in Figure 4. We believe industry players can and should "respond" first, e.g. proactively adapt—and that this presents a tremendous opportunity to "players" or potentially "teams of players" that do so.[35]

In a number of ways, particularly related to manufacturing (which includes development for larger, later stage clinical trials as well as after FDA approval) if not in all cases, as illustrated in Figure 5, the complexities of biotechnology manufacturing are lowering. One reason is the increasing use of organic sources, which can be consistently monitored, and typically have higher yield than synthetic chemicals given the site specificity of MAbs and versatility of biotechnology.[36] The difficulties facing production of MAbs, which are the most prevalent type of biologics, is primarily determined by the separation, maintenance of tertiary and quaternary structure, and quality maintenance in prevention of denaturation.[37] All of these issues are presently being addressed, with improvements occurring fairly rapidly. Additionally, related to research speed and productivity,

Macroeconomic Factors	Industry Specific Factors
•Fed/state gov't fiscal realities *"A strong wind's gonna blow"* •Control of the White House & Congress •US vs. international economic environment	•Further employer benefit design changes to control cost •Further reductions in employer-based insurance (retirees, et al) •ACA: Medicaid expansion, HIEs •Specialty manufacturers' competition for limited access •Struggles between different provider types for funding •CMS/CMMI changes •FOB introductions, pricing •Increased scrutiny of industry

Figure 4: U.S. private sector management of specialty drugs: 2014 and beyond

Source: Biotechnology Healthcare

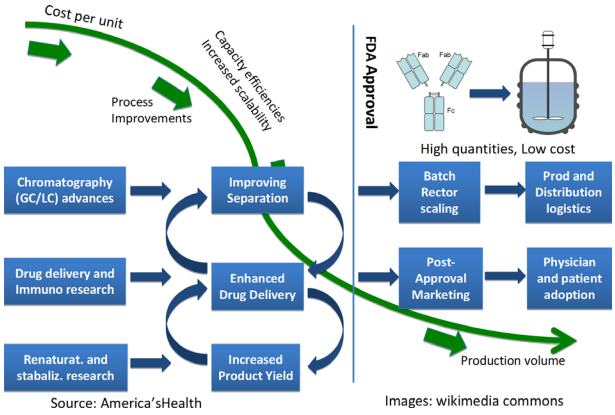

Figure 5: Manufacturing costs and quality
Source: America's Health

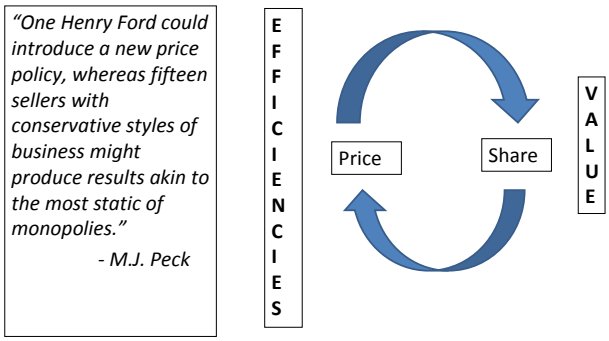

Figure 6: Potential market behavior change
Source: America's Health

developmental tools such as recently introduced Ultra Performance Liquid Chromatography (UPLC) and Mass Spectrometry techniques represent significant advances.[38] The high degree of substrate binding specificity and general efficacy of emerging biologics more than account for the difficulties in their separation and delivery, with greater advances in delivery systems pending.

At the same time, it is truly notable how many companies have or are entering the biosimilar industry, which itself suggests very high profitability as well as that the entry barriers of biotechnology development and manufacturing expertise and cost may well be lessening. It also means that substantial extra biotechnology industry expertise and capacity has and is being developed. It is also very interesting that unusual partnerships, involving nonpharmabio companies, such as Samsung, Hanwha Chemical and Fujifilm, are occurring.[39]

POTENTIAL FOR FUTURE CHANGE

Notably, the genesis of this article was an idea that the price structure of the biotechnology industry could be changed, as shown in Figure 6, whether by current companies or new entrants, as well as by concurrent changes in the payer environment.

The gain for a biotechnology or other specialty agent that is currently low share or in development in an *established* class, particularly when manufacturing economies of scale come into play and manufacturing efficiencies are found and implemented wherever possible, could be very favorable.

Jim Kenney[40], Pharmacy Operations Manager at Harvard Pilgrim Healthcare, reviewed the currently available classes with multiple biotechnology agents, looking specifically for classes where there were are at least several clinically comparable agents, and agents with lower share for which it would make sense for either the manufacturer or another entity to partner with payers to lower costs and drive share, thus substantially improving value. In the TNF class, Jim identified Cimzia as indicated for both RA and Crohn's; and that in these two indications, it is clinically comparable to other agents. As a lower share product, it could be a strong candidate for a strategy of lowering cost, and working with payers to drive market share. There are also multiple agents for MS. Jim noted Rebif as a product that has moderate share but could also be a valuable play for a cost-share play. Dr. Gary Owens, the former Senior Vice President of Medical Management of a 3 million member Blue Cross plan, as well as chairman of the Towers Watson RX Collaborative Pharmacy and Therapeutics (P&T) Committee, concurred that these types of strategies, and then employing a price/payer driven strategy to drive share and sales is workable in this cost-challenged, value conscious world.

Another therapeutic category where there are opportunities is hepatitis C, in which a number of available treatment options. New protease inhibitors are coming to market, which will be used in combination with current agents to substantially improve outcomes. Managed care payers will be looking for regimens that lower their overall costs for these biotechnology combination therapies and provide improved outcomes.

Pricing changes should be in products' average wholesale price (AWP), rather than discounts or rebates to a particular payer. This would provide benefits to patients [for example those who have coinsurance or high deductible health plans (HDHP/CDHP)[41]], as well as greater transparency, and reduced administrative burden for patients and payers.

Payers will be key in helping drive the biotechnology and specialty drug industry to a lower pricing structure. One payer strategy could be not only having a PA requirement, but also explaining the reason for it, and providing patients and doctors with comparative information, including costs, of the preferred agent and the alternate requested agent. Particularly with the increasing number of biotechnology agents, and that currently

there are multiple drugs available in established specialty classes, moving to coinsurance (% rather than $ cost-sharing) for the fourth tier—non-preferred brands—or having substantial differences in cost-sharing, could also drive share to preferred agents that are significantly lower cost. In categories like inflammatory conditions[42] or MS[43], where there may be adherence problems, if a manufacturer reduced its price by ~40% compared to the therapeutic class average, the payer could share the savings with patients for example via second tier (preferred brand) status, or no copays on physician visits. Additionally, physicians could be financially rewarded for a higher level of patient care leading to improved adherence and/or improved outcomes, for example fewer hospitalizations for MS patients.

A new strategy to substantially increase the share and sales of a clinically comparable product, via significantly lowering cost *and* working with payers before and after product launch, as well as communicating with physicians and patients, could not only be highly innovative, but also remunerative. A Booz & Company report illustrates that pharmabio companies are aware of the payer-driven challenges, many are expecting to increase their espenditures marketing to payers, change pricing strategies.[44] At the same time it indicates that a substantial number (29%) of pharmabio companies do not engage payers until after Phase III.[45] New strategies could also help to create a branding quality that explicitly incorporates clinical factors of effectiveness, safety and side effects and costs, and thus value. In the current United States economic and healthcare environment, a strategy of value, both in pricing compared to other biotechnology agents in the same class as well as cost-effectiveness, well and widely communicated, and consistently implemented may well not only resonate, but also relatively quickly lead to rapid market share gain.

Innovative business strategies have been used in a number of other industries current manufacturers, Follow-on Biologic (FOB) manufacturers, or new industry entrants could employ innovative strategies. For currently available agents, or agents in late stage development, a benefit is that the market creation and R&D work entailed would have been done, so that as a challenge and issue in this oligopolistic market would be overcome. As a parallel case, Vizio, a South Korean company worked with manufacturers of flat panel televisions, and Costco, one of the highest volume retailers in the United States, to enter and quickly gain share in the flat panel television market. For biotechnology agents also, scale and lowering barriers would be very important. Reducing these challenges, for example via purchasing a marketed agent or one in late stage development (or some form of rights). and working closely with major payers for "pull through" in terms of market share, would be key.

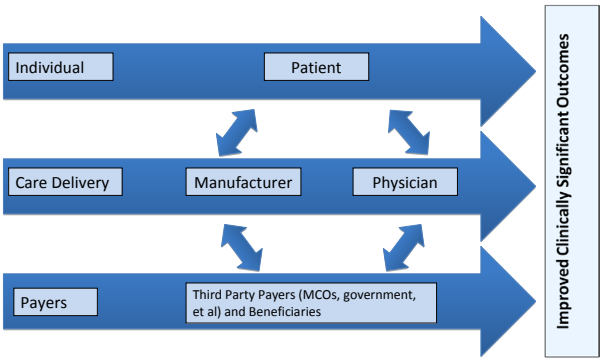

Figure 7: Partner-based strategies
Source: America's Health

Having a laser focus on manufacturing efficiencies, and quickly incorporating new advances to drive costs lower as technologies improve, potentially with a multi-plant strategy or working with FOB manufacturers that can convert existing capacity, could be another strategy to create value relative to other products in the therapeutic class. As products are approved for additional conditions, additional manufacturing efficiencies can also be created. Another possible strategy which could be particularly beneficial for new products could entail working with the FDA and CMS. As with the erythropoietin stimulating agent (ESA) class, where CMS's draft National Coverage Decision (NCD) followed an FDA change in the agents' indication within days, CMS and FDA have shown an ability to work together, or at least in parallel, and have also expressed a desire to jointly work with manufacturers.

A challenge for a new or existing agent to capture share in a particular therapeutic class is that patients and physicians may of course have strong perceptions of products that they are currently using. This is one reason why messaging strategy, wide communication and consistent implementation are so important. Our sense is that "consumers" don't really understand pricing in the biotechnology industry and its contribution to what they *do* understand, the onerous cost of their healthcare benefits, and the rising total cost of health care in the United States. A parallel for physicians is that their reimbursement rates for Medicare, as determined by the Resource-Based Relative Value Based System (RBRVS) have remained fairly stable, but in the last several years, increasingly large payment cuts have been "mandated," but then rolled back by Congress at the last minute. So, physicians are, by and large, another interest group that has competing interests with the biotechnology/specialty pharmacy industry.

However, in general, price transparency is increasing, for example via the internet for consumer products. Amazon is of course a company that has employed this to

Figure 8: Audiences for a specialty drug value message
Source: America's Health

lower costs in its initial industry, books and music, and move on to become a purveyor of many other products. It is becoming much easier to comparison shop, for example via Expedia, ebay, cars.com, travelocity, Edmonds.com and many more companies. *Consumer Reports* is another way that people can use to "comparison shop" over 25 drug categories, with all reports available for free on the web.[46]

This may well also be the type of area where a manufacturer would want to have a consistent strategy across brands, e.g., clinical quality and favorable cost, leading to value. A true value strategy and message "talk the talk, and walk the walk," consistently implemented and conveyed effectively across the spectrum could also be powerful.

CONCLUSION

The US economy and Americans have suffered significant blows, and a major turnaround is not expected in the short-term. The cost growth of healthcare to virtually all payers, and specifically specialty drug spending growth at 20%+ annually, is unsustainable. Additionally, the ACA, if implemented, will expand the beneficiary pool, but will also give MCOs and Medicaid programs more power, as well as powerful incentives for affordable care. For companies that are willing to adapt, there are substantial opportunities. Loosely translated, a Chinese proverb states, "A crisis is an opportunity riding the dangerous wind."[47] Biotechnology industry participants that show they understand the challenges payers face and adopt innovative business strategies now, rather than wait until the proverbial shoe drops, may well stand to gain in the medium and longer term. Innovation in business strategies, such as:

- Working with major governmental and private payers
- Considering value in pricing
- Creating manufacturing efficiencies and scale advantages wherever possible
- Messaging effectively to multiple audiences, can be as, or even more, powerful than clinical innovation.

REFERENCES AND NOTES

1. Louise Radofsky. Wall Street Journal, Tuesday January 2012. page A2
2. http://www.prnewswire.com/news-releases/us-healthcare-costs-annual-growth-rates-increase-in-october-2011-according-to-the-sp-healthcare-economic-indices-135655078.html
3. The Economist, December 17th, page 14 (all three statistics)
4. The definition of specialty drugs that Express Scripts used in developing its data (and used in a chart documenting growth in specialty spending in Figure 1) data is injectable, infused, oral or inhaled drugs that have one or more of the following key characteristics: requirement for frequent dosing adjustments and intensive clinical monitoring to decrease the potential for drug toxicity and increase the probability of beneficial treatment outcomes; the need for intensive patient training and compliance assistance to facilitate therapeutic goals; limited or exclusive product availability and distribution; specialized product handling and/or administration requirements; cost in excess of $500 for a 30 day supply.
5. The EMD Serono Specialty Digest, 7th Edition reports that "80% of payers typically classify a drug as specialty if the average monthly cost exceeds $1,200 and may include other factors, such as whether the product treats a rare disease, requires special handling, has a limited distribution network, or requires ongoing clinical assessment and monitoring or response and/or side effects." Page 10. Accessed from http://specialtydigest.emdserono.com/ on January 9, 2012
6. Express Scripts 2010 Drug Trend Report. Accessed from http://www.express-scripts.com/research/researc/dtr on January 8, 2012
7. Medco 2011 Drug Trend Report accessed from http://drugtrendreport.com on January 8, 2012
8. ESI reports prevalence of RA as 0.22%, and MS at 0.11% prevalence within its covered population.

9. Express Scripts 2010 Drug Trend Report. Page 68. Accessed from http://www.express-scripts.com/research/researc/dtr on January 8, 2012
10. Interview conducted with Jim Kenney, also supported by Express Scripts 2010 Drug Trend Report, accessed from http://www.express-scripts.com/research/researc/dtr on January 8, 2012
11. Interview with Dr. Owens January 5th 2012.
12. Medco 2011 Drug Trend Report. Page 37. Accessed from http://drugtrendreport.com on January 8, 2012
13. 2011 Orphan Drugs in Development for Rare Diseases. Pharmaceutical Manufacturers of America (PhRMA)
14. Ibid. Search for monoclonal antibodies (MAb) in report itself.
15. EMD Serono. EMD Serono Specialty Digest, 7th edition Managed Care Strategies for Specialty Pharmaceuticals. Page 10. A three tier cost-sharing system is typical, with generic agents as first tier (lowest copay), preferred brands as second tier, and non-preferred brands as third tier (higher copays). Some plans have added fourth tiers typically for more expensive drugs, such as specialty agents.
16. Ibid
17. Express Scripts 2010 Drug Trend Report. Accessed from http://www.express-scripts.com/research/researc/dtr on January 8, 2012
18. Dr. Michael E. Porter. Competitive Strategy Techniques for Analyzing Industries and Competitors. The Free Press. 1998, pages 7-13.
19. Shenkar, Oded. Copycats how smart companies use imitation to gain a strategic advantage. Harvard Business Press. Page 60. Chapter 3, footnote 33. 2010
20. Dr. F.M. Scherer, Dr. David Ross,. Industrial Market Structure and Economic Performance, Third Edition. Houghton Mifflin Company. 1990.
21. Ibid, page 32
22. Ibid page 226
23. Ibid, pages 248-249
24. Ibid, page 352
25. John Carroll. Everyone Wants in, but with no Ground Rules, the Biosimilar Business Remains Elusive/ Biotechnology Healthcare. Fall 2011. Page 12.
26. Express Scripts 2010 Drug Trend Report. Page 5. Accessed from http://www.express-scripts.com/research/researc/dtr on January 8, 2012
27. Joanna Brougher, The Biosimilars Act: Promoting or Discouraging the Development of Generic Biologics? Biotechnology Healthcare. Winter 2010. Page 22.
28. Institute of Medicine of the National Academies. 100 Initial Priority Topics for Comparative Effectiveness Research. Accessed from www.iom.edu/.../ComparativeEffectivenessResearchPriorities.aspx
29. The Economist, December 17th, page 14 (all three statistics)
30. http://www.ssa.gov/oact/COLA/AWI.html
31. Biotechnology Healthcare, Spring 2011. Page 22. Interview by Sarah Collins.
32. http://liheap.ncat.org/profiles/povertytables/FY2011/popne.html
33. Michael Dalzell. How will Biologics Fit Into Healthcare Reform? Biotechnology Healthcare. Winter 2011. pages 6 – 10.
34. Interview with Debra Stern, Vice President of Rxperts, January 5, 2012. Comments also by Kip Piper, former State Health Commissioner for Wisconsin. Both are long-term consultants in the managed care industry.
35. By "players" we mean individual companies or teams of companies. The first could be likened to a chess player, the latter to a basketball team.
36. Henry G. Grabowski, David B. Ridley, Kevin A. Schulman. Entry and Competition in Generic Biologics. Managerial and Decisions Economics 28 (2007): 439-51.
37. Annabel Keuk, Brian A. Hazelman. Immune-mediated Inflammatory Diseases and Biologic Therapy: A Medical Revolution. Postgrad Medical Journal 83 (2007) 251-60
38. Ian A. Sutherland. A Review of Liquid-liquid Chromatography Using Aqueous Two Phase Solvent System. Current Opinion in Drug Discovery and Development 10 (2007) 540-49.
39. John Carroll. Everyone Wants In, but with No Ground Rules, the Biosimilars Business Remains Elusive. John Carroll. Biotechnology Healthcare. Fall 2011, page 13. accessed from http://www.biotechnologyhealthcare.com/
40. Interview conducted July 11, 2011
41. High deductible or consumer driven health plans have high annual deductibles such as z$1,000 - $5,000 per beneficiary, that must be met before plan cost-sharing begins.
42. Express Scripts 2010 Drug Trend Report, Pages 65 & 67. Accessed from http://www.express-scripts.com/research/researc/dtr on January 8, 2012
43. Ibid, page 67
44. Booz&co. Pharmaceutical Sales and Marketing Trends 2011 – Key insights. Published February 2011. pages 3,5, 6 and 7.
45. Ibid, page 8.
46. http://www.consumerreports.org/health/best-buy-drugs/drug-report-archives.htm
47. http://thinkexist/quotation/a_crisis_is_an_opportunity_riding_the_dangerous/182149

Original Article

Biotechnology in Argentina: Development and resources

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ABSTRACT

Biotechnology related developments in Argentina have gained momentum in the past few years. The creation of the Ministry of Science, Technology and Innovative Production in 2007 that focuses on high-tech growth in technology related fields including biotechnology, demonstrates the public sector commitment to a field with a thriving business sector and promising improvements in research and development. By embracing its agricultural advantage and investing in research and innovation, Argentina has seen its stock of biotech companies grow to 120, of which 90 percent are domestic small and medium size. Today, biotechnology researchers in Argentina engage in international collaboration with other scholars and globally recognized institutions and the country has bilateral agreements with other countries to support biotechnology related research and development. There are many governmental and non-profit organizations that are influential in shaping Argentina's vision on biotechnology. Although the government places importance in providing support in biotechnology research, innovation and investment, the paper argues that the rapid growth trends in the industry requires biotechnology to become higher on the national agenda. The lack of a royalty collection system, the absence of patent protection, and the inadequate sources of venture capital still remain as important problems. Attracting new forms of foreign capital, higher investment in infrastructure, building on existing regional and global networks in research and development, are all important areas for improvement to advance biotechnology in Argentina.

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INTRODUCTION

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Traditionally focused on its comparative advantage in primary resource extraction and exportation, the period of import substitution industrialization that lasted until the 1970s witnessed the major Latin American economies focus their efforts on the cultivation of a vibrant industrial sector. Due to a

series of external events and internal structural problems, including oil price increases and a series of Volcker shocks during which the United States raised its interest rate a number of times, many Latin American economies became mired in an unsustainable burden of debt. Thus, the system of import substitution industrialization became untenable and national subsidies for bloated industries were dropped. The 1980s were a lost decade for many Latin American countries as they shifted back to their traditional comparative advantage, natural resource exploitation and the cultivation of primary commodities.

This regression to a dependence on the export of primary commodities occurred simultaneously with a rapid development of technological capacity in the United States and Europe. The rise of modern biotechnology has been one part of these recent technological advances, and one that Latin American countries, namely Argentina and Brazil, have taken advantage of in order to add significant value to their booming, resource-rich economies. In a broad sense, biotechnology deals with the application of science and technology to living beings, their parts and their products in order to modify their living and non-living genetic makeup in the production of knowledge, goods and services.[1] The development of a vibrant biotechnology sector requires not only public and private research and development, but a complex web of institutional support and finance mechanisms as well.

Biotechnology exists at an important nexus between basic science and technology. On one hand, it involves technological advances that offer important commercial opportunities, and on the other, it seeks to develop scientific fundamentals. The division between science and industry no longer exists as the production of knowledge occurs in private laboratories just as it does in universities and public institutions.[2] Biotechnology under the general life sciences industry has been recognized as one of the most promising industries in the contemporary knowledge economy due to its capacity to contribute to new discoveries, add high-skilled jobs and its ability to create synergies with other important high-tech sectors including nanotechnology and information and communication technologies.[3,4]

Many countries are now looking into biotechnology as a major source of global economic competitiveness. Argentina is one of those countries that recognizes the importance of biotechnology in relation to its environmental assets, research and development structure and policy environment. This paper explains the biotechnology environment in Argentina in relation to its resources and innovation structure.

BIOTECHNOLOGY BUSINESS ENVIRONMENT IN ARGENTINA

Commitment to biotechnology results from the global commitment to heal, fuel, and feed the world. [5] Biotechnology and life sciences are perceived as industries that provide the tools for issues of global significance related to reducing health care costs, providing food security, and creating renewable energy sources. Many country governments are providing funds and try to attract global and local investment opportunities in biotechnology. For example, the central government of India launched a US$2.2 billion venture fund to support drug discovery and research infrastructure development projects in 2010. Singapore's government is expected to spend US$12.5 billion on research innovation in biotechnology over the next five years, which represents a 20 percent increase compared to the previous budget.[6] Countries like Israel, which lack natural resources, place emphasis on human capital for success in biotechnology. Israeli Ministry of Foreign Affairs reported in 2010 that the country creates more medical devices per capita than any other country.[7] In Cuba, where sanctions are in effect, biotechnology industry continued to flourish with accomplishments in recombinant proteins, synthetic peptides, monoclonal antibodies, antigens, and developing generic drugs.[8]

Argentina is one of those countries that recognize the importance of biotechnology for its economic growth. With many accomplishments especially in agricultural biotechnology, Argentina is recognized as a regional leader in Latin America. Argentina is one of the nine countries in the world that has the capacity to clone animals.[9] Argentina is also reported as the first Latin American country that developed two generations of genetically modified cows that produce Human Growth Hormone.[10] In recent years, Argentina has had much advancement in its governmental policies and research and development activities focused on biotechnology.

Argentina has a strong tradition in research and development. The country has three Nobel Prize winners in science: Bernardo Houssay received a Nobel Prize in Physiology and Medicine in 1947, Luis F. Leloir won the prize in 1970 in Chemistry, and Cesar Milstein received a Nobel Prize in Physiology and Medicine in 1984. Ministry of Science, Technology and Innovative Production reported that in 2008, Argentina had the highest full-time equivalent (FTE) researchers as a fraction of the labor force compared to Brazil, Chile, Mexico, and Spain. Between 2006 and 2008, the ratio of published papers in international refereed journals divided by the number of FTE researchers increased percent.[11]

Despite the strong tradition of Argentina in solid basic science, the country lacked in commercialization of scientific discoveries. In the past, commercialization was

deemed rather unethical; creation of universal scientific knowledge was seen as the priority. This perspective set back the growth of applied sciences and industrial biotechnology in Argentina for many years and resulted in a large exodus of scientific professionals outside the country. During the current administration, this brain drain was reversed up to a certain point.

Developments in biotechnology in Argentina started in early 1980s with production undertaken by local companies. In 1982, a Biotechnology National Program was launched, which demonstrated the public sector commitment to biotechnology. Bilateral agreements were signed with Brazil, France and other countries in the European Economic Community. In mid 1990s, the financial crisis slowed down this activity.[12] In Argentina, most of the local pharmaceutical companies and other farming activities have been family owned enterprises. For a while, the market for these companies have been controlled by a small group of powerful families, such as Bago Laboratories, Finadiet, Elea Laboratories, Cassara Laboratories, Biosidus among others.

During the recent years, there are new developments in the Argentine biotechnology industry that signal growth.[12] The most important development is that in 2007, Argentina created the Ministry of Science, Technology and Innovative Production that specifically deals with the high-tech growth in industries including biotechnology. The ministry's targeted policies aim at increasing the tech value of local production, encourage innovative solutions to high-impact social and economic problems, and bridge the gap between private and public sector R&D.[11] In terms of high-technology, Argentina has three main technological platforms including biotechnology, nanotechnology, and information and communication technologies. It is important to note that all three of these platforms have the capacity to create important synergies and lead to better innovation. Under these three platforms, the Ministry of Science, Technology and Innovative Production defines four strategic areas: agroindustry, health, energy, and social development[11], which are in line with Argentina's natural resources and other issues of global significance.

A 2008-2009 survey of Argentina biotechnology companies reveals that there are 120 registered firms producing a diverse array of products.[2] Most of these firms are private firms, although around 80 percent of the firms depend on national capital. As shown in Figure 1, majority of the firms are agricultural firms producing inoculants and seed and plant varieties. Around 90 percent of the firms are domestic small and medium size. These firms are largely local and depend on national capital. There are also large global companies including Bayer CropScience and Dow AgroSciences and local leaders such as BioSidus, Bioceres and Biocientifica.[9] While only

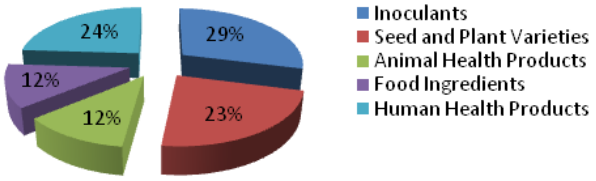

Figure 1: Percentage of firms in biotechnology sectors[13]

10 of the 120 biotechnology companies in Argentina are classified as large, they make up around fifty percent of total sales. These multinational firms focus on industrial applications, health and genetically modified seeds. In biotechnology, Argentina exports most of its products to Germany followed by France and Brazil. Argentina imports biotechnology products mainly from Europe. Countries including Germany, Ireland and Switzerland are at the top of the list in terms of imports.[11] In Argentina, there are import restrictions and required permits on various biotechnology related products including pharmaceuticals, chemical products, veterinary products, medical devices, and agricultural products.

Biotechnology sectors in Argentina are agriculture (inoculants and seed and plant varieties), food ingredients, human health, and animal health.[9] Among these sectors, the most dominant sector is agricultural biotechnology. In 2010, Argentina was the third largest producer of biotechnology crops after the United States and Brazil.[10] Outside of North America, Argentina is one of the largest cultivators of genetically modified soybeans, which actually became a problem in terms of the control of the smuggled seeds from the country.[15] Biotechnology sector employs more than 3,000 workers, has annual sales of $1 billion and exports add up to $260 million.[2] As seen in Figures 2 and 3, most of these figures are generated in agricultural biotechnology.

BIOTECHNOLOGY RELATED RESOURCES AND ASSETS IN ARGENTINA

Research and Development

Argentina currently spends around 0.4 percent of its GDP on R&D, which corresponds to 2.6 billion US dollars. This is behind the regional leader Brazil, which spends 0.9 percent of its GDP on R&D corresponding to 18.6 billion US dollars.[17] Figure 4 shows the top ten countries according to their 2010 R&D spending in comparison with Argentina and Brazil. Figure 5 shows the R&D spending of these countries as a percent of their GDP during the same year. Although these figures are not specific to biotechnology, they still show a commitment of national economies to science and technology including biotechnology.

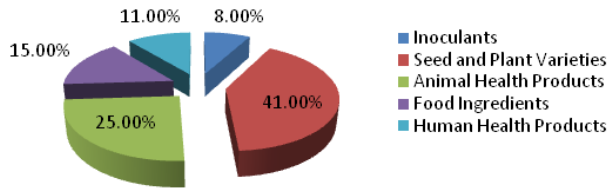

Figure 2: Percentage of sales generated in different biotechnology sectors[13]

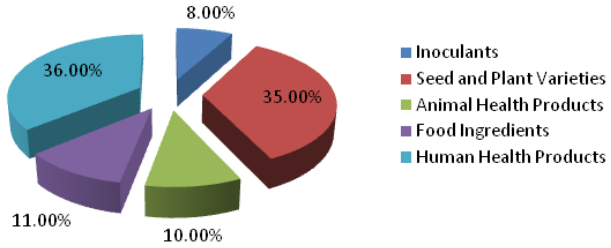

Figure 3: Percentage of employment generated in different biotechnology sectors[14]

Argentina has 129 research institutes including those specializing in biotechnology. The researchers in Argentina cooperates with other prestigious research institutions in projects and programs including Max Planck Institute, CERN laboratories, Pierre Auger Observatory, and SIASGE Space Program.[11] In Argentina, graduate and undergraduate programs in biotechnology are offered by more than 30 universities and higher education institutions. There are also opportunities for biotechnology researchers to advance their knowledge and skills. For example, The National Council for Scientific and Technical Research (CONICET) provides scholarships to researchers that pursue doctoral and postdoctoral degrees.[9] The country also has technological hubs and business incubators in biotechnology. Rosario Biotechnological Hub in Santa Fe is a major biotechnology cluster in Latin America specializing on vegetal biotechnology.[9]

Argentina has bilateral agreements with other countries that support private sector industrial research and development. An example for such agreements is that in 2006, Argentina signed a bilateral agreement with Israel that support joint commercially focused R&D projects between Israeli and Argentinean companies in all technological fields including biotechnology. In this agreement, it is stated that academic and other research entities are eligible to join only as sub-contractors.[16]

Funding

To provide funding in basic research and technological investment in biotechnology has been an important concern for the national government. Similar to Brazil,

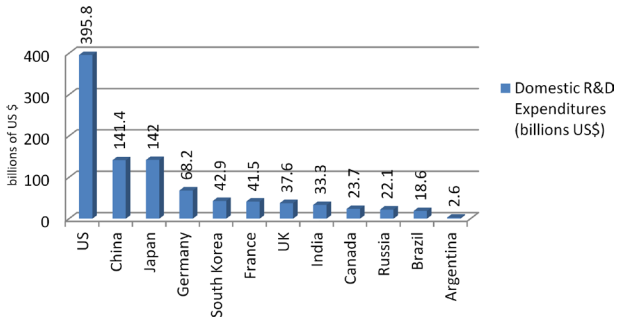

Figure 4: Domestic R&D expenditures of top ten countries, Brazil and Argentina in 2010[18]

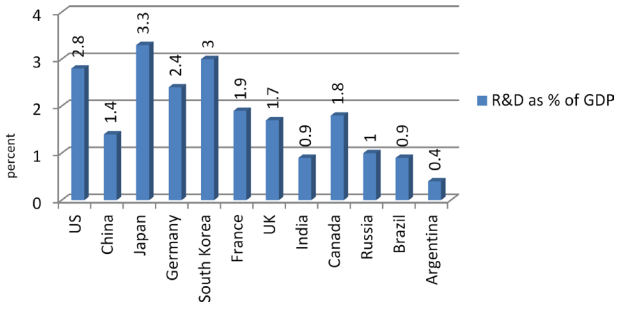

Figure 5: Domestic R&D expenditures of top ten countries, Brazil and Argentina as a percentage of GDP in 2010[18]

FONTAR 2000-2004	Number of biotechnology projects	Number of total projects in all sectors	Funding in biotechnology projects as a percent of funding in projects from all sectors
R&D	114	1480	8.30%
Infrastructure	12	48	18.34%
Total	126	1528	9.77%

Table 1: Biotechnology projects in the FONTAR[14]

venture capital is still yet to improve in Argentina. For this reason, the Ministry of Science, Technology and Innovative Production launched the CREARCIT program to attract more venture capital investment in all technological fields.[9]

The Ministry of Science, Technology and Innovative Production supports advancement in biotechnology with various funds including:

1. The Argentine Technology Fund (FONTAR): FONTAR is recognized as the main source of public financing, which is applicable to enterprises that are involved in the incorporation of scientific and technological knowledge and the forming of alliances with other institutions[19]. Table

1 shows that between 2000 and 2004, the number of biotechnology projects in the FONTAR is 8.25percent of the total projects and received 9.77percent of the total funding.

2. Funds for Scientific and Technological Research (FONCyT): FONCyT finances research and development activities mostly in institutes, universities and research centers.[20]
3. Argentine Sectoral Fund (FONARSEC): This fund is intended to finance projects of innovation in priority areas for the Ministry.[21]

Regulations and Support Institutions

In Argentina, the general legislative framework for biotechnology is provided by the National Constitution and specific regulations in different areas are determined by different departments of the State.[12] Developing countries with a regulatory framework on biotechnology, including Argentina, have mostly adopted models from the United States, which has the United States Department of Agriculture (USDA) and Animal and Plant Health Inspection Service (APHIS) for agriculture, Food and Drug Administration (FDA) for human health, Environmental Protection Agency (EPA) for environment related issues, and the Center for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) for research and development as its main institutions.[12] As stated, in this model, the major areas of emphasis are human health, agriculture, environmental regulations, and research and development.

Figure 6 is a diagram of the organizational structure of the regulatory institutions related to Biotechnology in Argentina. The main authority of biotechnology in agriculture is the Secretary of Agriculture, Livestock Breeding, Fishery and Food (SAGPyA) under the Ministry of Economy and Production.[19] Regulations in the human health area are the focus of the Drug, Food and Medical Technology National Administration (ANMAT) under the Secretary of Policy, Regulation and Institution. In terms of environmental regulations, the authority is the National Advisory Commission for the Conservation and Sustainable Utilization of Biological Diversity (CONADIBIA), under the Secretary of Environment and Sustainable Development. Both of these organizations and secretariats operate under the Ministry of Health.[19] As shown in Figure 6, the Ministry of Science, Technology and Innovative Production is the main authority in R&D and innovation in support of high-tech industries and it has many committees and organizations that are focused on biotechnology.[22] For example, the National Council for Scientific and Technical Research (CONICET) is the organization dedicated to the promotion

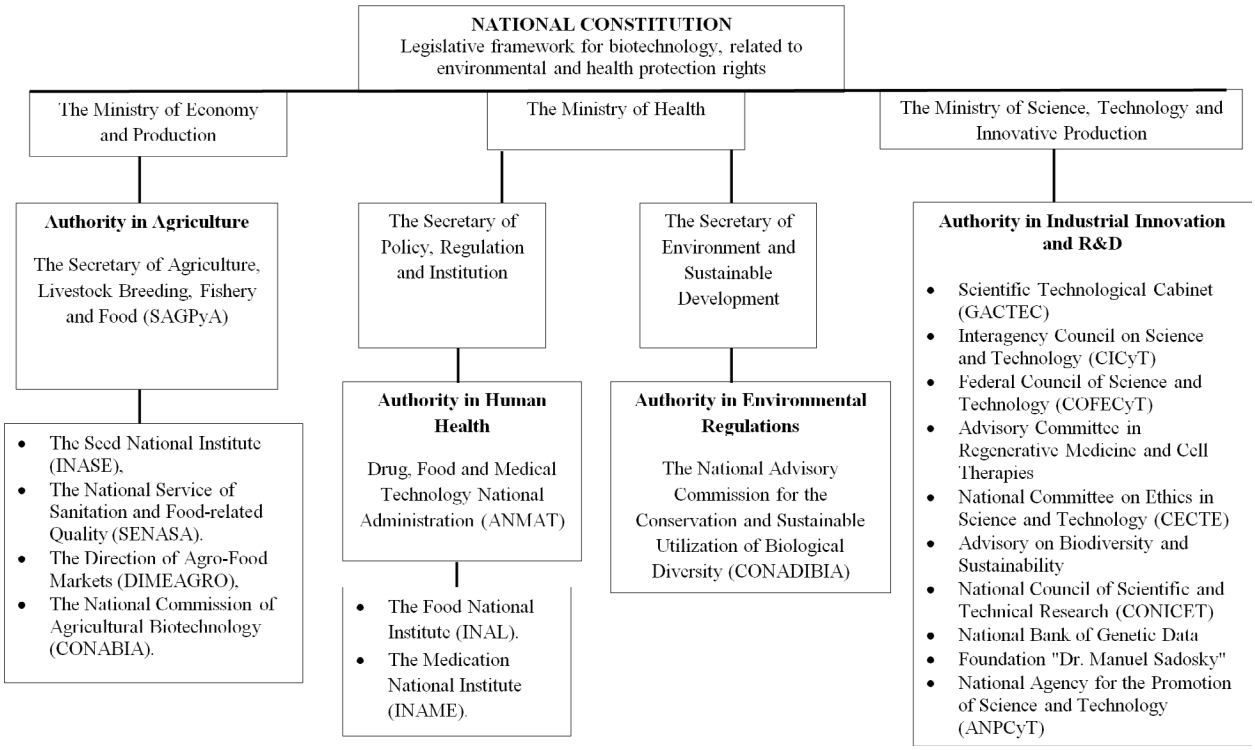

Figure 6: The organizational chart of biotechnology institutions in Argentina

of science and technology in areas including including agricultural sciences, engineering and materials; life sciences and health; natural sciences; social sciences and humanities.[23] The National Agency for the Promotion of Science and Technology (ANPCyT) focuses on technology transfers, by stimulating the increase in the number of innovative small and medium enterprises and by reinforcing the public university and private sector collaboration.[24]

Other important organizations that support biotechnology in Argentina are:

- Argentina Council for Information and Development of Biotechnology (ARGEN BIO) supports the development of biotechnology by disseminating information about its applications, benefits and safety.[25]
- Argentine Forum on Biotechnology (FAB) promotes collaboration among companies, researchers and the government. The FAB has an Honorary Committee Board formed by the National Secretariat of Science and Technology, National Secretariat of Agriculture, Food and Fishing, the presidents of the Science and Technology Committees of both Senate and Representatives chambers of the National Congress and the Argentine-Brazilian Biotechnology Centre (CABBIO).[26]
- Argentine-Spanish Center for Plant Genomics (CEBIGEVE) is a center of biotechnology research and development in the field of plant genomics, created with the collaboration of various agencies including the Ministry of Science, Technology and Innovative Production of Argentina and the Ministry of Education and Science of Spain.[27]

In terms of international collaboration in biotechnology and other related fields, Argentina follows a decisive path. In 2011, the Technological Scientific Pole was launched, which is a center of management, production and dissemination of knowledge. The center is seen as having national and internationally significance for the academic and scientific development. Located in the neighborhood of Palermo (in the grounds of the former Giol wineries), the Technological Scientific Pole will be have the headquarters of the Ministry of Science, Technology and Innovative Production and its two dependent bodies: The National Agency for the Promotion of Science and Technology (ANPCyT) and the National Council for Scientific and Technical Research (CONICET). Together with the ministry, these two agencies are the engines of national development in the field of science, technology and innovation in Argentina.[28]

The technological scientific pole will have an auditorium and a museum of science intended for scientific communication. As a symbol of the ties tends between science and society, the technological scientific pole will keep its doors open to the community through a restaurant, located in the Red Building, and a green square for public access. In addition, at the site will host four other international interdisciplinary institutes for innovation (I4), promoting international relations between Argentina and the world in terms of research and development in science, technology and innovative production.[28] These institutes are:

1. The Biomedicine Research Institute of Buenos Aires (IBioBA–MPSP) is a partnership between the CONICET and Germany's Max Planck Society, devoted to current issues in the biosciences, especially in the field of research in biomedicine.[28]
2. Research and Training unit of the International Centre for Genetic Engineering and Biotechnology (ICGEB), which is a multidisciplinary unit that focuses on the areas of bioethics, biosafety, intellectual property rights.[28]
3. Bilateral Centre for Industrial design (Argentina - Italy) dedicated to investigating the relationship between industrial design and new technologies, involving several Italian institutions including the Politecnico di Milano University, the Alma Mater Studiorum University of Bologna, the IUAV of Venice, and the Second University of Naples.[28]
4. Interdisciplinary Centre for Studies in Science, Technology and Innovation (CIECTI), which focuses on social sciences and works together with local universities and multilateral agencies. In a second phase the pole is expected to include a center for modeling and visualization and other institutes linked to nanotechnology, the Biofisicoquímica, and exact and technological sciences among other disciplines.[28]

In terms of regulations and support institutions, it is important to compare Argentina with its largest counterpart in Latin America, Brazil. Erber argues that since the mid1980s, two strong features emerge between these

two countries.[29] First, the degree of interdependence between the two economies in terms of trade and investment as a result of the bilateral agreements established in the mid1980s and the launching of MERCOSUR in the mid1990s and second is the similarities that exist in the policies pursued in the countries.[29] Based on these factors, especially transnational firms consider Argentina and Brazil as a single market, yet the integration of science and technology policies between these two countries remains in the low level[29], which is an area that might require further structural reforms.

Similar to Argentina, Brazil also emphasizes the human health, agriculture, environmental regulations, and research and development in its biotechnology framework through the participation of various organizations. In 2007, the National Biotechnology Committee (CNB) was launched in Brazil to coordinate and implement the Biotechnology Development Policy. This policy is set to enhance innovation, increase productivity and support business development in biotechnology. CNB has representatives from different ministries, institutes and agencies.[12] Brazil's National Biosafety Law that regulates the development and use of genetically modified organisms also sets a structure that brings together different organizations including the Biosafety National Technical Committee (CTNBio), which functions within the institutional framework of the Ministry of Science and Technology; various secretariats, agencies and committees from the Ministries of Health, Environment and Agriculture; the National Biosafety Council (CNBS); and the Biosafety Internal Commissions (CIBio).

Despite the similarities in institutional framework between Argentina and Brazil, there are also differences. For example, it is stated that for biosafety related issues, Argentina is closer to the American tradition, which is based on "risk assessment and management" for environmental issues and follows "substantial equivalence" for food-related matters.[12] On the other hand, Brazil follows the European tradition inspired by the Cartagena Protocol on Biosafety, which places more emphasis on the evaluation of environmental impact and food safety.[12]

There are two important organizations that feed the collaboration between Argentina and Brazil. The most major one is BIOTECSUR, which is a platform that brings together the private and public sector actors as well as the academic community from the four countries of MERCOSUR (Argentina, Brazil, Uruguay, and Paraguay) to create a regional and long-term vision in the context of new technologies to strengthen international cooperation.[30] The second one is CABBIO (Argentine-Brazilian Center for Biotechnology), which is the organization that promotes interaction between Argentina and Brazil in the context of scientific research and industry.[31] Based on their biotechnology related assets and expertise, innovative capacity and important developments in the biotechnology sector, enhanced collaboration between Argentina and Brazil will be more and more important for the economic development of the region.

INNOVATION INDICATORS

Patents and Intellectual Property

Between 2000 and 2007, 13342 patents were granted in Argentina, among which only 2.7 percent belongs to biotechnology. Among all the patents generated in biotechnology, 88 percent were granted to non-residents, among which the USA is the first country with 178 patents, followed by France with 21 and the UK with 20 patents.[19] Between 2001 and 2007, Argentina biotechnology sector has submitted 53 patents per year to the U.S. Patent and Trademark Office (USPTO) and 12 patents per year to the European Patent Office (EPO). USPTO granted 9 of these patents and EPO granted only 2 patents within the same time frame. In terms of patents registered in international databases, Brazil has more presence compared to Argentina. For instance, Brazil has 32 patents granted by the USPTO between 2001 and 2007.[19]

In terms of the protection of intellectual property of biotechnology inventions, there are two main laws: the law of patents and utility models and the law of seeds and plant varieties.[12] The lack of effective enforcement options, the absence of patent protection system and the lack of royalty collection system in biotechnology related inventions are reported as important problems in terms of the intellectual property system in biotechnology. This is the reason that large transnational seed companies are delaying the introduction of new technologies in Argentina.[10]

Developments in the soybean market during the past 15 years provide an important example of such reluctance of large companies to introduce new products in the country. 25 percent of Argentina's exports are comprised of soy-based products.[32] Soy exports have been bolstered by technological developments by large firms like Monsanto S.A.I.C. and Nidera S.A. Argentina embraced genetically modified organisms early on, as Nidera S.A. had its glyphosate-resistant soy approved for distribution in in 1996. This was in an era of liberalization that the Argentine government saw the value of embracing biotechnology as a tool to modernize its agricultural sector. The approval of glyphosate-resistant soybeans in 1996 encouraged Monsanto to introduce Bt/RR1 to the market. However, difficulties in royalty collection for seeds have made Monsanto reluctant to release this new seed in Argentina. This is also exemplified by the recent launch of Bt/RR2Y Soy in Brazil and Paraguay.

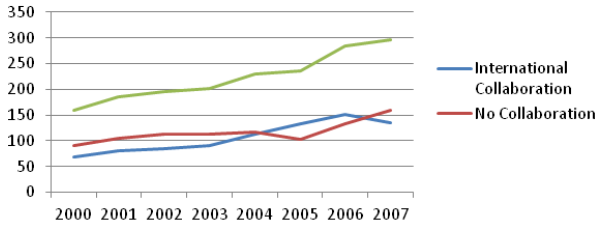

Figure 7: Argentine SCI biotechnology publications in international collaboration[14]

Both countries have recognized property rights for seed developers since 2004, which has encouraged Monsanto to sell its second-generation, glysophate-resistant soybeans in these countries, while avoiding riskier ventures in Argentina.[33] Thus, while the new variety promises a ten percent increase in yields for Argentine producers, it will remain unavailable until the regulatory framework suits Monsanto. Under the current "Seed Law," farmers do not pay royalties for genetically engineered seeds in Argentina. There is a need for changes in the current royalty collection system to further liberalize the transgenic seed market in Argentina and encourage innovation among large seed producers like Monsanto, Nidera, Novartis Agrosem and AgrEvo. During the last 15 years, 72 percent of profits earned from the export of transgenic soy beans went to producers, 21 percent to the state and just over six percent to technology providers. This is one of the key reasons that Brazil has overtaken Argentina in terms of biotechnology production. By modernizing its institutional framework, Brazil has been able to foster an environment conducive to innovation.[34]

As exemplified by the Monsanto's temporary withdrawal from the Argentinean soybean market, Argentina has seen rising tension between biotechnology companies and the government due to a weak intellectual property rights regime.[35] Thus, as the regulatory climate remains loose in its enforcement of intellectual property rights, Argentina may see investment dry up in search of more secure markets.[36] For examples, while Argentina was once a pioneer in the field of seed development, the cumbersome legislative process has impeded further developments. A fully functioning intellectual property rights regime may yield higher investment by private firms, desperately needed in order to maintain growth in the Argentine biotechnology sector.

Growth in R&D

The Government of Argentina places a high priority on stimulating biotechnology related research and innovation. In terms of research, a good indicator is the increase in the number of published articles in the biotechnology field. Figure7 shows that the biotechnology publications in Argentina that are included in the science citation index (SCI) have increased from 160 to 296 between 2000 and 2007. Also, as shown in the graph, between 2000 and 2006, there was a steady increase in international collaboration between authors. The top three collaboration are established with the United States, Spain, and Brazil.[19]

In terms of published research, Argentina is lagging behind Brazil. Between 2000 and 2007, the number of similar publications in Brazil in biotechnology increased from 400 to1137. This means that in 2007, 80 percent of all publications from the MERCOSUR countries and 2 percent of global publications in biotechnology related research came from Brazil. In terms of international collaboration within the MERCOSUR countries, Brazilian researchers has the majority of collaborations with Argentine researchers.[19] This shows that these two countries have established the basis of collaboration in research related activities. The increase in R&D also resulted in growth in industry. Between 2002 and 2008, it is reported that local pharmaceutical production grew at an annual rate of 16 percent and investments in this area have increased 10 times.[9] Argentina has shown progress in the development of transgenic cows beneficial for producing medicine such as human insulin. In 2007, Argentina became the second world producer of genetically modified crops, with 19.1 million hectares.[12]

CONCLUSION

The biotechnology sector in Argentina has been an important factor in the country's high and sustained growth rate in the past few years. By embracing its agricultural advantage and investing in research and innovation, Argentina has seen its stock of biotech companies grow to 120. Most of these are small to medium size enterprises, although ten are large, global companies that deal mostly with the production of transgenic seeds. While industry growth has depended on a somewhat favorable regulatory environment, public investment and research and development, present the challenges ahead.

An important beneficiary of record-high commodity prices, Argentina must take the opportunity of fortuitous financial circumstances to make investments in productive capacity. The biotechnology sector has demonstrated its capacity for rapid growth, and must be placed higher on the national agenda. The automotive industry dwarfs the nascent biotechnology sector, outselling it by twenty to one.[2] The biotechnology sector remains largely irrelevant when measured against dominant sectors like automobiles, tourism and textiles. This does not mean, however, that it must remain irrelevant. The biotechnology sector is unique in its inherent ability to create linkages between agriculture and technol-

ogy. Higher investment in infrastructure, attracting new forms of foreign capital, growing regional integration and increasing research activities are all important areas for improvement.

In terms of research, Argentine biotechnology companies outnumber Brazilian companies, 120 to 105, yet Brazil manages to publish 80 percent of biotechnology related publications in MERCOSUR. Research must keep up with industry in order to keep feeding the budding sector. Funding will remain a complicated issue as repercussions from the Argentina's default almost ten years ago continue to reverberate throughout the economy. Access to capital markets remains limited and friction with the United States has led to complications with funding from the Inter-American Development Bank. While the Argentina biotechnology sector faces several challenges, its rapid expansion in a time of global economic uncertainty bodes well for its future.

NOTES AND REFERENCES

1. Gutman, G., Lavarello, P. and Cajal J. (2006) La biotecnología y las industrias de ingredientes alimentarios en Argentina. Journal of Technology Management & Innovation, I(3): 121-130.
2. Guillermo, A., Bisang, R. and Stubrin, L. (2010) Las empresas de biotecnología en Argentina. UN: CEPAL - Coleccion Documentos de Proyectos. December 2010.
3. Ferrand, Y., Kelton, C.M.L., Chen, K., and Stafford, H.A. (2009) Biotechnology in Cincinnati: Clustering or Colocation? Economic Development Quarterly. 23 (2): 127-140.
4. Gertler, M.S. and Vindorai, T. (2009) Life Sciences and Regional Innovation: One Path or Many? European Planning Studies. 17 (2): 235-261.
5. Sherwin, S. (2011) Dr. Stephen Sherwin, BIO Chairman and Chairman & Co-founder of Ceregene, Addresses Attendees at BIO International Convention. http://www.bio.org/advocacy/letters/dr-stephen-sherwin-bio-chairman-and-chairman-co-founder-ceregene-addresses-attendee (accessed October 2011).
6. Ernst&Young. (2011) Beyond Borders: Global Biotechnology Report 2011. http://www.ey.com/Publication/vwLUAssets/Beyond_borders_global_biotechnology_report_2011/$FILE/Beyond_borders_global_biotechnology_report_2011.pdf (accessed October 2011).
7. Biotech-Tailor-made for Israel. http://www.mfa.gov.il/MFA/InnovativeIsrael/Biotech-tailor_made_for_Israel_%28Nov-2010%29.htm (accessed October 2011).
8. Randall, J. (2000) Despite Embargo, Biotechnology in Cuba Thrives. JNCI J Natl Cancer Inst 92 (13): 1034-1037.
9. ProsperAR. (2009) Biotechnology in Argentina: Knowledge + Innovation to meet global market needs. http://www.slideshare.net/ProsperArgentina/biotechnology-in-argentina (accessed October 2011).
10. USDA. (2010) Argentina: Biotechnology GE Plants and Animals 2010 Annual Biotechnology Report. http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Biotechnology%20-%20GE%20Plants%20and%20Animals_Buenos%20Aires_Argentina_1-13-2011.pdf (accessed October 2011).
11. Science and Technology; Perspective of Argentina's Government. Presentation by Alejandro Ceccatto Deputy Minister of ST&I. http://www.mincyt.gov.ar/multimedia/archivo/archivos/Presentacion_Ceccatto.pdf (accessed October 2011).
12. BIOTECSUR. (2008) Inventory of Biotechnological Rules and Regulations in the MERCOSUR. http://docs.biotecsur.org/informes/en/inventario/4_normativa_ms.pdf (accessed October 2011).
13. Data Source: ProsperAR. (2009) Biotechnology in Argentina: Knowledge + Innovation to meet global market needs. http://www.slideshare.net/ProsperArgentina/biotechnology-in-argentina (accessed October 2011).
14. Data Source: BIOTECSUR. (2008) Inventory of Biotechnology Capacities. http://docs.biotecsur.org/informes/en/inventario/2_capacidades_ms.pdf (accessed October 2011).
15. Richards, D.G. (2010) Contradictions of the 'New Green Revolution': A View from South America's Southern Cone. Globalizations, 7(4): 563-576.
16. Argentina Israel Cooperation Program. http://www3.matimop.org.il/1/foreign/argentina-israel.asp (accessed October 2011).
17. Battelle. (2011) 2011 Global R&D Funding Forecast. http://www.battelle.org/aboutus/rd/2011.pdf (accessed October 2011).
18. Data Source: Battelle. (2011) 2011 Global R&D Funding Forecast. http://www.battelle.org/aboutus/rd/2011.pdf (accessed October 2011).
19. BIOTECSUR (2008) Inventory of Biotechnology Capacities. http://docs.biotecsur.org/informes/en/inventario/2_capacidades_ms.pdf (accessed October 2011).
20. FONCyT. http://www.Agencia.gov.ar/SPIP.php?article28 (accessed November 2011).
21. FONARSEC. http://www.Agencia.gov.ar/SPIP.php?article995 (accessed November 2011).
22. ORGANIGRAMA. http://www.mincyt.gov.ar/ministerio/estructura/organigrama/index.php (accessed November 2011)
23. CONICET. http://www.conicet.gov.ar/web/conicet/inicio (accessed October 2011).
24. The National Agency for the Promotion of Science and Technology of Argentina (ANPCYT) - Biotecnology

2005: Patents for SMEs Grant Call. http://www.insme.org/tenders-calls/280 (accessed November 2011).

25. ARGEN BIO. http://www.argenbio.org/ (accessed October 2011).
26. FAB. http://www.foarbi.org.ar/ppal/english.php (accessed October 2011).
27. CEBIGEVE. http://fundacion-antama.org/cebigeve-nuevo-centro-binacional-de-genomica-vegetal/ (accessed October 2011).
28. Polo Cientifico Tecnologico. http://www.polo.mincyt.gob.ar/ (accessed November 2011).
29. Erber, F.S. (1999) Structural Reforms and Science and Technology Policies in Argentina and Brazil. Paper prepared for the seminar "Políticas para fortalecer el Sistema Nacional de Innovación: La experiencia internacional y el camino empreendido por la Argentina", organised by the Secretaria de Ciencia y Tecnologia, Buenos Aires, September. http://cdi.mecon.gov.ar/biblio/docelec/cyt/er.pdf (accessed October 2011).
30. BIOTECSUR. http://www.biotecsur.org/ (accessed October 2011).
31. CABBIO.http://www.mincyt.gov.ar/busqueda/index.php?Id_modulo=11&Id_idioma=1&Id_tag=274&nombreTag=CABBIO (accessed October 2011).
32. Lanteri, L. (2008) Argentina's Soybean Acreage Response to Changes in Price Incentives. Central Bank of Argentina, Economic Essays. 52 (October-December).
33. Manfroni, M. (2010) La soja BT RR ya está madura, pero sigue en lista de espera. La Nacion 17 April. http://www.lanacion.com.ar/1254859-la-soja-bt-rr-ya-esta-madura-pero-sigue-en-lista-de-espera (accessed December 2011)
34. "Beneficios de la Introducción de Nuevas Tecnologias de Soja" Seminario de la Asociasion Semilleros Argentinos, 12/7/2011 en Buenos Aires http://www.asa.org.ar/index.asp (accessed December 2011)
35. Kesan, J.P. and Gallo, A.A. (2005) Property rights and incentives to invest in seed varieties: Governmental regulations in Argentina. AgBioForum. 8(2&3): 118-126. http://www.agbioforum.org.
36. The Economist (2011) Cristina Prepares to Defy Gravity. 17 December. http://www.economist.com/node/21541850 (accessed December 2011).

Original Paper

What do hospital labs really need to streamline diagnostic testing: Apple vs. Microsoft environment?

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ABSTRACT

Molecular diagnostic (MDx) tests are now commonplace in virtually every hospital and pathology laboratory, however many questions have arisen, such as "What do diagnostic laboratories require from the MDx revolution in order to better improve patient care?" and "Is a fully integrated 'black-box' device the answer to simple rapid diagnostic testing or do mainstream laboratories require more in terms of available testing menu and streamlined workflow?" With more and more 'black-box' devices available on the market, laboratories need to first decide if they need to make such an investment, and if so, in which to make the most appropriate investment, whilst also considering the cost of consumables. Currently the associated costs of an integrated solution can be prohibitive for small to medium sized laboratories, however this does not necessarily mean that they need to miss out on the many benefits that MDx testing can bring. Here we examine what role an open-platform suite of MDx assays can play in the MDx testing landscape. In order to be successful we assume that open-platform tests will utilise a universal sample preparation method for all sample types and be compatible with a broad range of existing Real-Time PCR hardware. This is in effect the 'Microsoft' model, which provides software compatible with existing hardware, compared to the 'Apple black-box' model of supplying both the hardware and software. Clearly there is a place for both approaches in the clinical diagnostic sector, but until the 'black-box' systems broaden their testing menu for all sample types and reduce the cost of consumables, their use may be limited to single analyte niche testing rather than being a central workhorse in the mainstream hospital and pathology laboratories. The goal for testing laboratories is to provide rapid and definitive identification of pathogens in order to aid optimal patient management. In the current setting this is only available by using a battery of tests from different manufacturers, or by relying on traditional methods that can take several days to generate a result. It is proposed that a true open-platform MDx testing system may bring the benefits of rapid and accurate testing to many small to medium laboratories without the need for a large upfront investment and associated high consumable costs.

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Keywords: molecular diagnostics; open platform; black-box; multiplex PCR

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INTRODUCTION

THE MOLECULAR DIAGNOSTIC LANDSCAPE: CURRENT AND FUTURE TRENDS

The use of molecular diagnostics (MDx) has numerous advantages over conventional techniques used for infectious disease testing. Key advantages include speed, sensitivity, specificity and the ability to use such methods independently of sample viability. In addition, MDx tests can be performed on many different specimen types such as blood, CSF, sputum, swab samples and faecal material to determine the presence or absence of specific pathogenic microorganisms.

Molecular diagnostic testing is the fastest growing segment of the *in vitro* diagnostic (IVD) marketplace. The increase in consumption of these new technologies is being driven by multiple growth factors. These include the need for automation, ease of use and reliable sample processing methods. Currently immunoassays account for approximately 25% of the global IVD market place with MDx accounting for approximately 6%. However it is predicted that MDx is poised to take a substantially larger share of the marketplace. The molecular diagnostic testing segment was worth $6.4 billion in 2011 and in 2016 is expected to be worth nearly $14.6 billion, a compound annual growth rate (CAGR) of 17.8%.[1] Figure 1 shows the current percentage of the molecular diagnostics market, as can be seen infectious diseases holds the largest market segment accounting for 71% of the total MDx clinical diagnostic market. To date the infectious disease market was dominated by tests for the detection or quantitation of blood borne pathogens such as HIV and HCV with the remainder tests for STIs such as *Chlamydia*, *Gonorrhea* and HPV. This situation is likely to change with pathogenic microorganisms such as Multiple Resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* emerging as major hospital acquired infections. Furthermore, with the recent outbreaks of Influenza H1N1 09 and SARS molecular diagnostic approaches to respiratory tract infections will increase due to demand for rapid testing facilities at airports and border crossings in order to contain the possibility of new outbreaks of disease.

Figure 2 shows the CAGR expected from 2010-2015 by market segment and region. The molecular segment is the growth powerhouse of the IVD market and was able to achieve a 10% expansion in 2010 despite a difficult year for the global economy. The key areas of growth in the MDx segment are infectious diseases, oncology, genetic testing and blood banking, all of which are potentially influenced by the use of rapid and simple open platform diagnostic technology.

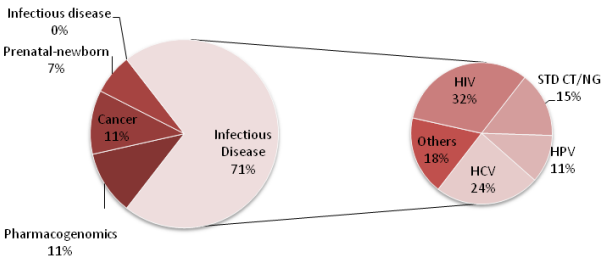

Figure 1: The current molecular diagnostics market share (source: US Molecular Diagnostic Market, Frost and Sullivan 2006)

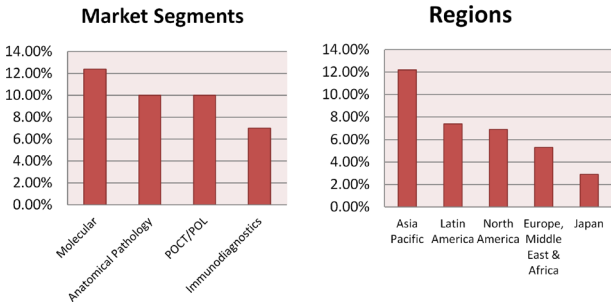

Figure 2: IVD market growth by segment and region expected from 2010-2015[2]

In 2010, estimates for the growth of the IVD market as a whole ranged from 4–5.5%. However, analysts agree that emerging markets such as Asia Pacific are reaching double-digit growth, a trend that's expected to continue (see figure 2). Overall high economic growth in emerging markets has lead to a thriving middle class and consequently greater demand for improved healthcare services. Governments in these regions are therefore investing substantially in the healthcare sector.

The emerging markets are not merely consumers of healthcare, but are gaining ground in their capacity to develop and manufacture the latest in medical technology. It has been speculated that these markets may surpass the developed countries in the production of innovative healthcare products over the next decade.

The U.S. still holds its position as global leader in medical technology and continues to show the greatest capacity for the development of new technologies and devices. However, it is predicted that the U.S. will lose ground to other countries during the next decade. By contrast, China, India, and Brazil are likely to see gains during the coming decade. China, which has demonstrated the largest improvement in its medical technology innovation capacity during the past 5 years, is expected to continue to grow rapidly and may outpace other countries and achieve a level comparable to the developed nations of Europe by 2020.[2]

The diagnostic pathology industry: An overview

The rising costs of hospital health care, illustrated in figure 3, are driving the need for rapid testing for infectious diseases to allow more informed patient triage in order to reduce transmission, prevent the use of unnecessary therapies and reduce hospital stays. Molecular diagnostic tests promise to answer the call for more community based testing and self-diagnosis, especially in the field of Respiratory Tract Infections (RTI), Sexually Transmitted Infections (STI) and Gastroenterology (GI). All of these conditions can be caused by any number of infectious agents and thus an accurate diagnosis requires a large number of traditional tests to be performed, or alternatively require the use of a MDx system with a broad testing menu.

Recent outbreaks of infectious diseases such as Influenza H1N1 09, avian influenza H5N1 and Severe Acute Respiratory Syndrome (SARS) and the rise of sexually transmitted infections (STIs) have highlighted the need for rapid testing in all areas of the community, particularly air travel, schools, and at national borders. Traditional laboratory based diagnostics cannot match the MDx approach in terms of speed, accuracy and utility, therefore molecular methods are gaining traction in almost all hospital pathology laboratories. Table 1 shows a comparison between closed systems versus a true open platform system for the use in hospital and pathology laboratories.

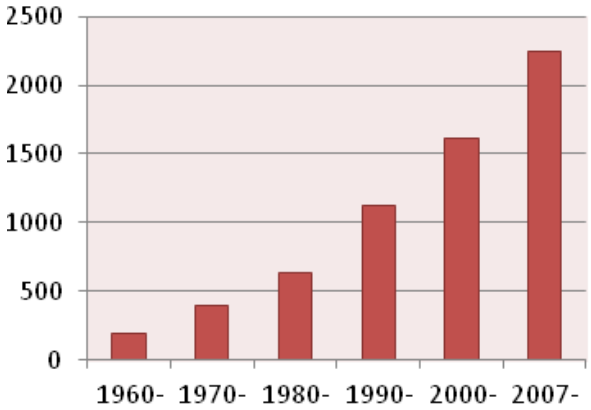

Figure 3: Rising healthcare costs 1960-2007 expressed in $B 2007[3]

Table 1: Closed vs. open platform systems upfront cost, consumables and test turn around times

	Closed Platform	Open Platform
Utilise existing infrastructure	No	Yes
Upfront instrument cost	$17,500 - >$100,000	N/A
Single analyte test	Yes	Yes
Full target menu	No	Yes
Run time	45mins - 2hours	Approx. 3hours
CLIA waved	Yes	No
Hands on time[1]	2 minute	10-20 minutes
Cost per test	$25-70[2]	$2-50[3]
Suitable for full screening purposes (e.g. GI, RTI and STI)	No	Yes
Maximum samples per run	1-16	96

[1] Hands on time per sample
[2] Single analyte test
[3] Multiple analyte test

Technology options for hospital and pathology laboratories closed vs. open platform

The Apple model: The closed technology option

Recently more and more companies are touting the use of closed 'black-box' systems that are able to extract nucleic acids from the primary patient sample and perform amplification and detection within an enclosed device. A number of systems have been developed including the GeneExpert™ (Cepheid, Sunnyvale California), Simplexa™ (FocusDx Cypress, California), IDBox™ (GenturaDx, Hayward California), Quidel instrument (San Diego, California), Biocartis instrument (Mechelen, Belgium), Panther™ (GenProbe San Diego, California) and Enigma ML (Enigma San Diego, California).

The advantages of these systems include ease of use and full integration from sample to result, allowing assays to be run using operators with little or no technical training (CLIA waved). However, such "black-box" systems also come with a number of disadvantages, the two most important being limited target menu (see tables 2, 3 and 4) and the high cost of consumables associated with the closed system platforms.

Target menu options closed vs. open platform systems

These limitations in target menu reduces the impact of the closed "black-box" system, especially when the result is negative, as the laboratory then has no choice but to

Table 2: GI target menu available for various molecular instruments

GI targets included in the system menu	
Cepheid	*C. difficile*, C. diff-epi*
FocusDx	C. difficile
Biocartis	N/A
Quidel	*C. difficile*
GenProbe	N/A
Open platform	*C. difficile*, C.diff-epi, *Cryptosporidium parvum*, *Giardia intestinalis*, *Dientamoeba fragalis*, *Entamoeba histolytica*, *Blastocystis hominis*, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Listeria monocytogenes*, *Yersinia entercolitica*, STEC, Norovirus GI, Norovirus GII, Adenovirus, Rotavirus, Astrovirus, Sapovirus

*C. diff-epi = Epidemic *C. difficile*

Table 3: RTI target menu available for various molecular instruments

Upper respiratory tract targets included in the system menu	
Cepheid	Flu A, Flu B, *Mycobacterium tuberculosis.*
FocusDx	Flu A, Flu B, H1N1, RSV
Biocartis	N/A
Quidell	N/A
GenProbe	N/A
Open platform	Flu A, Flu B, Flu A H1, H3 and H5, RSV (A & B), Metapneumonia, Parainfluenza 1,2,3,4, Rhinovirus A/B, C, Bocavirus, Adenovirus, Coronavirus NL63, OC43, HKU1, 299E, SARS, *Mycobacterium tuberculosis*

Table 4: STI menu available for various molecular instruments

Sexually transmitted infection targets included in the system menu	
Cepheid	N/A
FocusDx	N/A
Biocartis	N/A
Quidell	N/A
GenProbe	N/A
Open platform	HPV, *Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma genitalium, Trichomonas vaginalis*

revert to a battery of conventional tests in order to make an accurate patient diagnosis. Thus the inclusion of fully integrated systems in a laboratory setting does not necessarily help in streamlining workflows in situations where definitive pathogen identification are required.

Costs involved in MDx uptake by laboratories: Instruments and consumables

Another issue affecting the uptake of closed system MDx assays is the large investment required for proprietary hardware (in excess of $100,000 in some cases) and the high cost of consumables, which can be as high as $70 for a single test for a single analyte. This is particularly relevant as most hospital and pathology laboratories work around tight budgets and are bound by government reimbursements that do not always reflect the true cost of MDx testing. In some cases, running a single test on some closed system instruments costs much more than any available reinbursement. Alternatively a "user-pays" system that passes on the full cost of the test can push the price of each test to beyond the reach of most patients. A more cost effective system, with a broad screening menu of pathogen detection is required to provide economical optimal patient care by delivering the accurate and rapid diagnostics required for best practice patient management.

Clearly there are times when paying above reimbursement rates for a single analyte has merit. One hospital manager always runs an expensive Enterovirus assay on selected patients, as if the assay is positive the patient can be sent home with a paracetamol instead of taking up valuable space on the ward and creating further cost to the hospital. This is however the exception and not the norm as we are aware of another hospital manager who tested a black-box instrument for the detection of the common GI pathogen *C. difficile* and although the results obtained were superior and far more rapid that conventional EIA and cytotoxic culture, the machine was not placed within the laboratory for the following reasons:

1. Only a single GI analyte could be tested on the machine and no additional information could be obtained with that sample (as multiplexing was not possible on that system). Thus the lab still had to return to the sample and perform additional conventional tests increasing the overall workload not simplifying it and adding further cost to the department.
2. The cost of the consumables was above the budget of the department.

3. Other rapid molecular assays were available to the laboratory that could be run on existing equipment and provided more information on patient management.

The Microsoft model: Open platform plug and play with existing manufacturers

To address the high costs of proprietary hardware, MDx assays can be designed to be compatible with routine equipment that laboratories have already purchased, such as automated DNA/RNA extraction equipment and real time cyclers. Furthermore, as may laboratories are currently using this kind of instrumentation the end users have become increasingly well versed in the use and interpretation of results obtained using such equipment. In adopting an open-platform based MDx testing, laboratories can avoid another capital investment. Even though the hardware is becoming more common, there is currently little standardisation and end-users are free to choose an instrument from their manufacturer of choice. Table 5 shows a list of the most common molecular diagnostic hardware available from proven suppliers.

With the choices of hardware available any given laboratory may have use a different combination of instruments to other laboratories. In order to capitalise on existing hospital and pathology infrastructure it would be desirable to design multi-analyte diagnostics that are capable of running on all existing platforms. This is in stark contrast to expecting the institution to make a further capital outlay for a piece of equipment that can only assay for either one or a very small number of pathogens.

Centralisation of workflow to reduce departmental costs and improve patient care

Another issue limiting the uptake of MDx assays in conventional pathology laboratories is the lack of a centralised testing facility, as traditional testing was best peformed in separate independent departments by specialist technicians. A good example of the shortcomings of running independent departments is when a physician is looking for a rapid diagnosis of the microbial cause of a presenting GI case, yet is faced with a hospital that runs separate bacteriology, virology, parasitology and molecular divisions, each with its own nuances. However, in this same setting, an open platform system with a complete target menu would allow the molecular division to run all the preliminary testing, resulting in a more streamlined workflow and ultimately better patient management. Any presumptive positive samples could then be sent to the specialist division for further characterisation, such as antibiotic susceptibility testing.

Table 5: Sample processing and real-time PCR hardware found in hospital and pathology laboratories

Sample processing equipment	Real-time PCR hardware
Qiagen (M48, Qiasymphony, Qiacube, EZ1)	Roche Lightcycler™ I and 480
Roche MagnaPure systems	ABI Fast7500
Themo KingFisher Flex	Cepheid SmartCycler I and II
Biomerieux EasyMag	Qiagen RotorGene
	Biorad CFX96
	Stratagene Mx3000

To further streamline processes and remove boundaries between departments, testing laboratories should be able to collect a single sample from a patient, process the sample using an open platform protocol that allows for the simultaneous lysis for DNA containing pathogens (e.g *Cryptosporidium* and *Salmonella*) and RNA containing viruses (e.g Norovirus and Rotavirus). This would allow the laboratory to screen for all relevant pathogens from the same sample at the same time without the need for multiple independent tests, complex extraction procedures and independent amplification conditions. Indeed numerous managers have commented that a if such a broad menu open platform MDx option was available for GI testing they would utilise this option over the conventional methods thus streamlining and centralising patient testing.

Universal sample preparation is required for a true open platform solution

Traditionally each sample type had to be processed with separate extraction kits that have been optimised for the target organism of interest. A wide range of kits are commercially available from numerous suppliers for a number of different sample types. For example individual kits can be purchased for the purification of nucleic acids for gram negative bacteria, gram positive bacteria, viral samples, blood, sputum, faeces, plant tissues, human tissues and numerous other sample types.

In consideration of all factors limiting the use of MDx assays, our goal was to produce a simple reliable universal lysis/extraction method that would work under identical conditions for human cells, bacteria, RNA and DNA containing viruses that allow end-users to assay for bacteria, viruses, protozoan and human analytes from the same sample. This was achieved by developing a simple 15 minute method that does not require the addition of enzymes to assist in cell lysis and yet protects the labile RNA species in the sample from degradation during the processing step. This method is compatible with

downstream assays targeting double stranded DNA, double stranded RNA and single stranded RNA in the same tube from the same sample whilst reducing hands on time and costs.

Multiplexing capabilities can extend the test menus

Traditionally, molecular assays have been designed whereby a probe is labelled with a single colour and detected in a single PCR channel thus one analyte is detected per reaction. Most modern real time PCR instruments are capable of detecting at least 4 different coloured probes with a number of machines now able to detect up to 6 individual dyes. Using a multiplex approach whereby up to 6 probes can be labelled with different colours allows the detection of multiple targets in the same tube and further streamlines the molecular detection of infectious disease.

One way to improve the multiplexing capability of current real time instruments further is to use dual labelled probes (see figure 4) which can improve the multiplex capabilities of a four-channel machine to 10 analytes per reaction.[4] One drawback of this approach is that multiple infections can quickly become impossible to differentiate and cause the results to become uninterpretable. Multiple infections are particularly common in human papilloma virus infection and are also becoming more widely recognised in GI and RTI thus the use of such approaches although increasing multiplexing capabilities have to be viewed with caution.

Multiplexing has traditionally been difficult due to the different nucleic acid sequence composition of individual pathogens. In effect the temperature at which a PCR reaction can be carried out can become problematic as the primers and probes present in the reaction will bind to the targets at different temperatures and so some targets may be amplified more preferentially than others due to the kinetics of the reaction (see figure 5). We have developed a novel chemistry that reduces this temperature bias. This has the advantage that multiplexed reactions become far easier to design and all targets can be amplified at the same temperatures. This results in assays that do not favour the amplification of one target over another thus improving both assay sensitivity and specificity.

Existing intellectual property (IP) may be required to enter the MDx space

Another significant factor to the overall pricing structure of commercial molecular diagnostic reagents is the additional cost of licencing intellectual property (IP) from third parties so that the manufacturer has freedom

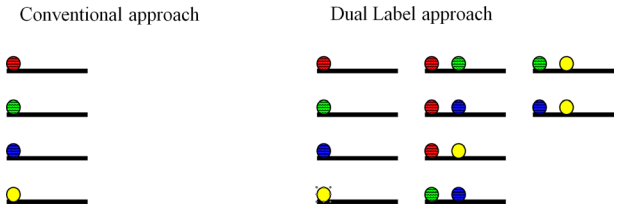

Figure 4: Increased multiplexing achievable using dual labelled probes versus single label probes

	Conventional sequence	Tm	Modified sequence	Tm
Primer1	GTACACACCGCCCGTCGCTCCTACC	77°C	GTATATATTGTTTGTTGTTTTTATT	52°C
Primer2	GAAGGAGAAGTCGTAACAAG	56°C	GAAGGAGAAGTTGTAATAAG	50°C
Probe1	TGAATAAAGAGGTGAAATTCTAGG	59°C	TGAATAAAGAGGTGAAATTTTAGG	59°C
Probe2	GAAGGGCCGCGAGCCCCCGCGC	87°C	GAAGGGTTGTGAGTTTTTGTGT	62°C

Figure 5: Improvement achievable using modified nucleic acid sequences to enhance the efficiency of real-time PCR multiplexing by converting C bases to T, thus resulting in a more similar melting temperature (Tm).

to operate within the jurisdiction that the test is being sold. Licensing fees and up-front payments can add millions of dollars to the development and production costs of a new diagnostic assay. These additional costs are absorbed in the final cost of the assay to the consumer. Thus novel companies having strong IP portfolios and who are not reliant on third party IP are able to offer cheaper assays to the end-user, as they may not have to pay additional fees to ensure freedom to operate. As previously stated this is particularly relevant to resource poor countries with emerging health markets such as India, China, and Taiwan, where the growing middle class markets are increasing the consumption of diagnostic technology. Thus open platform diagnostic assays that are compatible with the widest range of routine hospital hardware and are unencumbered from existing IP have the ability to penetrate the largest share of the current molecular diagnostic market including the developing countries.

Novel proprietary solutions have been developed that allows freedom to operate in the competitive MDx space without relying on third party licences. Such assays from Human Genetic Signatures Pty Ltd allow freedom to operate in most jurisdictions without infringing existing real-time patents reducing the end cost to the consumer. In addition, the 3base™ technology is not encumbered by any current DNA or RNA sequence-based IP. Furthermore, as noted above, the technology has now been refined to allow sample lysis to occur under universal conditions for any pathogen, allowing bacterial, viral and protozoan nucleic acids to be assayed at the same time in the same tube.

Advantages to the open-platform approach

The use of the open-platform approach has a number of advantages over closed systems for hospital and pathology laboratories that are equipped with the basic hardware to perform real time PCR.

- No capital outlay is required for the institution before they can run the assays on equipment that the technicians are already familiar with.
- A complete target menu is available, thereby streamlining the workflow of the laboratory and eliminating the need for multiple independent assays to be performed on the same sample.
- The assays are amenable for use in an emergency department setting as results are available in less than 3 hours, from sample to result. The physician can request a complete screen of possible bacterial, viral or parasitic infectious agents and can thus provide rapid and appropriate patient management,
- Our approach is unencumbered by existing IP resulting in tests that are more economical for the end user and importantly without the loss of sensitivity or specificity.
- The tests are ideal for use in resource poor settings that have centralised testing facilities that are predicted to become major markets in the next 5-10 years.
- The tests are available to the widest possible number of laboratories from the smallest pathology labs to the largest teaching hospitals.
- Sample extraction is universal for all pathogens whether they are DNA or RNA containing and can also be used on difficult to lyse organisms such as parasite cysts but has the advantage that labile RNA is protected during the critical sample-processing step.
- Samples can be processed using an automated system or can be processed manually depending on the resources of the institution.

CONCLUSIONS

There is no doubt that closed platform sample to result "black-box" type equipment has the potential to revolutionise the molecular diagnostic industry by providing easy to use assays that can quickly identify specific pathogens of interest. However, there seems to be an ever-increasing number of instrument manufacturers that are entering this particular niche. With so many instruments becoming available will the market soon be saturated with these devices? Which one should a hospital choose? If the wrong decision is made it could be a costly white elephant. This situation is analogous to the microarray market some years ago where numerous instruments became available from a wide range of vendors. These instruments cost in most cases in excess of $250,000 in capital outlay. In the end two instrument makers (Affymetrix and Illumina) became the dominant market forces leaving labs that purchased rival equipment out of pocket and with instruments that were no longer supported and could not be used due to the consumables being discontinued. A similar scenario is likely with makers of "black-box" type instruments in that the majority while appealing at the time will loose out in the end to one or two dominant players. However, whoever wins the majority market share will still be vulnerable to new technologies as is the case with next generation sequencing and the microarray market.

In addition, to date the menu of these devices has been severely hampered to that of "in-favour" and highly profit driven analytes with the exclusion of targets that are tested daily in the hospital and pathology labs. Thus a negative result means that the laboratory has to return to the sample and perform a further battery of more conventional test to isolate the pathogen causing the disease. Furthermore, the cost of these tests can become prohibitive when a single cartridge can be up to $70. On the up side with more and more companies entering this space costs will be driven down. But how far down can these costs ultimately come? With the high cost of producing and manufacturing equipment, cartridges and reagents coupled to the IP barriers that have to be negotiated prior to selling the test in specific territories, prices are unlikely to significantly decrease. However, each assay requires a separate cartridge to be run on the system and if the manufacturers wanted to include a complete menu, in excess of 10 cartridges may be required to run a complete GI pathogen detection program for example. This would drive the cost so high it could very quickly become so costly as to be prohibitive, limiting the use of "black-box" devices as a primary screening tool.

An alternative more cost effective approach that could be used as a primary screening tool for the diagnosis of GI, RTI and STI could be to provide open platform

solutions that have the widest target menu. This means that any laboratory that is equipped with a real-time PCR instrument, from any manufacturer, can immediately begin testing without further capital outlay. This approach also reduces the chances of a hospital acquiring an instrument that may become obsolete in a few years as conventional real-time PCR is unlikely to be superseded in the near future due to the low cost and proven track record of this technology. Whilst next generation sequencing has made tentative forays into molecular diagnostic space, it is unlikely to be used as a routine screening tool for hospital diagnosis of infectious disease in the near future due to the prohibitive costs, turnaround time and complexity required in data interpretation.

Using the open platform approach even the smallest of laboratories can have access to a system that will test for a wide range of specific pathogens even if they had traditionally been hampered by lack of specialists in that area. By providing a complete menu for each sample type the workload of the laboratory can be effortlessly streamlined so that one sample can be tested for all the targets that would previously have to be tested by different departments. Importantly, since common PCR consumables are inexpensive large screening panels can be run easily and cost effectively which could not be achieved using the cartridge-based system required for close "black-box" instruments.

Patient triage can be improved at admission and in the emergency department so that optimal patient care is provided at the earliest opportunity by testing samples using the widest possible platform menu with the effect of reducing hospital stay and reducing the economic burden of infectious disease to the individual hospital.

Reduced costs of reagents would also enable such tests to be widely adopted in the health care system and help the placement of these tests in resource poor settings which already have centralised testing facilities. Having universal extraction and PCR conditions also simplify the use of such assays for the operator as different targets do not have to be treated differently again streamlining the process of sample to result-without the 'black-box"?

REFERENCES

1. http://www.bccresearch.com/pressroom/report/code/BIO038C
2. http://www.aacc.org/publications/cln/2011/ExpoIssue/Pages/RecordBreaking2011ClinicalLab.aspx.
3. http://gulzar05.blogspot.com.au/2009/09/why-are-health-care-costs-rising.html
4. Multicolor combinatorial probe coding for real-time PCR. (2011) Huang Q, Zheng L, Zhu Y, Zhang J, Wen H, Huang J, Niu J, Zhao X, Li Q. PLoS One. 2011 Jan 14;6(1):e16033.

Case Study

Creating systemic oral transmucosal drug delivery strategies: Case study of APL-130277

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ABSTRACT

This article addresses the strategic application of systemic oral transmucosal* (i.e., sublingual and buccal) drug delivery. Circumvention of first-pass hepatic metabolism in the gut, rapid onset of action, easy access via the oral cavity, easy administration for patients with dysphagia and a high level of patient acceptance are the principal advantages of the oral transmucosal route. Key clinical and commercial strategies driving the development of oral transmucosal formulations are addressed. A case study of Cynapsus Therapeutics' APL-130277, a sublingual apomorphine formulation in clinical development for Parkinson's disease exemplifies the scientific, clinical and commercial considerations for systemic oral transmucosal drug delivery.

*Note: In this article, oral transmucosal delivery refers to systemic drug delivery through the sublingual or buccal mucosa. Local delivery to the oral mucosa is not included.

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INTRODUCTION

Drug development in alternative delivery systems is driven principally by unmet clinical needs that are not served by oral formulations or to overcome limitations of injectable delivery. Alternatives to systemic oral delivery are required for drugs that are degraded by liver enzymes in the gut (first-pass hepatic metabolism), have specific pharmacokinetic requirements, demonstrate poor gastrointestinal (GI) permeability or cause GI irritation. Transdermal, nasal, inhaled-pulmonary and oral transmucosal delivery formulations enable drug uptake directly into the blood, thereby eliminating first-pass metabolism. Feasibility requires an effective drug and a delivery system capable of safe and efficacious delivery. Successful development and commercialization require an intimate understanding of the indication, patient preferences, physicochemical characteristics of the compound, pharmacokinetics of delivery, prior approvals, regulatory pathways, intellectual property landscape, clinical market factors, development timelines and costs and return on investment, among others. To date, nearly all drugs that have been launched in alternative delivery systems were previously approved as injectable or oral formulations. Sublingual nitroglycerin for coronary artery vasodilation and nicotine for smoking cessation are exceptions.

APL-130277, a sublingual formulation of apomorphine in development for treatment of *off* episodes of Parkinson's disease (PD), has completed a Phase 1 human pilot trial. APL-130277 encompasses key factors that drive systemic oral transmucosal drug development: significantly improved delivery (in this case, the conversion of an injection-only into a non-injectable form), development of a proprietary product from a generic compound, pursuit of a shortened and less costly clinical development program via the FDA 505(b)2 bio-

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equivalence route and the potential to greatly expand the clinical utilization and market for a drug.

ORAL TRANSMUCOSAL DELIVERY

Route and physicochemical properties

Oral transmucosal delivery is based on direct uptake of the drug by the highly vascularized oral mucosa. Active drug and excipients are formulated as tablets, orally disintegrating tablets, buccal mucoadhesive tablets, films and patches, sublingual disintegrating thin films, sprays, chewing gum or lozenges. Upon administration into the oral cavity, the formulation dissolves in a small amount of saliva. Drug is released and diffuses across the epithelial barrier, primarily through intercellular spaces. Absorbed drug enters the systemic circulation through the jugular vein.

Permeability is a function of mucosal keratinization, thickness of the mucosa and physicochemical properties of the drug. One of the major challenges of buccal/ sublingual delivery is retaining drug on the mucosal surface to achieve efficient partitioning into the mucosal lining.[1] Sublingual thin films are designed to release drug in close proximity to the mucosa. Buccal mucoadhesive formulations physically retain drug against the mucosa and can achieve residence times of up to 12 hours, although patient compliance with formulations requiring long residence times may be problematic.

Physicochemical properties of compounds that are associated with achieving higher bioavailability include:

- Small size (MW typically < 500); compounds of MW 400-700 typically achieve bioavailability of 15-70%; peptides <25%
- Biopharmaceutics Classification System (BCS) class I (high permeability, high solubility) and class II (high permeability, low solubility)
- Log*P* (partition coefficient): approximately 2-4
- High solubility in saliva at a pH that maximizes the fraction unionized[1]

Physicochemical properties, vehicle systems, and other technical considerations for oral transmucosal delivery have been recently reviewed.[1-11]

Indication: Unmet need

Oral mucosal delivery is used for a wide variety of OTC drugs (e.g., chlorpheniramine and phenylpropanolamine for cough, Triaminic®/ Novartis; simethicone antacid (Gas-X®/ Novartis) and prescription drugs. Products range in clinical utility from *breakthrough* to *me-too*. The latter category includes many products (not listed in the table) introduced after the initial innovator, without improvement, which compete solely on the basis of price.

Table 1 lists oral transmucosal prescription drugs that have been launched in the US. Nervous system indications dominate. Elimination of first-pass metabolism was the development driver for many of the approved drugs. For example, pre-gastric absorption of selegiline circumvents first-pass metabolism of tyramine, which causes hypertension. Although rapid onset of action is most often thought of as a significant advantage of oral transmucosal delivery, slow absorption is possible and desirable for some indications (e.g., testosterone replacement). Effective delivery in the elderly, children and compromised patients with dysphagia drove the development of the fentanyl buccal lozenge. The promotion of patient compliance is a significant factor in the development of psychiatric drugs in oral transmucosal formulations.

Indications and strategies driving the development of new oral transmucosal drugs mirror those of the approved drugs, although several new indications (e.g., diabetes, cancer treatment) have emerged. See Table 2.

Two products, insulin buccal spray (Oral-lyn™; Generex Biotechnology) for diabetes and the Cynapsus sublingual apomorphine formulation (APL-130277), have the potential to become the only available non-injectable formulations of these drugs. [Oral-lyn and Mannkind's Phase III pulomonary-inhaled insulin (Afrezza®) are both in Phase III development.] The first conversion of an injection-only drug to a non-injectable formulation represents a *Holy Grail* of drug delivery with the potential to change clinical practice patterns, increase drug uptake and capture market share. Sumatriptan (Imitrex®/ Imigran®; GlaxoSmithKline) for the treatment of migraine is a well-known example. The drug was launched as an injectable formulation in 1993. Uptake among patients was very slow, however, spurring the company to launch tablet (1995) and nasal spray (1997) formulations. Worldwide sales grew from less than $350 million 1993 to more than $1 billion in 1997. Today, injectable forms account for a very small percentage of the $3.5 billion US triptan market; fast-acting ODT formulations are preferred.

COMMERCIAL STRATEGIES FOR ORAL TRANSMUCOSAL DRUGS

The history of oral transmucosal fentanyl product development represents the typical launch of an innovative formulation (Actiq®, 1998) and subsequent development of other buccal formulations and, most recently, sublingual formulations.

Innovator, then life cycle manager

Reckitt Benckiser obtained FDA approvals for sublingual formulations of buprenorphine (Subutex®) and buprenorphine + naloxone (Suboxone®) and went from innovator in both formulation and indication to effective life-cycle manager with the introduction of an improved formulation of Suboxone. The company developed the first sublingual formulations of these drugs and conducted approval trials in the non-pain indication of opioid dependence. Then, facing expiring patents, the company introduced a sublingual film formulation of Suboxone that is preferred by patients because it dissolves faster and tastes better, which enabled new patent protection. As is common with life cycle management efforts, the new formulation was introduced before the old patent expired, and it was promoted (continuing through 2012) with a $0 co-pay card (one prescription per month, up to $50) for users who switched to the film formulation. The campaign has been successful. The new Suboxone film formulation captured a 41.4% volume (mg) share of the US market by June 2011, which, combined with a 46.7% share in Suboxone tablet sales, totaled nearly 90% of the market. Subutex, on the other hand, could not be protected and has declined by 85% in the face of generic competition.[15]

Differentiation by niche indication

Identification of a new niche indication with substantial unmet need is a potential "differentiation by indication" strategy for developing new transmucosal formulations when others have already been approved. Transcept Pharmaceuticals developed a lower dose, sublingual tablet formulation of zolpidem (Intermezzo®) for "middle-of-the-night waking followed by difficulty returning to sleep," a difficult-to-treat subset of insomnia patients. The higher-dose tablet formulation (Ambien®; Sanofi) and other two other available formulations, zolpidem sublingual orally disintegrating tablets (Edluar™, Meda Pharmaceuticals) and zolpidem oral spray (Zolpimist®, ECR Pharmaceuticals) are not approved for this indication. The lower dose is utilized for middle-of-the-night waking because it decreases the chance for morning hangover effects, and the sublingual formulation may

Table 1: Systemic oral transmucosal drugs approved in the US*

Drug and formulation	Brand name	Company	Drug class	Indication	US approval
Fentanyl					
Fentanyl oral transmucosal (buccal) lozenge	Actiq®	Cephalon/ Teva	Opioid analgesic	Breakthrough cancer pain in opioid-tolerant patients	1998
Fentanyl buccal tablet	Fentora®	Cephalon/ Teva	""	""	2006
Fentanyl buccal soluble thin film	Onsolis®	BioDelivery Sciences International	""	""	2009
Fentanyl sublingual tablet	Abstral®	Kyowa Hakko Kirin (ProStrakan)/ Orexo	""	""	2011
Fentanyl sublingual spray	Subsys®	Insys Therapeutics	""	""	2012
Buprenorphine					
Buprenorphine sublingual tablet	Subutex®	Reckitt Benckiser	Opioid agonist/ antagonist	Opiate dependence	2002
Buprenorphine + naloxone sublingual tablet	Suboxone®	Reckitt Benckiser	Opioid agonist/ antagonist + opioid antagonist	Opiate dependence	2002
Buprenorphine + naloxone sublingual thin film	Suboxone® sublingual film	Reckitt Benckiser/ MonoSol Rx	""	Opiate dependence	2010

Table 1 continued

Drug and formulation	Brand name	Company	Drug class	Indication	US approval
Zolpidem					
Zolpidem sublingual tablets (orally-disintegrating tablets, see below and text)	Edluar™, Sublinox (Canada)	Meda Pharmaceuticals, Valeant (Canada)/ Orexo	Benzodiazepine receptor agonist	Insomnia, difficulties with sleep initiation	2009
Zolpidem oral spray	Zolpimist®	ECR Pharmaceuticals, Rechon Life Science (ex-US)/ NovaDel Pharma	""	Insomnia, difficulties with sleep initiation	2008 (2011 launch)
Zolpidem sublingual tablet CIV	Intermezzo®	Purdue Pharma/ Transcept Pharmaceuticals	""	Insomnia, middle-of-the-night awakening/ difficulty returning to sleep	2011
Other drugs					
Nicotine polacrilex, buccal	Nicorette® Gum	GlaxoSmithKline	Nicotine replacement	Smoking cessation	1984 1996 OTC
Nicotine lozenge, buccal	Commit® Lozenge (now, Nicorette® Lozenge)	GlaxoSmithKline	""	Smoking cessation	2002
Nitroglycerin tablet and spray, sublingual/ buccal	Nitrostat®	Pfizer	Vasodilator	Angina pectoris	First use: 1879
Nitroglycerin lingual aerosol	NitroMist™	Akrimax Pharmaceuticals/ NovaDel Pharma	""	Angina pectoris	2006 (2011 launch)
Testosterone, buccal	Striant®	Actient Pharmaceuticals	Androgenic steroid hormone	Testosterone replacement therapy	2003
Orally-disintegrating tablets**					
Olanzapine orally-disintegrating tablets	*Zyprexa® Zydis®*	Eli Lilly	Atypical antipsychotic	Schizophrenia, bipolar disorder	2000
Asenapine sublingual tablets	Saphris®, Sycrest®	Merck/ Schering-Plough / Lundbeck	Atypical antipsychotic	Schizophrenia, bipolar disorder	2009
Donepezil orally-disintegrating tablets	Aricept ODT®	Eisai	Acetylcholinesterase inhibitor	Alzheimer's disease	2004
Alprazolam, *orally disintegrating tablets*	Niravam™	Schwarz Pharma	Benzodiazepine	Anxiety disorders	2005
Selegiline orally-disintegrating tablets	Zelapar®	Valeant Pharmaceuticals	Monoamine oxidase-B inhibitor	Parkinson's d.	2006
Zolmitriptan orally-disintegrating tablets	Zomig-ZMT®	AstraZeneca	Triptan; 5-HT agonist	Migraine	2001

* Not a comprehensive list of systemic oral transmucosal drugs. Drug delivery for the treatment of oral mucosal lesions, such as mucositis, candidiasis, dental caries, xerostoma, carcinomas and other oral lesions is not included; reviewed in [12, 13]. Delivery systems for local oral delivery include mouthwashes, aerosol sprays, chewing gums, bioadhesive tablets, films, gels and pastes. Sublingual immunotherapy (SLIT) with allergen-specific (protein) immunotherapies/ vaccines is also not included. SLIT is a type of local therapy based on stimulating the oral immune system, which comprises various antigen-presenting cells. To date, more than 2 billion sublingual vaccine doses have been administered to humans, including allergens based on grass pollen, ragweed pollen, peanut, milk, German cockroach allergenic extract, B-subunit of non-toxic cholera toxin, house dust mites, Alternaria-Induced rhinitis, birch pollen, cat hair, Japanese cedar pollen and others; reviewed in [14].

** Orally dissolving tablet formulations may provide buccal absorption but drug may also be swallowed for GI delivery.

Table 2: Systemic Oral Transmucosal Drugs in Development*

Drug and formulation	Brand name	Developer	Drug class	Indication	Clinical stage**
Insulin buccal spray	Oral-lyn™	Generex Biotechnology	Antidiabetic	Type I and Type II diabetes	III
Insulin buccal film	Insulin loaded orally dissolved film	Hadassah Medical Organization	Antidiabetic	Type I and Type II diabetes	I (Israel)
Cannabidiol + tetrahydrocannabinol, buccal spray	Sativex®	GW Pharmaceuticals/ Otsuka Pharmaceutical	Cannabinoid	Cancer pain	III
Sufentanil/ triazolam sublingual nanotab	Sufentanil/ triazolam NanoTab™	AcelRx Pharmaceuticals	Opioid analgesic + benzodiazepine	Mild sedation and reduce anxiety and pain before and during a procedure	III
Sufentanil sublingual nanotab	Sufentanil NanoTab™ PCA System	AcelRx Pharmaceuticals	Opioid analgesic	Acute post-operative pain, patient-controlled analgesia system, breakthrough cancer pain	III
Rozerem sublingual (TAK-375SL)	Ramelteon sublingual	Takeda	Melatonin receptor agonist, high affinity for MT_1 and MT_2	Bipolar disorder	II
Flumazenil sublingual	FlumUP® SL (vial, pump, actuator)	Coeruleus	Benzodiazepine antagonist	Next day residual effect of sleep/ hypnotic drugs	II
ALKS 5461, sublingual	ALKS 5461	Alkermes	Kappa opioid antagonist (non-addictive)	Major depressive disorder	I/II
Buprenorphine buccal soluble film	BEMA® Buprenorphine	BioDelivery Sciences International	Opioid agonist/ antagonist	Moderate to severe chronic pain	III
Buprenorphine + naloxone buccal soluble film	BEMA® Buprenorphine/ Naloxone	BioDelivery Sciences International	Opioid agonist/ antagonist + opioid antagonist	Opiate dependence	I
Granisetron buccal soluble film	BEMA® Granisetron	BioDelivery Sciences International	5-HT3 receptor antagonist	Nausea/ vomiting	I
Apomorphine sublingual thin-film system; see case study	APL-130277	Cynapsus Therapeutics	Dopamine agonist	Parkinson's disease	I
Unidentified compounds (2), sublingual	UISH00	Beech Tree Labs	N/A	Urinary incontinence symptoms	I/II
Unidentified compound, sublingual	BTL TML HSV	Beech Tree Labs	N/A	Oral HSV symptoms	I/IIa
Misoprostol, sublingual	N/A	Generic	Prostaglandin E1 analog	Induction of Labor	III-IV
Imatinib, sublingual	N/A; Gleevec® brand (Novartis)	Kedem Pharmaceuticals	TKI	Hematological malignancies	N/A
Sildenafil, oral spray	Duromist™; Viagra® (Pfizer)	NovaDel Pharma	PDE5 inhibitor	Erectile dysfunction	IND submitted
Sildenafil, sublingual	Generic (Brazil)	Laboratório Teuto Brasileiro	PDE5 inhibitor	Erectile dysfunction	III
Sildenafil, sublingual	X-Excite; Viagra® (Pfizer)	Kedem Pharmaceuticals	PDE5 inhibitor	Erectile dysfunction	N/A
Agomelatine, sublingual	AGO178, Valdoxan (EU approved 2009)	Novartis/ Servier	Melatonin (MT1, MT2) agonist, 5HT2c antagonist	Depression	DC (US)

* Not a comprehensive list.

** Clinical trial stage may not accurately represent an approximation of a drug's progress in development if required for regulatory submission if FDA 505(b)2 or other shortened routes to regulatory approval are accessible.

also be faster acting than the tablet. Purdue Pharma will market Intermezzo.

According to *Advertising Age*, Purdue has budgeted $100 million for a media campaign that will focus on differentiating Intermezzo from Ambien and Lunesta (eszopiclone; Sunovion Pharmaceuticals). The introduction Lunesta was the last big budget launch for a blockbuster drug; $100 million was budgeted in 2005 and $320 million was budgeted in 2006; 2010 sales of Lunesta were almost $950 million.[16, 17] No other insomnia drug is approved for middle-of-the-night administration. A branded, low-dose doxepin tablet (Silenor®; Somaxon Pharmaceuticals) is indicated for insomnia characterized by difficulty with sleep maintenance. However, administration is at bedtime not middle-of-the-night, and sales have been very slow.

Hybrid buccal / oral delivery

Orally disintegrating tablets (ODT) represent a hybrid buccal/ oral delivery approach. ODT can be administered without water and dissolve on the tongue, which allows for buccal uptake of some of the drug and swallowing and GI tract absorption of the remainder. For some oral drugs, the ODT formulation serves simply as an easier method of administration for patients with dysphagia or compliance issues. Catalent, Cima Labs and Takeda led the development of the dozens of ODT formulations that have been launched, worldwide.

CASE STUDY: APL-130277 - SUBLINGUAL APOMORPHINE FOR *OFF* EPISODES OF PARKINSON'S DISEASE

Introduction

Cynapsus Therapeutics is developing a sublingual formulation of apomorphine, APL-130277**,** as a rescue therapy for *off* episodes in patients with Parkinson's disease (PD). *Off* episodes are motor fluctuations (hypomobility) that occur in patients despite treatment with optimized chronic oral therapy.[18-22] Apomorphine hydrochloride injection (Apokyn®; U.S. WorldMeds/ Britannia Pharmaceuticals) is *indicated for the acute intermittent treatment of hypomobility 'off' episodes ('end-of-dose wearing off' and unpredictable 'on/ off' episodes associated with advanced PD.*[23] Conversion to a sublingual formulation that maintains rapid onset of action could transform the clinical role of apomorphine, which is vastly underused because of the disadvantages and adverse effects of injection.

Indication and drug selection: informed opportunism

The selection of *off* episodes of PD as an indication and their treatment with apomorphine followed from the APL-130277 inventors'* long-term involvement at companies developing PD therapeutics.

Off episodes were identified as an area of great unmet need nearly two decades ago. In a previous company, a novel levodopa prodrug, levodopa methyl ester, was developed with the goal of reducing motor fluctuations by achieving rapid drug uptake and maintaining therapeutic plasma levels of levodopa. Pharmacologically, the drug performed as expected. However, although it improved some aspects of motor function and quality of life, it did not significantly provide rescue of *off* episodes.

With the founding of Cynapsus, the compound focus shifted away from levodopa. The consensus of key opinion leading neurologists was that new formulations of levodopa would not reduce *off* episodes significantly and that the approved drug, apomorphine, is very effective but its use by patients is limited because injection is required. Commercial opportunity for reformulating apomorphine was timely because the Orphan status of Apokyn was expiring in April 2011. Additionally, FDA approval of apomorphine for *off* episodes opened up the potential to pursue an optimal development route of therapeutic equivalence/bioequivalence via FDA 505(b)2. The question had been reframed: Could an alternative drug delivery formulation transform apomorphine from an injectable to a non-injectable, while retaining the rapid uptake kinetics?

Selecting the optimal delivery route

Identification of the optimal non-injectable delivery route for apomorphine rescue therapy was based on anticipated technical and clinical performance profiles, development and regulatory pathways, cost of production and other factors. Oral administration was quickly eliminated because of slow absorption, extensive first-pass metabolism and poor bioavailability. Figure 1 summarizes key findings from an analysis of alternative drug delivery routes for apomorphine treatment of *off* episodes in PD and provides a multi-parametric view of the relative advantages and disadvantages of each route of delivery.

The objective was to provide an alternative to injection because of user unfriendliness and the potential for irritation and other adverse effects. The transdermal route was ruled out because onset of action is too slow for

* Note: Adagio Pharmaceuticals Ltd., which was acquired by Cynapsus, developed APL-130277 initially.

rescue of *off* episodes. Also, the long duration of action of transdermal delivery is not desirable for this indication.

The pulmonary-inhaled route was eliminated because several factors suggested significant development risk and high costs. Onset of action is too fast to allow pursuit of a bioequivalence regulatory route for approval. Essentially, a full NDA development program may be required. Although some of the safety data from the approved apomorphine submission might be usable, safety concerns about systemic administration via the pulmonary route might emerge (e.g., pulmonary expiration volume changes). Although the pulmonary-inhaled route is not inherently unfriendly, PD patients in the *off* state might find it difficult to self-administer a dose because a synchronous hand movement and inspiratory effort are required (even if breath-actuated devices were developed). Also, maintaining a device and recharges is bulkier and mentally more cumbersome than a simple pill or other single-use formulation. The cost of goods of a pulmonary-inhaled product would be high because a device is required and drug manufacturing is complex (micronized API, consistent particle density and size, excipients to overcome particle interactions, others). FDA has approved only one pulmonary-inhaled product (insulin), and the manufacturer later withdrew it from the market. Two pending NDAs (insulin and loxapine) face intensive scrutiny. One inhaled-pulmonary apomorphine formulation completed a Phase II trial but the company plans no further development and has attempted to out-license the product.[24]

Previous nasal and sublingual formulations demonstrated some level of success in delivering apomorphine, and these routes could potentially meet bioequivalence criteria because of their rapid onset of action approximates that of injection. However, solution phase apomorphine is unstable and causes nasal irritation. Powdered formulations can overcome the stability but not the nasal irritation issues. The most recent effort to develop nasal apomorphine was discontinued because of irritation.[25]

Previous sublingual formulations demonstrated promise but were discontinued because clinically acceptable products could not be developed, including sublingual tablets that dissolved too slowly and a cumbersome kit product that required the patient to mix liquid apomorphine with buffer solution immediately before each administration.[18] Cynapsus believed that the sublingual route was the most apt for development and could meet all of the criteria of a rescue medication in PD.

Sublingual Thin Film Meets Technical Challenges

Apomorphine is unstable in solution and best formulated as a solid dosage form and/or in the presence of low pH excipients. Lessons learned from the failed product development efforts and technical feasibility assessment led the inventors to concentrate efforts on the SL route using a soluble thin film vehicle to overcome development challenges.

Thin film is a relatively new vehicle for prescription drug delivery. Only two prescription thin film formulations are FDA approved: Onsolis (fentanyl, 2009), Suboxone (buprenophine + naloxone, 2010). A thin film vehicle is ideal for sublingual delivery of apomorphine because a solid active ingredient and stabilizing excipients can be incorporated, and thin films dissolve rapidly in a minimal volume of saliva. Disintegration and dissolution occur with a high degree of intimacy between the drug and tissue where absorption occurs, which can improve absorption compared to sublingual tablet formulations. Buffer is included in the film strip to reduce acidity and the potential for irritation at the site and maintain optimal absorption kinetics. The product developed by Cynapsus, APL-130277, is a solid dosage form of apomorphine in a sublingual thin film formulation designed for rapid dissolution (typically in 1-2 minutes) and absorption directly into the blood.

Phase 1 Trial Confirms Proof of Concept & Development Pathway

In January, Cynapsus announced positive findings from a human Phase 1 pilot trial with sublingual APL 130277 (3 mg) that demonstrated proof of concept in the treatment of off episodes in PD. Pharmacokinetics and safety/tolerability were assessed in 15 healthy volunteers; 12 received drug product and 3 received placebo. After washout, subjects were dosed a second time with APL-130277 placed in a different orientation under the tongue. Key findings and implications included:

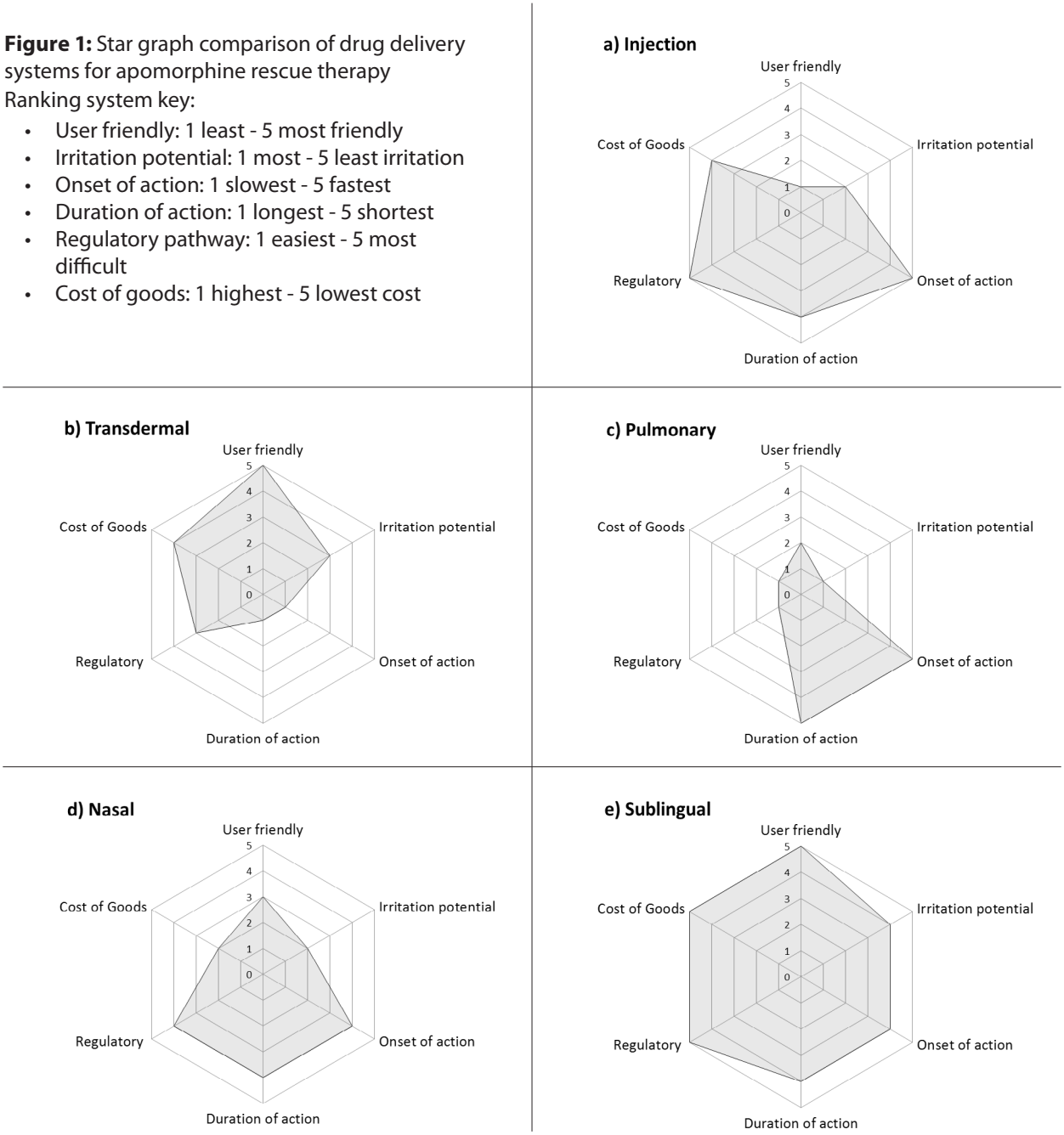
- Administration of sublingual APL 130277 reproduces the pharmacokinetic profile typically obtained by apomorphine injection.
- The mean T-max of less than 25 minutes observed in the study compares favorably to that of injected apomorphine. In the majority of subjects, maximum blood levels were reached within 20 minutes of administration. Rapid onset of action is required for the treatment of *off* episodes.
- APL-130277 was safe and well tolerated. Adverse events were mild. Two (17%) of APL-130277-treated subjects had at least one adverse event; one of the two had moderate nausea and dizziness. Systemic adverse effects were typical

of adverse effects commonly observed with apomorphine injection. One (33%) placebo-treated subject had at least one adverse event.

- Sublingual orientation affects the T-max and PK of APL-130277.
- Other pharmacokinetic parameters mirrored those observed with a subcutaneous injection of apomorphine after an expected dose adjustment.
- A majority of subjects had a T-max ≤ 20 minutes and the mean T-max was 25 minutes, which are comparable to subcutaneously injected apomorphine. These findings suggest that sublingual APL-130277 will reproduce the pharmacokinetic profile of the reference drug, allowing a bioequivalence route for an NDA submission.
- The bioequivalence route would be quicker, requiring only a Phase 1

Figure 1: Star graph comparison of drug delivery systems for apomorphine rescue therapy
Ranking system key:

- User friendly: 1 least - 5 most friendly
- Irritation potential: 1 most - 5 least irritation
- Onset of action: 1 slowest - 5 fastest
- Duration of action: 1 longest - 5 shortest
- Regulatory pathway: 1 easiest - 5 most difficult
- Cost of goods: 1 highest - 5 lowest cost



bioequivalence trial and, subsequently, a safety trial demonstrating tolerability in approximately 150 PD patients. An NDA might be submitted in late 2013 or early 2014.

Establishing clinical market potential

Establishment of compelling clinical market rationale is required to justify a full-scale development program for any drug. *Off* episodes in patients with PD are disabling and represent a significant clinical problem. They limit the patient's ability to move, his or her productivity and participation in activities of daily living and social activities. They may also cause severe anxiety and depression, the loss of a sense of self and other disabilities.[18-21,26] The unmet therapeutic need is great because, despite the acknowledged efficacy of the current standard of treatment, the many disadvantages and adverse effects of SC apomorphine render it inadequate and infrequently used by patients. They include needle aversion, injection pain, inflammation, panniculitis and nodule and scar formation. And many patients, particularly the elderly (in the *off* state), lack the manual dexterity required to self-inject, which may be required up to three or more times daily. Significant unmet need and the many previous failed attempts to develop an alternative to SC apomorphine indicate commercial viability of APL-130277. However, estimation of market potential required a bottom-up analysis based on the patient base and understanding of needs.

An independent global survey of 500 practicing neurologists who treat motor fluctuations in PD was conducted.[27] Key findings included:

- The segmentation of the PD population by severity was 41% mild, 42% moderate and 16% severe. The frequency and severity of *off* episodes increase as the severity of PD increases from mild to moderate to severe. The survey findings were consistent with the findings of a medical registry, *Implications of Motor Fluctuations in Parkinson's Disease Patients on Chronic Therapy* (IMPACT, 2005 data), which provides a comprehensive demographic and medical profile of PD patients experiencing *off* episodes.[18]
- The percentages of patients who would be candidates for treatment with APL-130277 within each severity category was 15% of mild, 38% of moderate and 49% of severe.
- The addressable markets by severity category were obtained by multiplying the total PD patient population (N) by the percentage of patients in each category and by the percentage of candidates for APL-130277 treatment in each category. The mild addressable market = N x 6% (41% x 15%); moderate = N x 16% (42% x 38%); severe = N x 8% (16% x 49%). The total addressable market for APL-130277 consists of 30% of patients with PD, which indicates substantial market potential.
- Estimates of penetration rates and number of daily doses for each severity level and average wholesale prices for the US, Europe and Japan (range: $5.95-$8.05) were applied to develop a revenue model. Peak sales estimates for the US, Europe and Japan, based on the lowest estimated penetration rate estimates, exceed $350 million, compared to current sales of about $40 million for the SC formulation. Depending upon performance characteristics of APL-130277, various factors affecting use and uptake and the significant projected increase in the numbers of PD patients over the next 8 years, peak sales might reach a 5x multiple of the conservative estimate.

CONCLUSION

A successful drug reformulation strategy requires a profound look at a broad set of factors that can influence the choice of delivery system and decision to invest in clinical R&D. APL-130277 exemplifies the application of a rational approach for meeting a significant unmet clinical market need and patients' expectations with a very efficient development program

REFERENCES

1. Mathias, N.R. and Hussain, M.A. (2010) Non-invasive Systemic Drug Delivery: Developability Considerations for Alternate Routes of Administration. *Journal of Pharmaceutical Sciences* 99: 1–20.
2. Dodou, K. (2012) Research and developments in buccal and sublingual drug delivery systems. *The Pharmaceutical Journal* 288:446.
3. Zhang H., Zhang J. and Streisand, J.B. (2002) Oral mucosal drug delivery: Clinical pharmacokinetics and

therapeutic applications. *Clinical Pharmacokinetics* 41: 661–680.

4. Narang, N. and Sharma, J. (2011) Sublingual mucosa as a route for systemic drug delivery. *International Journal of Pharmacy and Pharmaceutical Sciences* 3(Suppl 2): 18-22.
5. Patel, V.F., Liu, F. and Brown, M.B. (2011) Advances in oral transmucosal drug delivery. *Journal of Controlled Release* 153(2): 106-116.
6. Amir H. Shojaei *et al* (2001) Systemic Drug delivery via the buccal mucosal route. *Pharmaceutical Technology* June issue: 70-81. www.pharmaportal.com
7. Ilavarasan, P., Ezhumalai, K. and Rajalakshmi, A.N. (2011) Buccal patches as emerging trend. *International Journal Of Pharmacy & Technology* 3(2): 973-986.
8. Madhav, N.V. *et al* (2009) Orotransmucosal drug delivery systems: a review. Journal of Controlled Release 16;140(1): 2-11.
9. Pather S.I., Rathbone, M.J. and Senel, S. (2008) Current status and the future of buccal drug delivery systems. *Expert Opinion on Drug Delivery* 5:531–542.
10. Nicolazzo, J.A., Reed, B.L. and Finnin, B.C. (2005) Buccal penetration enhancers—How do they really work? *Journal of Controlled Release* 105:1–15.
11. Dali, M.M. *et al* (2006). A rabbit model for sublingual drug delivery: Comparison with human pharmacokinetic studies of propranolol, verapamil and captopril. *Journal of Pharmaceutical Sciences* 95:37-44.
12. Mizrahi, B. and Domb, A. J. (2008) Mucoadhesive polymers for delivery of drugs to the oral cavity. *Recent patents on drug delivery & formulation* 2(2): 108-19.
13. Holpuch, A.S. *et al* (2010) Nanoparticles for local drug delivery to the oral mucosa: proof of principle studies. *Pharmaceutical Research* 27: 1224–1236.
14. Moingeon, P. and Mascarell, L. (2012) Induction of tolerance via the sublingual route: mechanisms and applications (review article). *Clinical and Developmental Immunology*: 8 pp (Article ID 623474).
15. Thaxter, C. (July 25, 2011) *Reckitt Benckiser Pharmaceuticals CEO presentation*. http://www.rb.com/DocumentDownload.axd?documentresourceid=10470
16. Thomaselli, R. (Apr 9, 2012) Intermezzo rouses drug category with $100 million push. Advertising Age: http://adage.com/article/news/intermezzo-rouses-drug-category-100-million-push/234014/.
17. Drug information online. (2012) Drugs.com http://www.drugs.com/manufacturer/sepracor-inc-renamed-sunovion-pharmaceuticals-inc-163.html.
18. Stacy, M. and Silver, D. (2008) Apomorphine for the acute treatment of „off" episodes in Parkinson's disease. *Parkinsonism & Related Disorders* 14(2): 85-92.
19. Olanow, C.W., Stern, M.B. and Sethi, K. (2009) The scientific and clinical basis for the treatment of Parkinson disease. *Neurology* 72(21 Suppl 4): S1-136.
20. Schapira, A.H.V., Emrebe, M., Jenner, P., and Poewe, W. (2009) Levodopa in the treatment of Parkinson's disease. *European Journal* of *Neurology* 16: 982–989.
21. Khora, S.-P. and Hsub, A. (2007) The Pharmacokinetics and Pharmacodynamics of Levodopa in the Treatment of Parkinson's Disease. *Current Clinical Pharmacology* 2: 234-243.
22. Chen, J.J. and Swope, D.M. (2007) Pharmacotherapy for Parkinson's Disease. *Pharmacotherapy* 27(12 Pt 2): 161S–173S.
23. FDA Approved Labeling Text for NDA 021264 Dated 7/20/10; NDC code: 15054-0211-5; http://labels.fda.gov/packagecode.cfm.
24. http://www.vectura.com/news/releases/2010/2010-11-16a.aspx; 2010.
25. http://www.britannia-pharm.co.uk/news.html; 2009.
26. Espay, A.J. (2010) Management of motor complications in Parkinson disease: current and emerging therapies. *Neurologic Clinics* 28(4): 913-25.
27. Medacorp report. (Dec 2011) *Trends in the treatment of Parkinson's disease* prepared for Cynapsus Therapeutics.

From the Boardroom

Biomarketing strategy and tactics 101: Part II of III

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ABSTRACT

The American Marketing Association defines marketing as the activity, set of institutions, and processes for creating, communicating, delivering, and exchanging offerings that have value for customers, clients, partners, and society at large. According to the Pharmaceutical Research and Manufacturers of America appropriate marketing of medicines ensures that patients have access to the products they need and that the products are used correctly for maximum patient benefit. The most important promotional tools for biopharmaceutical firms are 1) personal selling, 2) advertising, 3) public relations and publicity, and 4) web promotion. Part I of this three-part article focused on the nature of the biopharmaceutical marketing's four P's, the importance of marketing strategy, the conduct of environmental analysis, and maket segmentation. Part II delves into the processes of targeting and positioning, marketing planning, as well as biopharmaceutical branding. Part III completes the series by focusing on the push and pull promotional strategies, advertising, selling, and biopharmaceutical web and social marketing.

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Keywords: biopharmaceutical, marketing, targeting, positioning, branding, advertising

TARGETING AND POSITIONING

Targeting

Having identified and profiled all relevant target segments (including prescribers, patients, institutional buyers, influencers, and others), biopharmaceutical marketers embark upon the targeting process. Here the main defining variable is market attractiveness, however there are multiple other variables that play a role in targeting a given segment. Let's review some of them:

- **Market attractiveness:** current volume (biopharmaceutical dosages) and value (US dollars) size, potential volume/value size, growth rate, profitability.
- **Competitor presence:** number, size, sales volume, sales growth, market shares, products, competitive advantages, competitive strategies.
- **Barriers to entry:** product approval, pricing and reimbursement, capital expenses, local market conditions, raw materials, laws and regulations, economies of scale.
- **Government restrictions:** clinical trials, marketing approval, pricing, reimbursement, formulary, pharmacovigilance, taxation, discounts required, local investment required.
- **Prescriber characteristics**, unmet needs, see part I.
- **Patient characteristics**, unmet needs, see part I.
- **Suppliers and buyers:** bargaining power, existence of alternatives, preferential relationships, local versus multinational.
- **Organizational capabilities:** intellectual property, period remaining under patent

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protection, product portfolio, competitive advantages, therapeutic area experience and expertise, opinion leader relationships, regulatory relationships, competitive strategy, available investments, know-how, priority, vision-mission-values, and more.

Based on all the above parameters, individual market segments are identified, profiled, and rated, while all relevant biopharma resources and capabilities are rated versus those of existing or expected competitors. The final outcome is the priority target segments (prescribers, indications, patients, institutional buyers, and local versus international) that need to be pursued by the biopharma according to detailed corporate strategy, business, and marketing plans that will be further discussed below. Figure 1 describes the biopharmaceutical targeting process we have just discussed.

Box 1: Actelion's commitment to pulmonary arterial hypertension (PAH)[1]

Actelion is a highly profitable life science firm as a result of our leading franchise in pulmonary arterial hypertension (PAH), where our three marketed products Tracleer, Ventavis and Veletri continue to bring significant value to patients. In 2010, we continued to invest appropriately in supporting our existing product portfolio. We also focused on two late-stage clinical compounds – macitentan and selexipag – both under investigation in PAH. The studies are designed to demonstrate that these two compounds significantly improve the outcome for patients by reducing morbidity/mortality.

Positioning

A biopharmaceutical product's positioning is "the place it occupies in its customers' minds." This position is primarily dictated by the product's own characteristics, for example its intrinsic efficacy, safety, tolerability, onset of action, mechanism of action, and more. However, it's not only its basic pharmacodynamic and pharmacokinetic properties that find their way into the customer mind. It's also the word of mouth, from fellow disease sufferers and their families. It's the opinion and recommendation of medical experts, for example the president of a medical association. It's the recommendation of a celebrity, who is either acting on its own, or has been employed by the biopharma as its spokesperson. It's also the product's pricing and reimbursement. It's the product's external thermo-insulated carrying case, its external packaging (white carton), the internal packaging (pre-filled multi-injector device, its ease of use, its practicality for special patient groups—e.g. kids' growth hormone or elderly patients' anti-Alzheimer's patch), and so on. Furthermore, it's the occasional unexpected moments e.g. while taken by a mother during pregnancy, taken by someone during their adolescent years, taken during a trip to the mountains, or purchased abroad. All in all, it's all those mo-

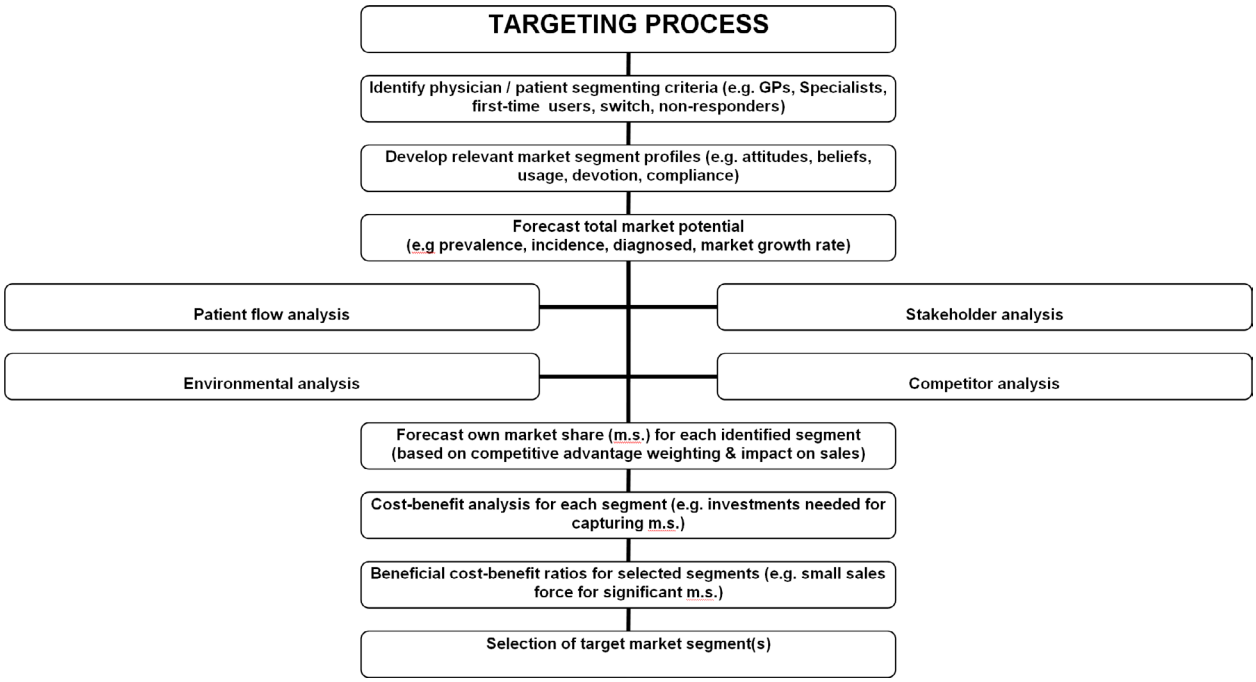

Figure 1: The targeting process

ments. Their collective influence (conscious and unconscious), patients' or that of others', stated or experienced, internal or external.

A biopharmaceutical's positioning encompasses all our life experiences with the given medicine. It is also relevant with the product's competitors' positioning. For example, we may consider our favorite NSAID the most effective, but unrealistically expensive (problematic positioning). Or, our own favorite brand may be the quickest to act, but with a syrup's taste to forget! Our product's positioning is "for us to create in the mind of our prescribers and patients".

Positioning process

The biopharmaceutical product positioning process is based on several distinct steps, for example: 1) Detailed market segment profiling, for example describing in depth the disease, the patients, the prescribers, and other stakeholders; 2) Identifying the unmet and satisfied needs and wants of each stakeholder; 3) Rating the importance of the identified product attributes; 4) Rating the possession of these attributes by our own product and those of the competitors; 5) Choosing our biggest competitive advantages that would most closely satisfy the needs and wants of our customers; 6) Presenting these advantages in an easy to understand, easy to remember, patient-friendly and compassionate manner; and 7) Occupying the desired customer mind space, and repeating our messages, using various communication channels, in such a way that we eventually OWN that space.

A distinction needs to be made between biopharmaceuticals still in development and those already commercially available. In the first case scenario our own positioning is based on clinical trial evidence (clinical endpoints, as well as on patient, prescriber, and nurse testimonials) which will suggest an initial positioning to be further refined during the marketing meetings. In the second case scenario, commercial products already occupy a positioning that was conquered by the product characteristics themselves, as well as the biopharma's actions to "place it" at a certain positioning.

Positioning strategy

As mentioned above, a positioning strategy is essentially based on the biopharmaceutical product's attributes, and how these better satisfy the unmet needs and wants of the product's target segments. Having chosen the best-suited competitive advantages, a positioning strategy then selects the proper communication messages, vehicles, and frequencies with which to be presented to the target segments. Figure 2 details the major steps of coming up with a biopharmaceutical brand's positioning.

- Identify competitive products
- Identify determinant attributes
- Measure existing perceptions
- Analyze relative position of alternatives
- Determine preferred set of attributes
- Define positioning
- Devise re-positioning

Figure 2: How do you come up with a biopharmaceutical brand's positioning?[2]

Box 2: Actelion's Zavesca[3]

- Zavesca is the only disease-modifying therapy reducing the progression of clinically relevant neurological symptoms in patients with Niemann-Pick type C.
- Continued commitment to patients with type 1 Gaucher disease.

The positioning statement

Having completed the positioning process, a biopharmaceutical startup's marketing team needs to come up with a single, brief, memorable, and powerful positioning statement, such as the following: "To (The Target Segment), Brand (X) is the (Frame of Reference) which provides a (Point of Difference)". A biopharmaceutical product's positioning may take several types, for example, based on product benefits, by user group, or compared to the competition. Figure 3 summarizes a plethora of biopharmaceutical positioning types.

Based on the issues discussed above, Figure 4 provides a concise example of coming up with a biopharmaceutical brand's targeting, profiling, and positioning statements.

DIFFERENT SEGMENT STRATEGIES

Following the identification of unique market segments and the analysis of their economic attractiveness, competitive intensity, and differential product advantages in each, biopharmaceutical marketing departments must decide on the segment strategies suitable for each of their products. According to Dogramatzis[2], the final selection may depend on the following factors: *market characteristics* (size, growth, competition, physician number, consumer attitudes), *regulatory environment* (reimbursement, pricing, cost-containment), *product characteristics* (differential advantage, life cycle stage, branding, pricing), and *company characteristics* (corporate strategy, portfolio priorities, therapeutic category expertise, re-

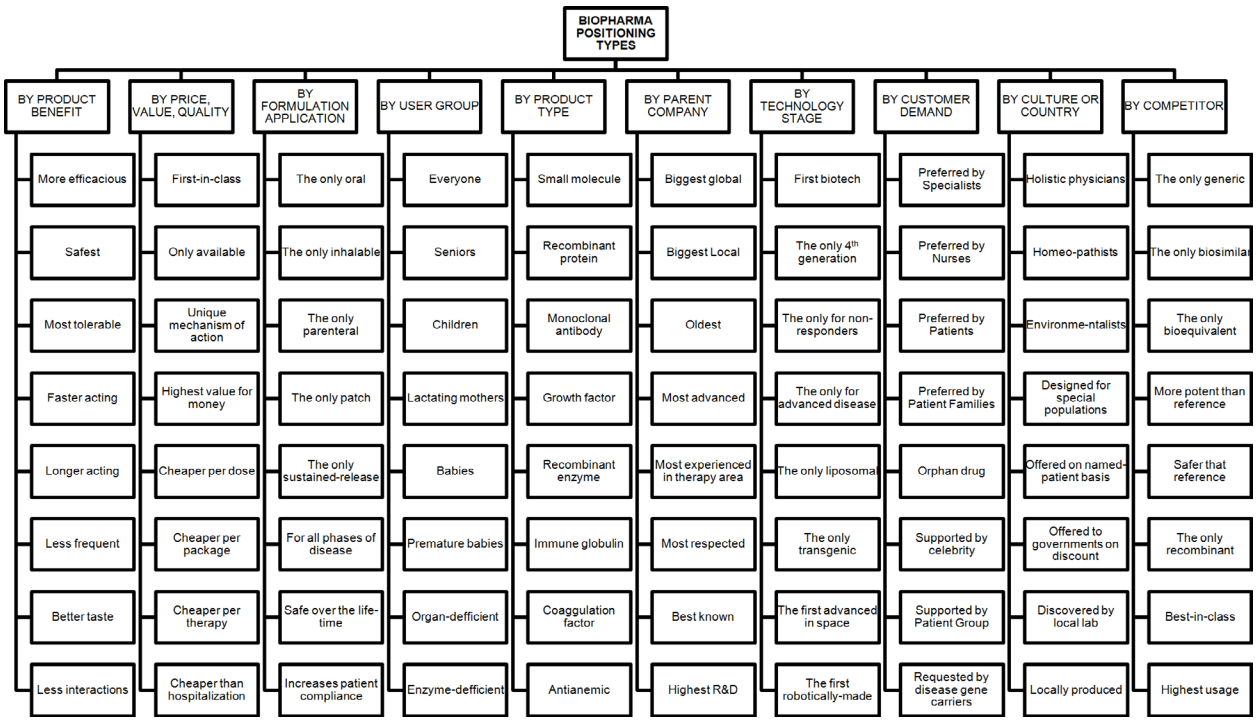

Figure 3: Types of positioning

Parameter	Targeting	Profiling	Positioning
Efficacy	Oncology specialists	Most efficacious in prolonging survival	First choice therapy for metastatic breast cancer
Safety	Gerontologists	Safest choice for patients under multiple Rx	For elderly insomnia sufferers
Other			

Figure 4: How do you come up with biopharmaceutical brand targeting, profiling, and positioning statements?[2]

sources). Segment strategies are broadly divided in four categories, namely mass, differentiated, niche, or custom, in increasing degree of segment differentiation.

Undifferentiated (or mass marketing)

An undifferentiated segment strategy implies that the product is to be marketed widely to the masses, employing a homogeneous marketing approach across all prescribing physicians, or dispensing pharmacists, or consuming patients. Obviously, the product characteristics support such a strategy by offering relief from a widely spread ailment (e.g. fever) often seen by all medical specialties, and acting through a safe and efficacious mechanism across all patients segments. This strategy requires marketing tactics that will appeal to all prescribers and patients alike, and offers the advantages of a universally homogeneous campaign.

On the other hand, vast amounts of marketing resources need to be budgeted towards multiple medical specialties and millions of patients around the world. Furthermore, it is difficult to create a unique competitive advantage when trying to appeal to a vast consumer base, and this increases the threat of competition. In trying to protect from competition, pharmaceutical conglomerates often rely on intensive branding campaigns, making their offerings stand out from the crowd.

Differentiated (or multiple-market or product-variety marketing)

Differentiated segment strategies call for the creation, implementation, and evaluation of multiple marketing campaigns aimed at different market segments. To illustrate the value of a differentiated strategy, let us envision a CNS-oriented biopharmaceutical company with a wide antidepressants portfolio. The company has identified the unique market segments of the adult depressed population, the elderly population, as well as the sufferers from obsessive-compulsive disorder (OCD) that may be helped by antidepressant therapy. In selecting its marketing strategies, the company may position a different antidepressant for each of the above segments (selective market strategy), or all products, at different prices or dosages, to a single segment (single-market, product-

Box 3: Astrazeneca's Crestor[4]

Since its launch in 2003, Crestor has continued to gain market share based on its differentiated profile in managing cholesterol levels and its more recent label indications for slowing the progression of atherosclerosis and reducing the risk of CV events in some markets. Crestor is the only statin with an atherosclerosis indication in the US which is not limited by disease severity or restricted to patients with coronary heart disease.

Box 4: Roche's focus on personalized healthcare[5]

As the world's largest biopharmaceutical company and the number one supplier of in vitro diagnostics, Roche has brought many highly effective drugs to market, including the industry's leading portfolio of cancer medicines. We were also one of the first companies to recognise the potential of personalised medicine. Today our expertise in molecular biology is enabling us to develop targeted medicines for specific patient groups. This contributes to better, safer, more cost-effective healthcare.

variety), or even one product (at different dosages) for all segments (single-product, multiple-market).

Before such decisions can be made, however, the company has to consider the following: Can our product serve the needs of multiple segments? Can we successfully invest in and defend several segments, simultaneously? And do we have the resources required? A differentiated segment strategy offers better chances of satisfying different customer needs, but may require increased marketing investments, compared to the undifferentiated strategy.

Single segment / niche (or concentrated or target marketing)

Focusing on a single segment (niche market), by building a prohibitive competitive advantage within that segment, and defending against any potential entrant is a common strategy among many small, or medium-sized biopharmaceutical companies which do not have the resources to compete with other giants on more, and wider market segments. For instance, a biopharma may try to become a world's specialist company in Parkinson's disease, avoiding competing in other CNS therapeutic areas, and diversifying previously existing business units in oncology or rheumatology. Such a strategy offers unique advantages, such as focusing all resources in one therapeutic area, building a formidable portfolio, constructing barriers to entry for new competitors, and implementing a sharply-focused marketing campaign.

A niche strategy, however, does not come without disadvantages. Strictly confined R&D programs have inherent risks of producing promising lead compounds failing to progress into marketable products, and thus delaying new product introductions for a long time. In addition, the niche market conditions may abruptly change, by either revolutionary new biological entities launched by a giant new entrant, or even a change in the regulatory environment leading to reduced prices or reimbursement coverage, sharply decreasing the biopharma's profitability. Furthermore, a niche market offers finite growth opportunities, and limits the company's long-term financial stability and survival.

Custom (or single customer marketing)

The dilemma of how small of a segment to focus on has also confronted other industry sectors, leading in some cases into the strategy called *mass customization*, meaning the micro-targeting down to the level of each individual consumer, such as in the case of custom-made blue jeans to fit the individual buyer size. One of the available techniques in targeting individual customers is *database marketing*, allowing the collection and management of large amounts of customer information.

BIOMARKETING PLANNING

Strategic marketing and its incorporation throughout the drug development process is a key to the success of new product development at biopharmaceutical companies. There are several key marketing considerations that should be examined well in advance of a product launch. In order to optimize the marketing efforts in the development of new biopharmaceutical products, it is important for biopharmas to examine these factors while the product is in development.

Biomarketing planning phases

In the R&D phase, it is important to identify the intellectual property positions on the compounds and review the discovery efforts to ensure they are in line with the overall strategic priorities of the biopharma. Because A biopharma startup is smaller and has limited funds for the very expensive development process, it must carefully select the potential products to pursue and then choose which ones to partner for and which ones to develop alone. To do this, the marketing team makes assumptions and builds estimates of the potential US markets for the products and indications that might be coming

Box 5: Merck Serono's 2011 forecast[6]

For the Merck Serono division, the Executive Board is expecting an increase in total revenues in 2011 ranging between 5% and 10%, relative to EUR 5,754 million in 2010, and predicts continued growth for 2012. Relative to EUR 565 million in 2010, we want to achieve significant growth in the operating result in 2011 and a further increase in 2012. The stronger increase as compared to total revenues can be attributed to a moderate cost increase, especially in marketing and sales.

out of its R&D department. It can then make more informed go/no go decisions and be more knowledgeable for potential partnering and alliance negotiations.

During the preclinical phase, it is important for biopharmas to begin developing a vision for the potential product as well as to identify the key attributes and value drivers that will make the product succeed. Once they enter phase I clinical trials, the company should be able to identify the minimum attributes that the compound must demonstrate in order to achieve success. During phase I/IIa trials, the company should also start to examine the patient flow within the market they are hoping to enter, identify what clinical endpoints they will eventually have to achieve in order to effectively compete with products currently on the market, and begin to think about the potential economics and pricing of the product they are developing.

During phase IIa trials, the company may also want to begin targeting key physicians, patient groups, and thought leaders in order to solicit important market research information and to increase awareness and acceptance of what the company is developing. After collecting this information, the company should be able to make some informed management decisions regarding the clinical trial strategy going forward and garner more clarity into likely investment levels. The company should also have a solid understanding of the competitive landscape and what the positioning strategy of their product will be.

During the phase IIb/III stages of development, the company should be developing a publications plan, identifying and communicating with key opinion leaders, and finalizing pricing and reimbursement strategies. During filing, the company should work to ensure that they have a competitive label and an appropriate channel strategy. After launch, the company needs to begin the process of life cycle management and start to examine new claims, indications and formulations for the product. In general, biopharmaceutical marketing tactics follow strategy, as can be seen in Figure 5. As far as the biopharmaceutical planning process is concerned, Figure 6 describes the main biopharmaceutical planning stages, while Figure 7 describes the process of the annual global biopharmaceutical planning cycle. Furthermore, Figure 8 explains how you come up with a biopharmaceutical brand action plan, while Figure 9 provides a useful template for forecasting the marketing contribution for a biopharma launch.

BIOPROMOTION

The cumulative place that every biopharmaceutical occupies in the minds of a market's customers is also called a brand. Since this place is of paramount importance for the product's commercial success and profitability,

Strategy	Tactics
Become market share leader	Hire and train 15 new sales representatives
Grow sales by 20% every year	Visit key accounts once weekly
Penetrate 10% of market in launch year	Prepare 3 new detail aids per year

Figure 5: How do biopharmaceutical marketing tactics follow strategy?[2]

Identify and evaluate opportunities	Analyze market segments and select target markets	Plan a market position and develop a marketing mix strategy	Prepare a marketing plan - Execute the plan	Control efforts and evaluate the results
Identify unmet ther. needs				
Assess total market size				
Construct patient journeys				
Identify target physicians				
Evaluate physicians' needs				
Identify pipeline candidate				
Assess candidate's profile				

Figure 6: Which are the main biopharmaceutical planning stages?[2]

STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5	STAGE 6	STAGE 7	STAGE 8	STAGE 9	STAGE 10
MARCH		APRIL	MAY	JUNE	JULY - AUGUST			SEPTEMBER - OCTOBER	
BOARD	**CORPORATE MARKETING**	**CORPORATE THER AREA**	**REGION**	**SUBSIDIARY**	**SUBSIDIARY MARKETING**	**SUBSIDIARY THER AREA**	**LOCAL REGIONS**	**LOCAL SALES AREAS**	**CONSOLIDATION & SUBMISSION**
Vision	Ther Areas	Product mix	Growth targets	Growth targets	Product mix	Product mix	Growth targets	Physician targeting	Bottom-up consolidation
Mission	Product mix	Product launches	ROI targets	ROI targets	Timings	Product launches	ROI targets	Physician segmentation	National ther area consolidation
Objectives	Product launches	Product withdrawals	Headcount targets	Headcount targets	Responsibilities	Product withdrawals	Headcount targets	Physician profiling	Subsidiary consolidation
Growth targets	Sales targets	Global internal analysis	Product mix	Product mix	Workshop schedule	Local internal analysis	Physician targeting	Physician prescribing targets	Subsidiary presentation to regional
ROI targets	ROI targets	Global stakeholder analysis	Marketing research update	Timings	Plan writing schedule	Local stakeholder analysis	Physician segmentation	Hospital prescribing targets	Subsidiary plans approved
	Timing	Global competitive analysis	Clinical trial update	Responsibilities	Consolidation schedule	Local competitive analysis	Physician profiling	District prescribing targets	Regional presentation to corporate
	Resource allocation	Marketing research update	Publication schedule	Planning deadlines	Local presentation schedule	Marketing research update	Activities for physicians	Local target consolidation	Regional plans approved
		Clinical trial update	Congress schedule		Regional presentation schedule	Congress schedule	Activities for regulators	Local activities planned	Corporate marketing presentation to Board
		Publication schedule	Marketing materials			Marketing materials	Activities for patients	Physician budgets planned	Other functional presentations to Board
		Congress schedule	Opinion Leader update			Opinion Leader update	Activities for media	Sales targets proposed	Board approval of functional & regional plans
		Marketing materials	Organization chart			Marketing support	Sales call planning	Sales budgets proposed	Top-down global communication of targets
		Opinion Leader update	Regional & corporate reporting			Marketing templates	Key account planning	Headcount proposals	External announcement of targets
		Marketing support	Timings			Financial templates	Budgets requested		
		Marketing templates	Responsibilities						
		Financial templates							

Figure 7: The process of the annual global biopharmaceutical planning cycle

BIOPHARMACEUTICAL BRAND:																			
ACTION PLAN: 2011																			
KEY SUCCESS FACTOR:														OBJECTIVE:					
Marketing Activity	Key	Code	Budget Actual	Start	End	Response	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Impact
A																			
B																			

Figure 8 How do you come up with a biopharmaceutical brand action plan?[2]

Reporting Currency: USD	YEAR -3	YEAR -2	YEAR -1	LAUNCH	YEAR +1	YEAR +2	YEAR +3	YEAR +4	YEAR +5
	2008	2009	2010	2011	2012	2013	2014	2015	2016
Volume (Units)									
Average Unit Price (ASP)									
Other									
TOTAL MARKETING EXPENSES									
Medical Affairs									
Local Clinical Trials									
Other									
TOTAL COMMERCIAL EXPENSES									
Marketing Headcount									
Medical Affairs Headcount									
Other									
TOTAL COMMERCIAL HEADCOUNT									
Brand Contribution									
Sales Force Cost									
Other									

Figure 9 How do you forecast the marketing contribution for a biopharmaceutical launch?[2]

brand management is specifically targeted at applying all pertinent marketing techniques in order to increase the biopharmaceutical product's perceived value to the customer.

By carefully and gradually building a valuable brand, biopharmaceutical marketers aim to increase the product's profitability and sustainability since a brand: 1) increases the perceived value of the product in the customer's mind, 2) implies a higher product quality, which can dependably be purchased again in the future, 3) makes a product unforgettable, recognizable, and sought after, 4) increases customer loyalty, and 5) allows a product to be priced with a premium. Based on these factors, a brand can significantly increase a product's sales and profitability, both of which can be used as indicators of a brand's success.

Box 6: Johnson & Johnson's Remicade[7]

REMICADE® (infliximab), a biologic approved for the treatment of a number of immune mediated inflammatory diseases, achieved sales of $4.6 billion in 2010, with growth of 7.1% over the prior year. U.S. export sales grew 24.3% versus the prior year primarily driven by market growth. REMICADE® is competing in a market that is experiencing increased competition due to new entrants, including the successful launches of STELARA® (ustekinumab) and SIMPONI® (golimumab) and the expansion of indications for existing competitors.

BIOPHARMACEUTICAL BRANDING

We have just described a biopharmaceutical brand as the cumulative place it holds in all its customers' minds. These places are occupied by either: 1) rational values (my medicine takes away my arthritis pain), 2) emotional values (my medicine allows me to be a full-time mom close to my kids, instead of being bed-ridden), 3) qualities (my medicine comes with a practical auto-injector device, and is fast-acting, and well-tolerable), and associated services (my medicine comes with free homecare support and a 24-hour hotline). Furthermore, a biopharmaceutical brand may belong to a single product (a rheumatoid arthritis medicine), multiple products (a class of erythropoietic medicines), or a biopharmaceutical corporation (a corporate brand belonging to a California-based biotechnology pioneer).

As mentioned above, a brand is carefully and gradually constructed by biopharmaceutical marketers. This is achieved by providing memorable and enjoyable marketing communications, showcasing and strengthening the product's value and quality, while at the same time the actual customer experience is delivering upon this promises, which consistently satisfy the needs of its customers and increase its cumulative satisfaction and customer loyalty. Let us now review how a biopharmaceutical brand is comprised of multiple layers.

The Layers of a Brand

Biopharmaceutical brands are made up of four layers: the core product or service, the basic (actual) brand, the augmented brand, and the potential brand (see Figure 10). Let's see what these mean.

Biopharmaceutical brands are prescribed by physicians and taken by patients for the provision of a core effect(s). For example, a rheumatoid arthritis biopharmaceutical reduces the signs and symptoms of the disease, prevents further damage to one's bones, and helps one's ability to perform daily activities. The same product's actual brand is comprised of actual characteristics, for example its external packaging, its patient information leaflet (PIL) insert, its auto-injector device, its accompanying instructions for usage, and obviously its pharmacy purchasing or home delivery at a refrigerated temperature, with a guaranteed quality (for example free of contaminations, in a tamper-resistant packaging), etc. These are all basic product characteristics that the customer expects from this product, wherever it was purchased from. In addition to the previous two layers, the brand may also come with an augmented layer. For example, instead of making the painful trip to the pharmacy, an RA sufferer may expect free home delivery, several initial homecare nurse visits at the initiation of home therapy, easy-to-understand multilingual instructions (in paper, or video/DVD), and also significant product reimbursement (or reduced/no patient co-payment).

Finally, the same biopharmaceutical brand may have a potential (or enhanced) layer. For example, the RA biopharmaceutical may have a patient advocacy network built around it, patient networking, patient adherence-improving tools and services, a very famous celebrity acting as its spokesperson, etc. These additional products and services, most of which are offered by the biopharmaceutical manufacturer at no additional cost to the patient or his/her insurance provider, make the collective value of the given brand so powerful and desirable, that the customer feels a strong, life-long relationship with the brand, leading to increased therapy adherence and customer loyalty.

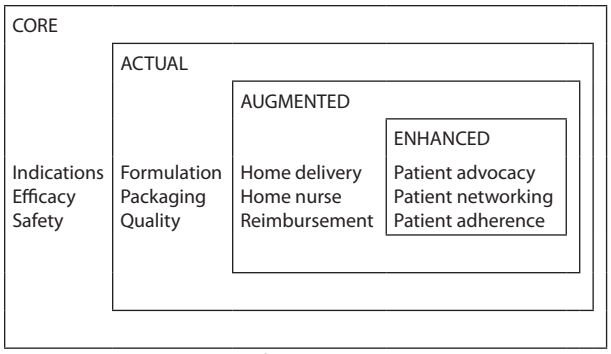

Figure 10: The layers of a brand

Box 7: The Bayer brand[8]

The Bayer brand has a special charisma and is among the most famous worldwide. Around the globe, the name "Bayer" stands for innovative, high-quality products. At the same time, our brand symbolizes trust and reliability and therefore makes the company more competitive. That is why we are further raising our brand profi le by using our umbrella brand even more systematically and effectively.

Box 8: UCB'S Cimzia offering[9]

Underlining our commitment to patients, UCB offers Cimzia® in an exclusively designed pre-filled syringe and easy-to-open packaging, thanks to our partnership with OXO®, the maker of the Good Grips® brand of household tools. Various aspects of the syringe and packaging were designed in close collaboration with patients in order to ensure the challenges associated with self-injection were alleviated.

BRAND ASSET MANAGEMENT

As mentioned above, by carefully and gradually building a valuable brand, biopharmaceutical marketers aim to increase the product's profitability and sustainability. The creation of such a brand is one of the responsibilities of brand asset management, or brand management. Let's see what tasks are included within this critical marketing function. Brand building is the selection of a brand identity, including its name, associated trademark, images, colors, sounds and other elements used to create a memorable and enjoyable brand experience. Figure 11 provides a summary of assets used in building a biopharmaceutical brand identity.

Creating a global branding strategy (see below) is the selection of common strategies, names, messages, images, and communication tactics that are to be used across the world, so that a powerful, global brand identity emerges and creates value for the brand in a proactive, strategic, consistent, multiethnic, and multilingual manner. Building brand architecture indicates the existence of multiple product brands, or product family brands, or corporate brands that need to be carefully constructed so that they complement and support each other, in a clear, strategic, and consistent manner (see product width, length, and depth below). For example, Figure 12 provides a concise guide on how to brand a biopharmaceutical product towards its various stakeholders.

Brand rationalization refers to the occasional reduction of the promoted brands, either due to a product discontinuation at the end of its life-cycle, or an abrupt product withdrawal due to serious side effects, or the introduction of an improved version (new dosage, administration route, formulation, etc). In this case the biopharma's brand portfolio needs to be carefully realigned, so that the new products overtake the old one

	Biopharmaceutical brand identity components
1	Description of the brand
2	Audience
3	Tone of voice
4	Background
5	Brand objectives
6	Our customer emotional values
7	Barriers
8	Bonds
9	Communication objectives
10	Positioning promise

Figure 11: How do you create a biopharmaceutical brand identity?[2]

Stakeholders	Product	Category	Corporate	Industry
Consumers	+++	+	++	+++
Managed care customers	+++	++	+	+
Payers	+++	++	+	+
Others	+++	+++	++	+

Figure 12: How do your brand a biopharmaceutical product towards its various stakeholders?[2]

in the mind of the customer, without causing confusion, or allowing a competitor to capture that valuable space.

Brand repositioning (or rebranding) indicates the attempt of a biopharma to reinforce a product's image, by either improving its positioning and moving its position in the mind of the consumer, or attempting to prevent the damage from a competitive brand launching, or moving its positioning due to changing customer demands (for example patients demanding an increased quality of life, and not only high efficacy with severe side-effects). The brand repositioning, or portfolio alignment effort, involves three distinct steps: 1) what is the brands' positioning today—how are they perceived: disease-modifying, symptom-reducing only, safe, quick onset, cheap, quality; 2) Where should the brands be positioned in the future for maximum cross-coverage – brand A as disease-modifying, first-line, powerful treatment, brand B as second-line, combination-only, and brand C as cheapest generic alternative for uninsured, out-hospital, or low-reimbursement patients; 3) What brand moves are necessary for the portfolio realignment, for example what clinical trials, opinion leader articles, or patient testimonials can gradually establish these moves?

Brand orientation refers to the importance given to brand management by a biopharmaceutical corporation, and its brand management dedication and expertise. For example, a young biopharma launching its first commercial product with limited branding support, may lose valuable market share opportunities, even if it has a beneficial product profile (second-generation product), over the older, but more established and better supported existing biopharmaceutical (first-generation) brand.

BIOPHARMACEUTICAL BRAND WIDTH, LENGTH AND DEPTH

In building biopharmaceutical brand architecture, we have previously mentioned about the existence of multiple branding strategies. Let's see what these may be. Figure 13 summarizes six different branding approach-

LINE EXTENSION	BRAND EXTENSION
Existing Brand – Existing Product e.g. New formulation, new dosage	Existing Brand – New Product e.g. New longer-acting molecule administered once monthly
MULTIBRAND	**NEW BRAND**
Existing Product – New Brand e.g. Growth hormone for a new indication	New Product – New Brand e.g. New coagulation factor acting at different step
CENTRALIZED	**DECENTRALIZED**
ARTITROPIN A, ARTITROPIN B Both made by company ARTION	FERTITROPIN, ARTITROPIN, ERYTHROTROPIN made by MICROPROT

Figure 13: Biopharmaceutical brand strategies (fictitious brand names)[2]

BIOPHARMACEUTICAL PRODUCT MIX		
PRODUCT WIDTH	**PRODUCT LENGTH**	**PRODUCT DEPTH**
Number of different product lines	Number of products within the lines	Number of versions of same product
Long-acting molecule	100 International Units (I.U.) per vial	100 I.U. Single vial package
Median-acting molecule	50 International Units (I.U.) per vial	100 I.U. 3-Vial package
Short-acting molecule		100 I.U. 5-vial package

Figure 14: Product mix[2]

Box 9: Astrazeneca's Seroquel[10]

Seroquel IR (quetiapine fumarate) is an atypical anti-psychotic drug generally approved for the treatment of schizophrenia and bipolar disorder (mania, depression and maintenance). Seroquel XR (an extended release formulation of quetiapine fumarate) is generally approved for the treatment of schizophrenia, bipolar disorder, MDD and in some territories for GAD. Approved use for Seroquel IR and Seroquel XR varies based on territory.

es, for example a centralized versus a non-centralized approach, as well as launching a new brand versus a brand extension strategy. Furthermore, Figure 14 introduces the meanings of product width (number of different product lines), product length (number of products within the lines), and product depth (number of versions of the same product).

GLOBAL BIOBRANDING

International government healthcare regulation is imposing, widely diverse, and constantly changing. For example, every single aspect of biopharmaceutical markets is regulated in some way, including clinical trials, brand naming, marketing approval, pharmacovigilance, pricing, reimbursement, formulary inclusion, prescribing, advertising, and more. In addition, global populations are diverse, with different values, attitudes, needs, wants, standard of living, purchasing power, and more. Why then do more and more biopharmaceutical companies adapt global biobranding strategies, under the light of such diverse customer segments, living under different conditions or regulations?

WHY GLOBAL BIOBRANDING

Despite the diverse conditions mentioned before, the reasons for global biobranding are multiple. First, disease manifestations are identical in their nature, excluding minor ethnic differences among populations. Second, global political and economic country unions are constantly expanding (e.g. European Union, British Commonwealth, NAFTA, ASEAN), bringing the standards of living and applicable regulations closer together. Third, increased patient mobility leads to common needs and wants. Fourth, increased patient access to Internet searching, e-mail, social networking, web telephony, and web conferencing bring patient networking to new levels, never before possible. Fifth, the patient advocacy movement is becoming stronger, more proactive, highly educated, and media-adept, leading to new demands for increased quality of life across national borders.

Sixth, opinion leader and prescriber mobility and web access lead to the creation of widely accepted treatment guidelines. Seventh, international regulatory agencies are moving closer to global harmonization. Eight, biopharmaceutical products take longer to develop, leaving reduced time under patent protection, thus necessitating the globally simultaneous commercial launches in every market. Ninth, as more patient populations enter the global healthcare markets (due to higher standard of living and increased education and transparency), biopharmas are faced with enormous promotional campaign expenses, if they were to be nationally implemented, instead of in a global cascade manner. Tenth,

Box 10: Actelion's commitment to a global infastructure[11]

In 2010, Actelion also continued to strengthen its global reach and its global infrastructure. Actelion now has 29 operative affiliates and is thus present with sales, marketing, distribution, regulatory and medical capabilities in all key pharmaceutical markets. This is true even in Japan, where no other biotechnology company has built up its own presence from its inception.

increased industry competition, more biopharmaceutical players in every therapeutic area, and rising commercialization risks make the global biobranding strategies a must.

Creating a global branding strategy

Faced with the changing geopolitical and healthcare conditions mentioned above, biopharmaceutical marketers are driven toward the strategic, proactive, global, and coherent biobranding model across all reachable commercial markets. The process of creating a global campaign, however, is not an easy task by itself, and is far from a corporate team devising and cascading its proposal across remote biopharma subsidiary operations. Instead, global biobranding is primarily focused on six contributing elements: 1) the corporate R&D scientists, 2) external opinion leader input, 3) global patient input, 4) dedicated and specialized external marketing consultants (marketing research, pricing, naming, reimbursement, formulary, positioning, and others), 5) corporate therapeutic area executives, and 6) core subsidiary therapeutic area experts (USA, EU, Japan, Asia-Pacific, Latam). If all these elements are proactively and strategically invited to participate and contribute, through a series of successive biobranding strategy formulation meetings, the final outcome is a globally acceptable, prescriber-validated, patient-driven, and corporate/subsidiary-adapted branding for maximum global impact. Figure 15 provides a practical summary of some of the required biopharmaceutical global branding characteristics.

Box 11: Astrazeneca's global strategy[12]

All our markets have an important role to play in delivering our commercial strategy. They are the base from which we drive growth and achieve business performance, while both ensuring that costs remain under control and our capabilities are strengthened. Nevertheless, we need to prioritise our investment in markets to ensure we allocate resources in the most cost-effective way. We did so in 2010 according to criteria such as market size and growth, risk profile, our current position in a market and its commercial relevance. This allows us to identify those markets of major significance to us, those that will become important drivers of our business in the future and those Established Markets where we need to change our approach to deliver sustained success.

Most important components in defining a global brand	Existing barriers to the development of global brands
Same name	Market differences
Same positioning	Affiliate resistance
Other	

Figure 15: Global branding characteristics[2]

BIOBRAND NAMING

One of the most important aspects of biopharmaceutical branding is its naming. Drug names need to be submitted and approved by the relevant regulatory agencies. In addition, they must be distinctive, suggestive of product benefits and qualities, as well as easy and global in their characteristics. Figure 16 gives several examples of the drug naming prerequisites.

Biopharmaceutical naming process

Industry marketers, together with specialized external branding and naming specialists, start working on biopharmaceutical names during phase II clinical trials. Armed with the initial clinical trial results, they start constructing the product's pharmacodynamic and pharmacokinetic profile that gives rise to distinct competitive advantages. Following a process of physician- and patient weighting, the product's unique characteristics are rated versus the competition and its unique selling points (USPs) start to emerge.

DISTINCTIVE	SUGGESTIVE OF PRODUCT BENEFITS	SUGGESTIVE OF PRODUCT QUALITIES	EASY	GLOBAL
Bold	Epo...	Effective	To remember	Multilingual
Decisive	Gene...	Safe	To recognize	Multi-ethnic
Inspiring	Huma...	Fast-acting	To pronounce	Accent-free
High tech	Rec...	Tolerable		Not judgemental
				Not nationalistic
				Respectful

Figure 16: Powerful biopharmaceutical brand names[2]

Initial naming candidates focus on the product's USPs, which are either core, actual, or augmented (see layers of a product, above). These USPs may remind the patient of the product's core benefits (e.g. efficacy, safety, onset of action, mechanism of action), its actual characteristics (e.g. a unique dosage and formulation), or its expected – augmented – benefits (e.g. increased mobility, leading to more family-time, and a better quality of life). The naming candidates then follow the following arduous process: 1) individual interviews and focus groups with prescribers, pharmacists, nurses, patients and their families, 2) preliminary trademark (patent office) and regulatory (FDA) screening, 3) short-listing by biopharma executives, 4) full legal and regulatory search, 5) global linguistic analyses (for being multi-ethnic, accent-free, not judgemental, and respectful), and 6) final name selection by the biopharma.

Eventually, the chosen biopharmaceutical name is submitted to the authorities for approval (FDA's Guidance for Industry, February 2010). Quite often the submitted names are rejected, leading to significant delays in the product's marketing authorization approval, usually for being similar to other approved products, which tends to lead to prescribing and dispensing errors, with serious consequences.

Naming techniques

There are various biopharmaceutical naming techniques used by branding experts. Before delving into some of them, we will briefly mention the use of sophisticated naming software, which are basically constructed around three pillars: 1) multi-lingual dictionaries, including ancient languages and even slang 2) the ability to construct new variants, often combining multiple words or devising a new one, and 3) the ability to pre-screen these word constructs for spelling, linguistic, and phonetic user-friendliness.

Armed with this technology, naming experts rely on certain naming techniques that may follow naming trends and fashions. Some of the most commonly used naming techniques are: 1) using an ancient language such as Latin, to borrow a word that means dreaming as indicative for a sleeping-aid, 2) a word indicative of the product's attributes, e.g. its mechanism of action, its quick onset, its efficacy, its amino-acid sequence, its enzyme interaction, 3) a word indicative of the product's chemical/biochemical composition, e.g. acid, basic, phenol, monoclonal antibody, 4) an inspirational word, e.g. life-, neo-, mobile-, vivacious-, energy-, joy-, 5) a male-sounding word, e.g. referring to strength, stamina, musculature, competitiveness, 6) a female-sounding name, referring to youth, beauty, motherhood, kindness, caring, 7) a kids-sounding name, referring to truthfulness, exuberance, playing, joy, a smile, 8) a molecular-sounding word, e.g. protein-, gene, antibody-, inhibitor-, blocker-, and more.

BOX 12: Amgen's Neulasta (pegfilgrastim) and Neupogen (filgrastim)[13]

Neulasta and NEUPOGEN stimulate production of certain white blood cells known as neutrophils.
NEUPOGEN is our registered trademark for Filgrastim, our recombinant-methionyl human G-CSF.
Neulasta is our registered trademark for pegfilgrastim, a pegylated protein based on the Filgrastim molecule. A polyethylene glycol molecule ("PEG") is added to enlarge the Filgrastim molecule, thereby extending its half-life and causing it to be removed more slowly from the body.

HOW ARE BIOPHARMACEUTICALS PROMOTED?

In general, a biopharmaceutical firm has four major promotional tools in its possession, namely 1) personal selling, 2) public relations and publicity, 3) sales promotion, and 4) advertising. Some of these tools may be implemented only after a product's marketing authorization approval, while others may be implemented even during the research and development phase. Furthermore, promotional activities may be directed toward the product portfolio, or the biopharmaceutical company itself. Let's look at these activities briefly.

1. **Personal selling** involves the use of company sales personnel who directly interact with the company's stakeholders, mostly medical professionals, other healthcare professionals, and regulators, in the stakeholder's working setting, and inform them about the company's and product's characteristics and benefits. The sales personnel are usually life-sciences graduates who receive additional company training on the disease, product, company, and competition attributes so that they better interact with the stakeholders. The essence of personal selling is building a personal relationship and eliciting an interaction that is aimed at satisfying the stakeholder's needs and wants, either for information, education, company

interaction, inclusion into clinical trials, etc.

2. **Public relations** and publicity involves all the company's activities aimed at interacting with the wider public, for example the disease patients and their families, patient advocates, the general public, the media, financial analysts, investors and others. The aim is that the company's values, intellectual property, innovation, therapeutic areas, products and services are widely known, and they in turn elicit a greater awareness, interest, willingness to try, usage, and eventually loyalty to the company's offerings. The essence of public relations is reaching wider audiences, in a more lay, easy-to-understand, and friendly manner.
3. **Sales promotion** usually refers to the consumer goods, where a manufacturer may offer price discounts, or purchase refunds, or free offers, expecting wider awareness, trial, and hopefully usage of its products. In the biopharmaceutical industry per se, the product pricing is often state-regulated and price discounts and offers are often limited or prohibited all together. Hoverer, biopharma manufacturers may offer free services associated with their product's purchase, such as free homecare support, telephone hotlines, reimbursement assistance and more.
4. **Advertising**, either product- or company-related, can be used where allowed, since product promotion to the general public (direct-to-consumer-advertising or DTCA) is not allowed in most biopharmaceutical markets. Instead, biopharmas may only advertise to medical and healthcare professionals, through their industry publications, conferences etc.

All the above elements of biopharmaceutical promotion will be further discussed below. Figure 40 summarizes the main characteristics of the four elements of the biopharmaceutical promotion.

We have previously mentioned that while personal selling is aimed at creating personal relationships and eliciting customer interactions, public relations is aimed at reaching wider audiences and eliciting customer

Box 13: Amgen's marketing[14]

We maintain sales and marketing forces primarily in the United States, Europe and Canada to support our currently marketed products. We have also entered into agreements with third parties to assist in the commercialization and marketing of certain of our products in specified geographic areas. Together with our partners, we market our products to healthcare providers, including physicians or their clinics, dialysis centers, hospitals and pharmacies. We also market certain products directly to consumers through direct-to-consumer print and television advertising, and also through the Internet. In addition, for certain of our products, we promote programs to increase public awareness of the health risks associated with the diseases these products treat, as well as providing support to various patient education and support programs in the related therapeutic areas.

	Personal selling	Advertising	Public relations	Sales promotion
Advantages	High credibility & impact Sale can be closed	Massive reach Proactive planning	Diverse audiences Large impact	Direct influence on usage Effect on final customer
Communication objective	Indirect sales through prescribers by specialized representatives	Boost image (brand / corporate) Inform, Persuade, Remind, Sell	Gain public understanding and acceptance	Provide short-term incentive to prescribe / purchase (trial / rebuy)
Cost per contact	High	Low	Low	Low
Direct feedback	Yes	No	No	Yes
Disadvantages	High cost Inconsistency in message delivery	High overall cost Inflexible message	No immediate effect Diverse audience needs	Significant logistical needs May cause discount war

Figure 17: What are the characteristics of the four elements of biopharmaceutical promotion?[2]

awareness and interest. It is easy to understand that all biopharmaceutical promotional activities can thus be rated according to customer interaction and intimacy, forming an advertising and promotion pyramid, such as the one shown in Figure 17.

REFERENCES AND NOTES

1. ACTELION (2011) Annual Report 2010. Allschwil, Switzerland: Actelion, p. 5.
2. Dogramatzis, D. (2001) Pharmaceutical Marketing: A Practical Guide. Englewood, CO.: IHS Health Group.
3. ACTELION (2011) Annual Report 2010. Allschwil, Switzerland: Actelion, p. 23.
4. ASTRAZENECA (2011) Annual Report 2010. London: AstraZeneca, p. 55.
5. ROCHE (2011) Annual Report 2010. Basel, Switzerland: Roche, p. 5.
6. MERCK (2011) Annual Report 2010. Mainaschaff, Germany: Merck AG, p. 100.
7. JOHNSON & JOHNSON (2011) Annual Report 2010. New Brunswick, NJ: Johnson & Johnson, p. 32.
8. BAYER (2011) Annual Brand 2010. Leverkusen, Germany: Bayer, p. 7.
9. UCB (2011) Annual Report 2010. Brussels, Belgium: UCB, p. 17.
10. ASTRAZENECA (2011) Annual Report 2010. London: AstraZeneca, p. 64.
11. ACTELION (2011) Annual Report 2010. Allschwil, Switzerland: Actelion, p. 6.
12. ASTRAZENECA (2011) Annual Report 2010. London: AstraZeneca, p. 35.
13. AMGEN (2011) Annual Report 2010. Thousand Oaks, CA: Amgen, p. 24.
14. AMGEN (2011) Annual Report 2010. Thousand Oaks, CA: Amgen, p. 34.
15. Dogramatzis (2010) Healthcare Biotechnology – A Practical Guide. Boca Raton, FL: CRC Press.
16. The present article's figures have been modified form the author's previously published books, references 2 and 15 above.

From the Boardroom

Disaster planning for biotechnology companies

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ABSTRACT

An earthquake in Japan cuts off the supply of key equipment and/or pharmaceutical ingredients to a biotechnology company with facilities in the U.S. High winds and flooding from a hurricane along the East coast—home to a notable number of biotechnology facilities—causes catastrophic property damage. What these cataclysmic events have in common is the wide scale business interruption that is left in their wake. While no company is immune to the threat that natural disasters pose to operations, biotechnology companies also face an increased risk of manmade disasters, from chemical spills and steam explosions to fires intensified by combustible dust. A business interruption of any kind jeopardizes a company's critical output and its financial security—a reality that some never recover from. In order to withstand the crisis and return to business, developing and implementing a business continuity plan, which includes the purchase of insurance protection, is integral to the recovery process. Although the development and implementation of a business continuity plan may require a serious initial financial commitment, it can help protect your biotechnology firm against greater physical and financial loss.

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INTRODUCTION

From Joplin, Missouri, to Christchurch, New Zealand—and in small villages and big cities around the globe—people continue to cope with the aftereffects of 2011's unprecedented onslaught of natural disasters. Economic losses from natural catastrophes reached $350 billion in 2011, the highest ever in a year, according to Swiss Re, a Zurich-based reinsurance company. Tornadoes in the United States devastated towns in the South and Midwest. Earthquakes flattened buildings in New Zealand and Turkey and set off a tsunami in Japan that killed more than 20,000 and caused a nuclear crisis. Flooding inundated towns in the United States in the Upper Midwest and the Mississippi River Valley and devastated parts of Australia, Thailand and the Philippines. In the U.S., Hurricane Irene knocked out power to more than seven million homes and numerous businesses along the East Coast, while drought and wildfires scorched millions of acres in Texas.

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While the loss of human life is surely the most tragic outcome of natural disasters, the consequences are also devastating for many businesses. Some 650 of the 6,200 licensed businesses in Tuscaloosa County, Alabama, were damaged or destroyed in the April tornado[1], and while some rebuilt, many others did not have the resources to recover. In Japan, the earthquake and tsunami created havoc with the global supply chain for auto parts, electronic components and key pharmaceutical ingredients. Businesses dependent on Thai factories for computer hard drives or automotive parts were projecting severe production slowdowns and lower earnings subsequent to the flooding in that country.

In many respects, the threats that biotech firms face are not very different from those of other companies. Fires, floods, hurricanes, tornadoes and earthquakes can affect any type of business. In some ways, though, biotechnology firms face greater risks and consequences. Even as many states offer incentives to lure biotechnology businesses, most companies are located in clusters along the East and West coasts, where they are vulnerable to hurricanes and earthquakes.[2] Biotech firms are also particularly susceptible to manmade disasters, from chemical spills and autoclave steam explosions to fires caused or exacerbated by combustible dust. Systemic power outages may not take down a building, but they

can destroy perishable cell cultures or damage expensive laboratory equipment.

It is true that nobody ever succeeds in business without taking risks, but it's equally true that the most successful companies are those that manage risks well. The ability of a business to recover from a devastating incident depends on effective planning and implementation of risk mitigation strategies before the disaster strikes. The risks of *not* developing a business continuity plan have never been higher. A disaster could easily destroy the assets necessary to a biotech firm's survival. Could a firm survive the death of a key scientist, damage to sensitive equipment, the loss of research animals or tissue samples, the contamination of a certified clean room, or the destruction of high value research notes and test results?

Even a catastrophe that has no direct physical impact on a biotech firm could have disastrous consequences. If an earthquake halfway around the world cut off supplies of a key ingredient, would the company be forced to halt its operations?

Almost any disruption in the supply of a significant ingredient or any property loss in a laboratory or manufacturing facility can spark a series of disruptive and financially lethal chain reactions. The combination of property loss and business interruption can be especially dire for research startups dependent on milestone payments to further R&D operations. That trend is growing more widespread as venture capitalists also adopt the "biobucks" model that drip feed capital to emerging biotech companies.[3]

The loss of valuable research and failure to meet deadlines can also deal a fatal blow to a biotechnology firm's reputation and its ability to win new financial support from the angel or venture communities, or contracts.

Even if a recovery from a disaster were possible, many biotech firms are so financially fragile that they lack the funding to sustain themselves during the time it takes to get back in business.

In fact, a lack of resources—financial and personnel—is a common reason biotech firms neglect business continuity planning. Of course, biotechnology companies are not the only ones that leave themselves exposed. A worldwide information security survey by Ernst & Young found that only 53% of organizations had a business continuity plan, and many of those were not well developed or tested.[4] Nevertheless, with lean operations intensely focused on research and development, biotechs may be less likely than other firms to dedicate the resources required to developing and maintaining a comprehensive business continuity plan.

Companies that have put off developing a business continuity plan to this point may not be able to avoid it much longer. In the virtual company model so common in the life sciences industry, many firms outsource key business activities, from research and clinical testing to manufacturing and sales. The risk that a business partner will fail to deliver is too high to leave to luck. When PricewaterhouseCoopers compared the performance of pharmaceutical companies that reported supply chain failures with an unaffected peer group, it found that share prices fell 7% in the two days following the announcement of a disruption and a year later their stock prices were still underperforming their peers by 4%.[5]

As a result, the operations and risk management practices of biotech firms that provide products and services to large pharmaceutical companies are now subject to intense scrutiny from customers. Customers require vendors to have a solid business continuity plan as a condition of doing business, and they are conducting vigorous audits to ensure they are updated and tested. A biotech firm that is being asked to demonstrate its own commitment to business continuity planning should be demanding the same of its own key vendors.

Large pharmaceutical companies that invest in biotechs are also pouring over business continuity plans as part of their due diligence. These investments are assuming greater importance as big pharma looks to biotechs to produce the next blockbuster that will replace key products coming off patent.

Directors and officers may also demand that a company put a business continuity plan in place. Should a disaster interrupt the smooth and profitable running of a publicly owned company, shareholders and their attorneys may try to hold the the firm's management team legally responsible for the drop in stock value. Or, customers may hold a business responsible for their loss of revenues if it is unable to provide them with the product or service they need to continue their own operations. Even if the pursuit of a claim against a company's directors and officers does not succeed, the cost of defending it can run to the millions of dollars.

With a business continuity plan in place, a biotechnology company will be in the best position to help protect employees, laboratory equipment, their balance sheet and valuable research as well as to minimize interruptions to its operations. The longer a company's operations are disrupted, the greater the damage to its reputation and the more severe the financial consequences.

BCP NUTS AND BOLTS

A business continuity plan really consists of three distinct parts: a disaster preparedness plan, an emergency response plan and a business recovery plan.

Creating a disaster preparedness plan begins with an in-depth assessment of the firm's vulnerability to a wide range of events, from natural threats like hurricanes and floods to technological threats, such as power failures and data security breaches. A biotech firm must also consider other threats, such as the dangers of hazardous materials incidents, supply chain disruptions and the loss of critical raw materials. After identifying the threats, the firm should rank them based on their probability of occurring and the impact on the business if they were to occur. Another important consideration is the quality of existing controls to reduce the risk and limit physical and financial harm.

Once a company assesses and prioritizes its vulnerabilities, it can take steps to make sure it is protected. For example, state of the art temperature alarms and an automatic, self-starting back-up power supply can prevent or minimize the potential that years of research will be destroyed in the event of a power supply failure. Other disaster preparedness measures include fire protection systems and security systems.

In a biotech firm, protecting records, costly equipment and sensitive materials is vitally important. To help prevent the theft of proprietary R&D information and expensive equipment and supplies, companies need to establish clear security policies and measures. Duplication procedures for lab books, electronic data, samples/cell lines and cultures should be established and followed carefully. All critical records and lab records should be backed up regularly and kept in fireproof file cabinets and protected from water damage. Duplicate documents, cell lines and cultures and other critical research materials should be stored offsite. This will allow staff scientists or technicians to swiftly recreate research without significant interruption of their work if a disaster strikes.

A study found evidence that taking steps to protect against a disaster pays off even if nothing ever happens. The study found that companies that employed the best practices in managing property risk produced earnings on average that were 40% less volatile than companies with weaker risks management.[6]

In addition to their own physical risks, biotech firms need to understand the ability of their own vendors and suppliers to meet customer needs if they experience a disaster. The more discussions that a biotech firm has internally and with its suppliers the better able it will be to evaluate the possible threats and implement controls to mitigate them.

The emergency response plan outlines actions that a firm should take when an unexpected event, like an autoclave explosion or contamination of a clean room, occurs or when a natural disaster, like a hurricane, is imminent.

Geared for a quick response, the plan should address everything from communicating with the media to emergency procedures for evacuating employees, handling hazardous materials and securing the facility against further damage. The plan should identify a response team and assign specific responsibilities to each team member in the event of an emergency.

A crucial but often overlooked piece of the emergency response plan addresses how to communicate in a crisis. A study by Oxford Metrica found when companies face a threat that can erode their reputation, those with an effective communications strategy can actually enhance their reputation while those that communicate poorly suffer long-lasting effects. Winners in the study disclosed information promptly and with candor and took appropriate responsibility for actions. Companies that were slow to communicate issued opaque responses and attempted to shift blame, making the situation worse.[7]

GETTING BACK IN BUSINESS

The final element of the business continuity plan focuses on recovering operations. It should focus on how to keep the company viable after a disaster so it can respond to client needs for as long as it takes to return to normal.

The goal should be recovery of the most critical functions first and then, over time, the restoration of all business processes. Each department should be asked to answer a questionnaire that will help the team identify critical business functions, understand the impact of a disruption on those functions and plan for everything necessary to restore those functions at an alternate site. The plan will spell out strategies for replacing equipment, power, data, research and personnel.

After conducting a business impact analysis, a biotech firm may decide to establish a fully equipped secondary lab that is always available in case the primary location is inaccessible. For many companies, however, that level of protection may prove too costly. As an alternative, a company might keep a list of potential sites where it can relocate temporarily and prearrange with suppliers for both equipment and biologic materials. This is especially important for key equipment like automated cloning machines, gas chromatographers, mass spectrometers, bioreactors and refrigeration equipment.

Many biotech firms may survive the immediate aftermath of a disaster only to find that they don't have the resources—such as enough insurance—to fully recover. Or they might have insurance to pay for property damage, but insufficient business interruption insurance to keep operations afloat during the time that it takes to restore normal operations. Many biotechnology companies also lack dependent business premises insurance to protect them against disruption of their business activi-

ties because of a property loss at a third party facility, such as a contract manufacturer of a key ingredient or service, such as lyophilizers, fill and finish or sterilization facilities.

The process of developing a business continuity plan can seem overwhelming, and that's one reason that many biotechnology firms put the idea on the back burner. But companies will be ill equipped to deal with a disaster until a team, working with the full support of top management, sits down and lays out the scenarios, including the time required to return operations to the level that would have existed but for the disaster. The team, working under the direction of a coordinator responsible for overseeing the process, should represent all critical business areas, such as research and development, production, human resources, quality assurance, marketing, safety surveillance and finance.

After the plan is developed, it must be tested to verify the soundness of the recovery strategies in it. The testing can be as simple as a tabletop exercise during which the staff discusses the steps required to respond to a disaster scenario and how the business would resume operations if the main location were unavailable for a month.

Biotechnology businesses are not static, and neither is a business continuity plan. The business continuity planning process is a cycle that requires continual reviews, updates and adjustments based on changes in the operations of a business and personnel.

The development and implementation of a business continuity plan takes a serious commitment of time and investment of financial resources, but once accomplished it becomes a roadmap for protecting a biotechnology firm, physically and financially, against the potentially devastating effects of a disaster.

REFERENCES

1. Patrick Rupinski, "Businesses Damaged by Tornado Strive to Open Up Again," May 29, 2011, Tuscaloosa News.com. http://www.tuscaloosanews.com/article/20110529/news/110529639?tc=ar
2. Massachusetts Biotechnology Council. Strategic Outlook for 2015 and Strategic Plan. April 2009. http://www.massbio.org/writable/files/2015_Report/full_2015_report_for_distribution.pdf
3. Ernst & Young. Beyond Borders: Global Biotechnology Report 2011. http://www.ey.com/Publication/vwLUAssets/Beyond_borders_global_biotechnology_report_2011/$FILE/Beyond_borders_global_biotechnology_report_2011.pdf
4. Ernst & Young. Global Information Security Survey 2002.
5. PricewaterhouseCoppers. KnowledgeLine: Supply chain risk assessment. June 2009. http://www.pwc.be/en/pharma/pdf/supply-chain-risk-assessment-PwC-09.pdf
6. FM Global. The Risk/Earnings Ratio: New Perspectives for Achieve Bottom-Line Stability. 2010. http://www.fmglobal.com/assets/pdf/P09232.pdf
7. Oxford Metrica. Reputation Review 2011. http://www.oxfordmetrica.com/public/CMS/Files/825/Aon_Oxford%20Metrica%20Reputation%20Review_2011.pdf

From the Classroom

A general model for training the next generation of biotechnology entrepreneurs based on recent experience of USA-UK-South Africa collaborations

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ABSTRACT

Preparing students for future entrepreneurial activity in the biotechnology industry is an important issue in many parts of the world because most countries seek to reap the benefits of investments in university-based teaching and research through the development of a knowledge-based economy driven by a highly skilled work force[1,2]. The current generation of biotechnology students will begin their professional lives in a globalized society. This means that flexibility, creativity and critical thinking are essential personal skills that need to be cultivated by students at universities in order for graduates to be competitive in the job market of a fast-moving world. It is no longer sufficient for universities to teach students to be passionate about science and to enjoy learning and discovering new things. Biotechnology students, in particular, need to be trained to identify the connections between science and its commercial applications.

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INTRODUCTION

Many countries, particularly in the emerging economies like South Africa, are experiencing a major scarcity of individuals who are appropriately trained with high-level technical skills, complemented with business-oriented professional skills and an entrepreneurial spirit. At the same time, many universities are becoming increasingly involved in research and development activities that lead directly towards commercialization. This has resulted in a more complex "entrepreneurial" university model that incorporates the commercialization of knowledge and an active contribution to the development of private enterprises in the local and regional economy.[2] Although biotechnology is viewed as highly important for economic development in countries, such as South Africa,[3,4,5] biotechnological research is often un-focused and ideas originating in universities are rarely translated into commercial opportunities. In our opinion, one of the goals for biotechnology education is for students to be taught to understand how entrepreneurial skills can be exploited in both the academic and the corporate setting. Such training will demonstrate how scientific innovations can be efficiently translated into business opportunities, thereby addressing the educational needs and economic realities of the country.

In order to achieve this goal, universities and biotechnology industries should work more closely together. The business community needs to become more active at all levels of education and research by partnering with universities to develop new training programs that will allow biotechnology students to make the transition from the academic to the entrepreneurial environment. These programs need to include a broad awareness of the scale and scope of activities in biotechnology companies, with exposure to patents, other intellectual property opportunities, business management and cross-disciplinary team science. Furthermore, it should be recognized that innovation and creativity are also vital parts of entrepreneurship. Technological innovation is relatively uncommon in universities since their mission is not normally to introduce products directly into the market. However, in order to fuel the process of technological innovation[6,7], universities should broaden their mission to support both "blue-sky basic research" and also "use-inspired basic research." Moreover, they should develop appropriate training programs to support the development of business-oriented and entrepreneurial thinking among their research trainees.

Post-graduate science students usually receive adequate research training in preparation for a future academic career, but few educational programs provide training in entrepreneurial skills for these students. New courses focused on translating a discovery out of academia into the commercial world are therefore crucially important. Universities in South Africa, for example, normally teach basic sciences, such as genetics, biochemistry, molecular biology, microbiology and plant sciences with a rather narrow academic perspective and without sufficient reference to the possible commercialization of ideas and new technologies. In South Africa up to 75% of PhD graduates remain in higher education, state research institutes or public service. Therefore, relatively few post-graduate students currently consider industry as a future employer.[5] Similarly in the USA, although some universities provide Professional Masters Degrees or certificates in biotechnology[8,9], a recent survey among postgraduate students has indicated that most universities still fail to train students adequately for an industrial or entrepreneurial career.[10] In order to promote the transfer of knowledge and the progression of students from academia into industry, new models of cooperation and communication will be required. But how can government agencies and businesses invest more in this activity and how can faculty be encouraged to become more involved in these programs?

Several hurdles need to be overcome. A major obstacle is that academic scientists seem to be most comfort-

able when they are simply "cloning" themselves by producing a new generation of academic researchers. They are reluctant to include additional training of students for entrepreneurial activities, in part because they have had no personal experience of life in industry and they lack the range of industrial contacts or networks that are necessary in order to expose their students to industrial thinking. Because they consider industrial careers as inferior in quality, they often discourage their best students from considering this option. Furthermore, business schools rarely see entrepreneurship in science as part of their portfolio: conversely, science faculties rarely see training in entrepreneurship as part of their mission, so the topic is missing from the national training curriculum. This is particularly true in developing countries, such as South Africa, but it is also true in fully developed economies such as the USA and UK. Although there are many Professional Science Master's Programs in the USA[10], they still only produce a tiny proportion of all the graduate degrees in the sciences.

A second major obstacle is that post-graduate programs offered worldwide are focused primarily on academic research objectives, since most of the research activities are supported through grants. Therefore, an industrial internship for some months as part of the degree is often regarded as unacceptable because it would reduce the time available for university-based research and perhaps reduce the probability of acquiring the next round of funding for the academic supervisor. South African scientific research is frequently caught in this circle where most of the research funding comes from government sources or student tuition payments. A third challenge is to provide sufficient resources to develop the training programs for the more generic aspects of career and professional development for entrepreneurs. The design and delivery of training programs in professional skills and entrepreneurship require a significant commitment of time and effort and such courses are not normally considered as part of the accepted teaching load for research faculty.

Although biotechnology is a buzzword amongst South African scientists and the general public, graduates entering the job market have frequently not acquired the range of technical and professional skills that they will need in order to contribute effectively in industry. Because of the strong academic focus of their university-based training, graduates often emerge with a very narrow specialized training and consequently they may be poorly equipped to adapt to the challenges of technology and entrepreneurship. In response to the need for more entrepreneurial scientists[4,11], the University of Pretoria in South Africa has recently developed training activities to introduce students to concepts and working practices that they will need in the entrepreneurial world of biotechnology.[12] A BSc-Honors course termed "Biotechnology in the Workplace" (BTW) has been introduced for students in their fourth year (i.e the first post-baccalaureate year). When the course was first introduced in 2006, it was based on a model offered by Case Western Reserve University (USA).[13] In the early stages, a certain degree of resistance was experienced from the science faculty, who could not see its immediate benefits to their research programs. The result was that only a few students (4 to 6) were initially recruited to the course, because it was not actively promoted in the science departments. However, student recommendations gradually increased the popularity of the BTW course because it was seen to be "different" from traditional post-graduate courses offered by the University. In the last three years, the course has become a required component of the Biotechnology BSc-Honors degree program and the enrolment has increased to 14-16 students. The course is now becoming one of the most popular for BSc-Honors students and is also being taken by MSc students as an elective. Following on from the BTW course, the majority of students have participated in research internships in local and/or overseas research institutions before registering for an MSc degree in Biotechnology. Feedback from these students has indicated that they positively valued the BTW course and considered the skills developed as being very helpful for their future career, whether in academia or industry. Similarly, those students leaving research after their Honors year have used the experience of the BTW course in a variety of ways, for example to attend law school, to work towards a certificate in project management or marketing, or to join an NGO. In general, the experience of students attending the BTW course at the University of Pretoria is similar to what has been found previously by students on a similar course at the University of California, Davis.[14]

One objective of the BTW course is to involve the students in the development of a biotechnology business plan. They receive active mentorship from experienced entrepreneurs whom they meet either "face-to-face" or through internet-based interviews on Skype. This training activity is coupled to a Biotechnology Entrepreneurship Workshop: students are organized into small teams which compete in the development, presentation and judging of potential business ideas. There was also a Biotechnology Careers Symposium involving a wide range of participants from bio-industry and other potential employers of Biotechnology graduates. The symposium focused on what employers are looking for in recruitment and on how biotechnology students (at BSc-Honors, MSc and PhD level) could prepare themselves to compete in the job market through career and professional development.

The successful implementation of the BTW program at the University of Pretoria should encourage other universities in Africa (and elsewhere) to adopt a similar approach to career and professional development for biotechnology students. However, in order to sustain these innovative training programs within universities, it will be important to provide special resources from government agencies and from the bio-industries who will be the ultimate beneficiaries of the skilled biotechnologists being developed by this initiative. Cooperation along these lines would help to promote skills development and greater interaction between academic and entrepreneurial sectors, both nationally and internationally.

One important issue is to establish the correct balance between specialized research training and the more generic skills that are oriented towards professional and career development (for example, training in team science, project management and effective communications). Clearly, the BSc-Honors and other post-graduate research students should maintain their primary focus on research, but it should still be possible to provide a brief introduction to the world of biotechnology entrepreneurship as a counterpoint to their core training in academic research methodologies. As a rough guide, it is suggested that research trainees should devote 2-3 percent of their time to training in career-oriented and professional skills: this is equivalent to one or two weeks per year. With this in mind, it is possible to extend the training approach to young researchers at MSc and possibly also PhD level to encourage even more translation of scientific discovery into commercial products and the evaluation of the potential of such discoveries.

In general, post-graduate biotechnology students leaving university with a Masters-level qualification might be expected to go on to manage small start-up companies because they would have both the scientific knowledge and the relevant business experience. By contrast, PhD students and post-doctoral scientists might be the biotechnology innovators and chief scientific officers of fledgling biotechnology companies who will communicate their science to the Masters level entrepreneurs and will be involved in writing business plans and marketing the company. At the PhD level, this type of training program might be more difficult to implement, since a PhD degree requires predominantly an intensive training in scientific research methodology. However, it needs to be recognized that many of the same skills needed to move from an academic setting to a commercial one are also required by any academic researcher. A new faculty member needs to view her/his position as that of a sole proprietor where they are required to manage the business (balancing research and teaching), be their own marketing manager and raise funds, while still having the personnel management skills to effectively oversee and develop the "company" workforce (comprising post-docs, graduate students and technicians). A frequently overlooked activity is accounting practices necessary for developing and managing research budgets. Thus, the provision of training programs for professional and career development will not only help to improve the overall translation of research for all science graduate students but, more specifically, it will also contribute to the success of new faculty members within the academic setting.

How important are internships as part of a biotechnology degree program for the introduction to the world of biotechnology entrepreneurship? An interesting model is to be found with the MSc in Biotechnology Entrepreneurship at Case Western Reserve University (USA)[13], which is one of the Science and Technology Entrepreneurship Programs (STEP).[15] These programs require a year-long internship which usually involves the preparation of business plans and grant proposals, technology assessment, market potential and some technology development. The experience of the internship activities in many small companies across STEP has been that the interns were highly productive and they often raised sufficient funds to support their eventual hiring by the company, but the success of the program is directly tied to the length of the internship. Information has been provided by sponsors of internships regarding the resources and revenue directly or indirectly attributed to the activities of the STEP trainee, either as an intern or subsequently as an employee. The data for the past five years combined for all STEP students (51 students) showed that $30 million could be directly attributed to student efforts and an additional $95 million was indirectly associated with the presence of the students within the organization.[16] An essential activity in the vision of the Case Western Reserve University program is to have these interns placed in academic laboratories to evaluate technology being developed and then to play a part in any initial commercialization effort. Besides placing an intern into a small or medium entrepreneurial company, newly established technology transfer offices in Southern Africa might also be well suited for internships with the goal to evaluate possible scientific discoveries and business opportunities originating from outputs of academic research. This would allow the subsequent employment of these interns as participants in the management teams of new start-up companies in order to commercialize the scientific discoveries of the universities. Such an initiative could help to counteract the tendency of faculty to publish before thinking about the possible commercialization opportunities that could arise from their own research since the evaluation could be concluded before the manuscript was ready for submission.

In South Africa, there are encouraging developments whereby such longer-term internships (between 6-12 months) in companies are currently offered by the Department of Science and Technology together with the National Research Foundation. We suggest that industrial internships (either locally or internationally) should become an important component of any biotechnology degree offered in South Africa. For example, several post-graduate students from University of Pretoria enrolled in a biotechnology degree have recently carried out 5-month research placements at the John Innes Centre, a UK center for plant and microbial biotechnology which has a strong technology transfer program[16]. Although the John Innes Centre is a government-sponsored research institute, rather than a biotechnology company, this training was viewed very positively by all the students because it "broadened their horizons": their experiences provided strong endorsement for the concept of internships in general and international experience in particular.

Clearly, there is an urgent need to bridge the innovation chasm[6] between universities and industry through the development of joint training programs for mutual benefit. The South African experience in developing these programs and the international relationships necessary for their success could, in principle, be replicated throughout Africa. Much emphasis in international aid programs is directed towards the provision of research interactions (for example the recent NSF and USAID International, Inter-agency PEER Program to Advance Science Collaboration with the Developing World). However, much less attention and support has been directed towards the translation of that research in order to develop a more vibrant and successful biotechnology industry. This will repay investment by providing employment for skilled graduates and by contributing to economic growth and social well-being, both nationally and internationally.

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REFERENCES AND NOTES

1. Etzkowitz, H., Webster, A., Gebhart, C. and Terra, B.R.C. (2000) The future of the university and the university of the future: Evolution of ivory tower to entrepreneurial paradigm. *Research Policy* 29(2): 313–330.
2. Wong, P.K., Ho Y.P. and Singh, A. (2007) Towards and "Entrepreneurial University" model to support knowledge-based economic development: The case of the National University of Singapore. *World Development* 35: 941-958.
3. Cloete, T.E., Nel C.L. and Theron J. (2006) Biotechnology in South Africa. *Trends in Biotechnology* 24: 557-562.
4. Okole, B. (2011) http://blogs.nature.com/tradesecrets/2011/03/22/the-south-african-government-biotech-and-growth
5. A National Biotechnology Strategy for South Africa (2002): http://www.pub.ac.za/pdfs/biotechstrategy_2002.pdf
6. Stokes, D.E. (1997) Pasteur's Quadrant: Basic Science and Technological Innovation. Brookings Institution Press 1997 c. 196 pp.
7. Kahn, M. (2011) Where the 2030 vision blurs. Mail & Guardian, December 9 to 14, 2011. http://www.mg.co.za/education
8. Friedman, Y. (ed.) Best practices in Biotechnology education. Washington DC: Logos-Press. 342 pp.
9. http://nciia.org/
10. When Push Comes to Pull: Society, Higher Education and Technology. CollabTech 2011, Case Western Reserve University (http://www.case.edu/collabtech/welcome.html)
11. Okole, B. (2011) http://blogs.nature.com/trade_secrets/2011/04/13/south-africans-tia-plans#comments
12. Kunert, K, Vorster, J., Chikwamba, R. and Schlüter, U. (2008) Biotechnology entrepreneurship and education: A South African experience. In: Y. Friedman (ed.) Best practices in Biotechnology education. Washington DC: Logos-Press, pp. 3-12
13. Cullis, C. (2008) Masters of Science in Biotechnology Entrepreneurship Program: One of the Professional Master's in Science and Technology Entrepreneurship Programs at Case Western Reserve University. In: Y. Friedman (ed.) Best practices in Biotechnology education. Washington DC: Logos-Press, pp. 173-182.
14. Kjelstrom, J.A. and Jamison-McClung, D. (2008) UC Davis Biotechnology Program. In: Y. Friedman (ed.) Best practices in Biotechnology education. Washington DC: Logos-Press, pp. 85-111.
15. http://step.case.edu/
16. John Innes Centre News (2011) http://news.jic.ac.uk/2011/06/jic-hosts-south-african-students/

Legal and Regulatory Update

Are laboratory notebooks necessary in a first inventor to file world?

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ABSTRACT

The importance of laboratory notebooks was long touted in the US to prove a date of invention. With the dawning of a first-to-file era in the US, the importance of laboratory notebooks has been questioned. A perspective on the importance of laboratory notebooks is provided as well as an answer to the question whether laboratory notebooks are necessary in a first-to-file regime.

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INTRODUCTION

After many years of congressional action on patent reform, the America Invents Act (AIA) was enacted in law on September 16, 2011. President Obama stated that this "long overdue reform is vital to our ongoing efforts to modernize America's patent laws." The changes mostly harmonize US patent law with the rest of the world.

Prior to enactment of the AIA, the US was the last country that granted patent rights to the first party to invent rather than the first party to file a patent application. If there was a dispute as to the first inventor, an interference proceeding was conducted by the US Patent and Trademark Office to determine the first party to invent.

To be successful in an interference proceeding, a party needs to prove they are the first to invent. Doing so requires proof of an earlier date of invention. Laboratory notebooks that accurately record a date of research conception and development may be relied upon as evidence of an invention date. For even more accurate record keeping, notebook entries should be signed and witnessed by a third party attesting to the contents in the notebook.

Therefore, properly kept laboratory notebooks are important not only for record keeping, but also to document invention dates. Such documentation was important not only to establish an invention date for an interference proceeding, but also to overcome a cited prior

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art reference during patent prosecution. In other words, a prior art reference with an availability date less than one year prior to the filing of a patent application may be eliminated if an inventor is able to prove an earlier date of invention by "swearing behind" the availability date of the reference with a declaration attesting to an earlier invention date and documented laboratory notebook pages.

A major change is the shift from a first-to-invent system to a first inventor to file system. The first inventor to file system, which goes into effect on March 16, 2013, reveals a few twists relevant to patent protection in the US.

First, the inventor who files a later application is permitted to contest inventorship on a previously filed application only if it is shown that the subject matter disclosed in the previous application was derived from the inventor who files the later application. This occurs through a derivation proceeding, which replaces interference proceedings.

Second, inventors still have a one-year grace period during which the inventor's own disclosures or disclosures of others who derived their invention from the inventor may not be used as prior art if they occurred within 12 months prior to the effective filing date of the invention.

Under a first inventor to file system, an inventor can no longer swear behind a third party disclosure. In other words, an inventor will no longer be able to prove an earlier date of invention than a third party reference.

Because of a shift to a first inventor to file system, are laboratory notebooks necessary for record-keeping to document earlier dates of invention? Even though an inventor can no longer swear behind a third party disclosure, laboratory notebooks remain relevant. In particular, laboratory notebooks and record keeping remain important for (a) derivation proceedings, (b) to demonstrate first to disclose and (c) prior user rights.

In a derivation proceeding, the true inventor alleges that the first inventor to file derived the invention from the true inventor, hence why the term "first inventor to file" is used for characterizing the new US system. The true inventor must file a patent application and may copy the first-to-file inventor's patent application and make any changes to reflect the invention. A petition for a derivation proceeding must be filed within one year after the first publication of the first inventor to file application.

The petition must be supported by substantial evidence addressing the communication of the derived invention from the true inventor to the first inventor to file as well as a lack of authorization for the first-to-file inventor's patent application filing. Furthermore, evidence supporting the communication of the derived invention from the true inventor to the first inventor to file will likely need to be corroborated, as in present US interference proceedings (wherein the issue is who is the first inventor).

In this instance, laboratory notebooks are useful to document the true inventor's claim to an invention, especially because laboratory notebooks are detailed and may also provide an indicia of unexpected results. Inventors may also consider including communications with potential collaborators in laboratory notebooks. These communications may provide evidence of communication of the derived invention from the true inventor to the first inventor to file, especially when the notebook is witnessed. In this instance, the notebook may be helpful for more than recording data.

Another instance in which laboratory notebooks remain useful is the one-year grace period during which the inventor's own disclosures or disclosures of others who derived their invention from the inventor may not be used as prior art if they occurred within 12 months prior to the effective filing date of the invention.

For example, to prove disclosure, it would be helpful to have records of what an inventor disclosed, such as abstracts, manuscripts, oral presentations or posters. It would also be helpful to know the audience of the disclosure, for example, conference or meeting attendees, journal reviewers or journal subscribers. All of these records may be included in laboratory notebooks and may provide evidence of a disclosure, especially when the notebook is witnessed.

Finally, the AIA introduces a defense to assertions of patent infringement, namely prior user rights. Specifically, in certain instances, a prior user of an invention can avoid liability and continue to practice. However, this will require having proof of prior use of the invention. Prior us can be best proven with laboratory notebook records, akin to how they would be kept in anticipation of a derivation proceeding.

In sum, laboratory notebooks are even more important under the AIA first inventor to file and prior user rights regime. The notebooks may provide corroborative evidence for an inventor to prove true inventorship, first disclosure and prior user rights.

Legal and Regulatory Update

Mayo "nays": The Supreme Court says no to patenting laws of nature

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ABSTRACT

On March 20, 2012, the U.S. Supreme Court handed down its decision in *Mayo Collaborative Services, et al v. Prometheus Laboratories, Inc* ("*Mayo*") and ended an eight-year legal battle over patents covering processes for determining patient-specific dosing for a thiopurine drug to treat autoimmune diseases. In a unanimous decision, the Court held that the claimed processes are not patent-eligible subject matter under 35 U.S.C. §101 of the U.S. patent laws, and overturned the decision of the Court of Appeals for the Federal Circuit.

The Supreme Court decision in *Mayo* established that the machine-or-transformation test is not the definitive test for determining the patent-eligibility of process claims, including process claims that embody laws of nature or natural phenomena. In its analysis, the Court considered whether the claims were drawn to patent eligible subject matter as provided under 35 U.S.C. §101 of the U.S. patent laws. The Court held that the process claims were essentially drawn to the laws of nature themselves and thus fell into the laws-of-nature exception to §101. This decision has clear implications for the biotechnology industry that go beyond diagnostics and personalized medicine. As such, biotechnology companies should re-evaluate their patent position and adapt their patent strategies in view of *Mayo*.

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INTRODUCTION

On March 20, 2012, the U.S. Supreme Court handed down its decision in *Mayo Collaborative Services, et al v. Prometheus Laboratories, Inc*[1]. ("*Mayo*") and ended an eight-year legal battle over patents covering processes for determining patient-specific dosing for a thiopurine drug to treat autoimmune diseases. In a unanimous decision, the Court held that the claimed processes are not patent-eligible subject matter under 35 U.S.C. §101 of the U.S. patent laws, and overturned the decision of the Court of Appeals for the Federal Circuit.

The specific question addressed by the Supreme Court was whether the process claims covered subject matter that fell into an exception for patent-eligibility. The claims at issue were directed to newly-discovered correlations between the concentration of metabolites in a patient's blood and the efficacy or toxicity of an administered dosage of a drug. The relationship manifested by the correlation is a law of nature or natural phenomena, both of which are judicially-created exceptions to the statutory categories of patent-eligible subject matter.

Because the very foundation of biotechnology is rooted in laws of nature and natural phenomena, *Mayo* will have immediate and long term implications for the biotechnology industry. The decision draws a line between discovery and invention, and it challenges the industry to find that line in biotechnology innovation.

PATENT-ELIGIBILITY UNDER 35 U.S.C. §101

At the center of the controversy in *Mayo* was the question of whether the challenged claims were directed to processes that are eligible for patenting under 35 U.S.C.

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§101, or whether they were directed to specific exceptions that are not eligible for patenting.

Under 35 U.S.C. §101, patent eligible subject matter includes any new and useful process, machine, manufacture or composition of matter. However, in *Diamond v. Chakrabarty*[2] *("Chakrabarty")*, the Supreme Court described three exceptions to the broad categories of patent-eligible subject matter. Those exceptions are laws of nature, physical phenomena, and abstract ideas. In *Gottschalk v. Benson*[3] *("Benson"),* the Court found that those exceptions effectively preclude the patenting of phenomena of nature, products of nature, and mental processes. The Court reasoned that "[p]henomona of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable as they are the basic tools of scientific and technological work."

In *Chakrabarty*, the Court illustrated the distinction between an invention that constituted patent-eligible subject matter, and that which falls within an exception to 35 U.S.C. §101. The claims at issue in *Chakrabarty* were directed to genetically-engineered bacteria comprising plasmids encoding enzymes involved in different hydrocarbon degradative pathways. The recombinant bacteria could break down multiple components of crude oil. It had markedly different characteristics that had been acquired through human effort, and were not simply a newly-discovered but previously existing natural phenomenon. As such, the Court held that the recombinant bacteria was a patent-eligible composition of matter.

In contrast, in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*[4] *("Funk Brothers")*, the Court held that a mixed-species culture of bacteria that was capable of inoculating a broader range of plants than a single-species culture was not a patent-eligible composition of matter. The invention was based on the discovery of certain bacterial strains having a trait that allowed them to be co-cultured, whereas other known strains could not. Because none of the species of bacteria covered by the patent claims in *Funk Brothers* had acquired any different properties or uses by virtue of any human intervention, the Court found that the mixed-species culture of bacteria was not patent-eligible subject matter. In a subsequent decision, the Court cited *Funk Brothers* for the premise that "[h]e who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end."[5] The Court noted that the same principle applied whether the patent claims in question cover 'products' or 'processes.'

THE PROCESS CLAIMS AT ISSUE

Prometheus Laboratories, Inc. ("Prometheus") is the exclusive licensee of U.S. Patent Nos. 6,355,623 (the "'623 patent") and 6,680,302 (the "'302 patent"). These patents describe processes for optimizing the therapeutic efficacy and reducing the toxicity of thiopurine drugs used to treat autoimmune diseases such as Crohn's disease and ulcerative colitis. Individual patients metabolize these drugs differently so the optimal dosage must be determined on a patient-by-patient basis by measuring the concentration of certain metabolites in the patient's blood after administration of the drugs. The metabolites of interest in this case are 6-thioguanine and its nucleotides (6-TG), and 6-methyl-mercaptopurine (6-MMP).

At the time that the '623 and '302 patents were filed, thiopurine drugs were already in use for the treatment of autoimmune diseases. In fact, scientists were already aware that the optimal dosage of such drugs is patient-specific, and that the efficacy and toxicity is correlated to the levels of 6-TG and 6-MMP in the patient's blood. The discovery embodied in the '623 and '302 patents concerned the precise correlations between the levels of these metabolites and likely efficacy or toxicity of the administered dosage for the thiopurine drug. The first claim of the '623 patent is representative of the subject matter covered under the patent:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

THE DISTRICT COURT INVALIDATES THE PROCESS CLAIMS

Prometheus had developed a metabolite test for use in optimizing the dosage of a thiopurine drug in individual patents and sold these tests to Mayo Collaborative Services ("Mayo") and others. However, in 2004, Mayo announced that it planned to use and sell its own version of the test, differing only in the levels of 6-TG and 6-MMP designated as indicative of a need to increase or decrease the dosage of the drug for subsequent administration. Prometheus sued Mayo for infringement of the '623 and '302 patents in the District Court for the Southern District of California.[6] On summary judgment, the district court found that Mayo infringed the patents, but also found that the patents were invalid because the processes covered by the patents were not patent-eligible subject matter. More specifically, the district court found that the patented processes covered, in essence, the correlation between the concentrations of the metabolites and the therapeutic efficacy or toxicity in the patient taking the drug. As such, the district court held that the correlations were natural phenomena and not patent eligible because the correlations were a product of a natural body process (*i.e.,* the thiopurine metabolism in the human body). The district court determined that because the process claims covered the correlations themselves, the claims would wholly preempt the use of the correlations for any and all purposes.

THE FEDERAL CIRCUIT TWICE CONSIDERS PROMETHEUS'S APPEAL

Prometheus appealed the district court's decision at the Court of Appeals for the Federal Circuit.[7] On appeal, the Federal Circuit held that Prometheus's claims were patent-eligible under §101, and reversed the district court's decision. In reaching its decision, the Federal Circuit applied the so-called "machine-or-transformation" test as the definitive test for determining whether a process claim is drawn to patent-eligible subject matter. Under the machine-or-transformation test, "[a] claimed process is surely patent-eligible under §101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing."[8] The use of a particular machine or the transformation of an article must impose meaningful limits on the scope of the claim in order to be eligible for patenting, and the involvement of the machine or transformation must be central to the purpose of the claimed process. Insignificant extra-solution activity will not suffice.[9]

Applying the machine-or-transformation test, the Federal Circuit found that (i) the step of administering the thiopurine drug caused a transformation of the human body from the metabolism of the drug; and (ii) the step of determining the metabolites levels caused a transformation of the patient's blood because some form of manipulation was necessary to extract the metabolites form the patient's blood in order to measure the concentration. As such, the Federal Circuit held that the claimed processes satisfied the machine-or-transformation test and were therefore drawn to patent-eligible subject matter.

Further, the Federal Circuit held that the district court erred in finding that the claimed processes entirely preempted the use of the correlations between the metabolite levels and the efficacy or toxicity. According to the Federal Circuit's decision, the inventive nature of the process claims stems not from preemption of all use of the natural processes, but from the application of a natural phenomenon in a series of transformative steps comprising particular methods of treatment. In summarizing its analysis, the Federal Circuit said that because the claimed processes met the machine-or-transformation test, they do not preempt a fundamental principle. Mayo appealed the decision at the U.S. Supreme Court.

In reaching its decision, Federal Circuit relied heavily on its opinion in an earlier case, in *In re Bilski*.[10] Yet, by the time the Federal Circuit handed down the decision in *Mayo*, the *Bilski* decision was already under appeal at the Supreme Court. In *Bilski*, the claimed invention was a process for instructing buyers and sellers how to protect against the risk of price fluctuations in a discrete section of the economy. The Federal Circuit had determined that the *Bilski* process was not patent-eligible subject matter under §101 because it did not satisfy the machine-or-transformation test. On appeal, the Supreme Court declined to apply the machine-or-transformation test but affirmed the Federal Circuit's decision on the grounds that the process claims of *Bilski* were essentially drawn to an abstract idea—*i.e.,* the concept of hedging risk and the application of that concept to energy markets—and were therefore not patent eligible.[11] The Court cautioned that allowing the patenting of risk hedging would "preempt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea." The Court emphasized that the machine-or-transformation test is not the sole test for patent eligibility under §101; but should be seen only as a useful and important clue or investigative tool in determining whether a process is patent-eligible under §101. After rendering its decision in *Bilski*, the Supreme Court summarily vacated the Federal Circuit's decision in *Mayo* and remanded it back to the Federal Circuit for reconsideration in view of the Court's decision in *Bilski*.

On remand, the Federal Circuit again upheld the validity of Prometheus's process claims and reversed

the district court's holding.[12] Addressing the Supreme Court's decision in *Bilski*, the Federal Circuit said that the question of patent-eligibility "turns on whether Prometheus's asserted claims are drawn to a natural phenomenon, the patenting of which would entirely preempt its use…or whether the claims are drawn only to a particular application of that phenomenon." The Federal Circuit pointed out that "[i]n our pre-*Bilski* decision in this case, we held not only that Prometheus's asserted claims recite transformative "administering" and "determining" steps, but also that Prometheus's claims are drawn not only to a law of nature, but to a particular application of naturally occurring correlations, and accordingly do not preempt all uses of the recited correlations between metabolite levels and drug efficacy or toxicity." Moreover, the Federal Circuit emphasized that the Supreme Court had not rejected the use of the machine-or-transformation test, but only the *exclusive* use of the test as the 'definitive test' for patent-eligibility. Indeed, the Supreme Court reiterated in *Bilski* that the machine-or-transformation test as a useful and important clue for determining whether some claimed inventions are patent eligible processes under §101. As such, the Federal Circuit again applied the machine-or-transformation test and found that the administering and determining steps were transformative and that the claims did not wholly preempt all uses of the correlations. The Federal Circuit concluded that Prometheus's process claims satisfied the preemption test as well as the transformation prong of the machine-or-transformation test and, as such, were drawn to patent-eligible subject matter.

THE SUPREME COURT WRITES THE FINAL CHAPTER

Mayo again petitioned the Supreme Court hear an appeal of the Federal Circuit's decision.[13] This time, the Court granted Mayo's petition and heard oral arguments from both Mayo and Prometheus. In a unanimous decision, the Court found that Prometheus's process claims effectively covered laws of nature and, as such, the claims were not drawn to patent eligible subject matter. Accordingly, the Court held that the process claims at issue were invalid and reversed the Federal Circuit's decision.

In reviewing the standard for patent eligibility under §101, the Court focused particularly on the judicially-created exceptions: laws of nature, natural phenomenon, and abstract ideas. Consistent with prior Supreme Court decisions, the Court expressed the concern that allowing the patenting of such basic tools of scientific and technological work might hinder innovation, rather than promote it. Notwithstanding the foregoing, a process that applies a law of nature or a mathematical algorithm may be eligible for patenting if the process includes other elements or combinations of elements that are sufficient to ensure that the patent claim, in practice, amounts to significantly more than the natural law itself. Limiting the use of an abstract idea to a particular technological environment or adding insignificant pre- or post-solution activity is not sufficient to render an abstract idea eligible for patenting.

THE CLAIMED PROCESSES ARE NO MORE THAN LAWS OF NATURE

With respect to the claims at issue in *Mayo*, the Court found that, other than the natural laws themselves, the processes recited only steps involving routine activities previously engaged in by researchers in the field. The patents, if upheld, would risk preempting the use of the underlying laws of nature in making further discoveries. The Court stated that the patent-eligibility of the process is a question of whether the process, as claimed, adds enough to the statement of the law of nature to transform it into a patent-eligible process that *applies* the law of nature.

The Court found that the claimed processes of Prometheus only set forth a law of nature and did nothing to transform the processes into patent-eligible applications of the laws of nature. This was true because the processes simply described the relationship between the levels of metabolites and the likelihood for efficacy or toxicity in a particular patient. Furthermore, the levels of the metabolites were a consequence of the way that the body naturally metabolizes the thiopurine drugs, notwithstanding the human action of administering the drug required to set off the metabolism. The Court found that the 'administering' step only directed the claim at a particular, pre-existing audience, *i.e.*, doctors who are interested in treating patients with thiopurine drugs. In effect, that step limited the use of the processes to a particular technological environment. As to the 'wherein' clause, the Court found that it did no more than inform the doctor about the relevant laws of nature and suggests that he or she consider those laws when determining a dosage for subsequent administration. Finally, as to the 'determining' step, the Court found that it instructed the doctor to determine the concentration of the metabolites in the blood by any available means but did not necessarily require the transformation of the blood to do so. Methods for measuring analytes in a blood sample were well-known and conventional. Such conventional extra-solution activities are rarely sufficient to transform a law of nature into a patent-eligible application of the law.

The machine-or-transformation test is reined in

Addressing the Federal Circuit's decision, the Supreme Court noted that the Federal Circuit relied on the Court's determination that "'[t]ransformation and reduction of an article to 'different state or thing' is *the clue* to the patentability of a process claim that does not include particular machines'," (citing *Benson*, *supra,* emphasis added by the Court). Using the machine-or-transformation test, Federal Circuit reasoned that the claimed processes were patent eligible because they involved transforming the human body by administering a thiopurine drug and transforming the blood by analyzing it to determine metabolite levels. The Court dismissed that reasoning by pointing out that the first step was irrelevant because it simply identified the target audience who would likely be interested in applying the relevant laws of nature, and that the second step did not require that blood be transformed in measuring the levels of metabolites. The Court stated "[r]egardless, in stating that the 'machine-or-transformation' test is an '*important and useful clue*' to patentability, *we have neither said nor implied that the test trumps the "law of nature" exclusion…* That being so, the test fails here." (Citing to *Bilski, supra,* emphasis added by the Court).

Laws of nature cannot be unduly preempted by patent claims

At the heart of the Court's analysis in *Mayo* was the concern that patent law not preempt further discovery by limiting access to future uses of laws of nature—*i.e.*, the basic tools of scientific research. The Court stated that "there is a danger that the grant of patents that tie up [the use of laws of nature] will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to 'apply the natural law,' or otherwise forecloses more future invention than the underlying discovery could reasonable justify." While the laws of nature embodied by Prometheus's process claims had limited applications, they still raise concerns that they would preempt further discovery. In particular, the Court noted that the claims threaten to limit further discovery and improvement to treatment recommendations that combine the correlations embodied in the claimed processes with later discoveries concerning the metabolites or human physiology, for example.

Prometheus argued that because the particular laws of nature embodied by the processes at issue were narrow and specific, the patents should be upheld. Prometheus's argument, according to the Court, encouraged drawing distinctions among laws of nature based on whether or not they will interfere significantly with innovation in other fields. Declining to draw such distinctions, Court commented that even a patent claim drawn only to a narrow law of nature can inhibit future research. In concluding its discussion of Prometheus's argument, the Court stated that its prior cases "have not distinguished among different laws of nature according to whether or not the principles they embody are sufficiently narrow…Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like."

The reach of *Mayo v. Prometheus*

The process claims at issue in *Mayo* were directed to the fields of diagnostics and personalized medicine. Since the decision came down, stakeholders in these fields have been analyzing the patent portfolios of their companies, as well as their competitors, to reassess the relative strengths and weaknesses. To be sure, the decision in *Mayo* was a call to these stakeholders to re-evaluate and, if needed, revise their patent and product commercialization strategies to survive in a world where the machine-or-transformation test is not the 'definitive test' for determining if process claims drawn on natural phenomena are patent eligible. Yet, the *Mayo* decision reaches beyond the fields of diagnostics and personalized medicine. The decision will have a clear impact on the process patents found everyday in the commercial and industrial biotechnology industry. The patenting of research tools, protein design algorithms, and biocatalytic processes, for example, are all frequently approached via process claims that embody, explicitly or otherwise, some manifestation of nature.

Furthermore, the decision in *Mayo* is unlikely to be limited to process claims. Just six days after the *Mayo* decision, the Supreme Court remanded to the Federal Circuit another case concerning the question of patent-eligibility of processes and compositions of matter based on natural laws and phenomena. In that case, *The Association of Molecular Pathology et al., v. United States Patent & Trademark Office et al*[14]. ("*Myriad*"), the specific question on appeal for the Supreme Court was whether claims covering isolated genes that are associated with breast cancer recited patent eligible subject matter. However, on March 26, 2012, the Court issued a summary disposition, vacating the Federal Circuit decision in whole, and remanding the case back to the Federal Circuit with the mandate to reconsider *Myriad* in view of the Court's decision in *Mayo*. As the Federal Circuit's decision in *Myriad* also addressed the patent eligibility

of diagnostic and screening processes, it seems likely that the Federal Circuit will revisit its analysis of the patent-eligibility of both types of 'process' claims as well as the 'product' claims (covering the isolated genes) in light of the guidance provided in *Mayo*.

It is still too early to determine the full impact of Mayo in the biotechnology industry. In the immediate term, *Mayo* has caused a perception of shifting patent leverage as broad claims once considered to be strong may now be vulnerable to attack under the framework of *Mayo*. For other companies with narrower claims, the perception may be of greater strength under the framework of *Mayo*. In any event, the immediate implication is that any biotechnology company that derives significant value from a strong patent position, whether real or perceived, should re-evaluate their position in light of *Mayo* and implement strategies for regaining or maintain that position.

Longer term, as patents issued under the guidance of *Mayo* come online, the biotechnology industry may see fewer blocking patents on pre-competitive technologies; that is, technologies that are useful during the research & development stage of a product but not intended to be embodied in the commercialized product. As a consequence, it seems possible that the pace of discovery and advanced innovation may eventually pick up as researchers gain greater access to newly-discovered laws of natural and natural phenomena. Will *Mayo* have an impact on the levels of investment in biotechnology, or on the motivation for companies to develop diagnostics, therapeutics and personalized treatments? Perhaps in the short term, but it seems unlikely in the long term. Opportunities for meaningful patent protection in the biotechnology industry still abound, but the challenge of *Mayo* may be in finding the opportunities further downstream in the innovation process that is currently customary. If the past is any indication of the future, the biotechnology industry will rise to the challenge.

CONCLUSION

The Supreme Court decision in *Mayo* established that the machine-or-transformation test is not the definitive test for determining the patent-eligibility of process claims, including process claims that embody laws of nature or natural phenomena. In its analysis, the Court considered whether the claims were drawn to patent eligible subject matter as provided under 35 U.S.C. §101 of the U.S. patent laws, or patent ineligible subject matter excepted from §101. The Court held that the process claims were essentially drawn to the laws of nature themselves and thus fell into the laws-of-nature exception to §101. The process claims did not cover patent-eligible processes of applying certain laws of nature. This decision has clear implications for the biotechnology industry that go beyond diagnostics and personalized medicine. As such, biotechnology companies should consider re-evaluating their patent position and adapting their patent strategies in view of *Mayo*.

NOTES

1. Case No. 10-1150, decided March 20, 2012
2. 447 U.S. 303 (1980)
3. 409 U.S. 63 (1972)
4. 333 U.S. 127 (1948)
5. *Gottshalk v. Benson*, 409 U.S. 63 (1972)
6. Case No. 04-CV-1200, 2008 WL 878910 (S.D. Cal. 2008)
7. 581 F. 3d 1336 (Fed. Cir. 2009)
8. See also *In re Bilski*, 545 F. 3d 843 (Fed Cir. 2008)
9. *Id.*
10. 545 F. 3d 843 (Fed Cir. 2008)
11. 130 S. Ct. 3218 (2010)
12. Case No. 2008-1403, decided Dec. 17, 2010
13. Case No. 10-1150, decided Mar. 20, 2012
14. Case No. 2010-1406, decided July 29, 2011

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ABSTRACT

UK and European content is compiled and written by Bird & Bird LLP, an international law firm which advises Life Sciences clients on:

- licensing intellectual property and know-how
- R&D agreements and other commercial contracts
- clinical trials
- regulatory issues
- risk management
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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought.

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INITIAL ATTEMPTS TO APPLY THE RECENT CJEU CASE LAW ON SPCS

The Court of Justice of the EU (CJEU) has in recent months given a number of important judgements and reasoned orders concerning Supplementary Protection Certificates (SPCs) for combination products, including its judgments of 24 November 2011 in Cases C-322/10 *Medeva* and C-422/10 *Georgetown University* and its consequential reasoned orders in Cases C-630/10 *Queensland*, C-518/10 *Yeda* and C-6/11 *Daiichi Sankyo*.

National courts and patent offices must now try to apply the principles set out by the CJEU. The English Patents Court is one of the first courts to have to do so. Thus in *Medimmune v Novartis* it considered what the CJEU meant by "identified" in its decision and in *University of Queensland* it considered whether an applicant could only get one SPC per basic patent, as although this had not been in issue in the *Medeva* case such a statement did form part of the CJEU reasoning.

In *Medimmune v Novartis* the issue was whether the patent in issue, were it to be found valid and also infringed by the monoclonal antibody ranibizumab, could constitute a basic patent for ranibizumab. In his judgment of 10 February 2012 the Patents Court judge, Arnold J., observed that the claim in issue merely identified the product of the method as "a molecule with binding specificity for a particular target," which "covered millions of different molecules of various kinds" and was "not even limited to antibodies." Since there was nothing at all in the wording of the claim, or even the lengthy specification of the Patent, to identify ranibizumab as the product of the process in question he held that the patent in issue could not constitute a basic patent for ranibi-

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zumab. However Arnold J. also criticised the CJEU for failing to answer the first question he had referred to it in Case C-630/10 *Queensland* (asking what were the criteria for deciding whether a product was protected by a basic patent), and also the reasoning by which the CJEU had come to such limited conclusions as it had. However he declined to refer any questions in this case to the CJEU, largely because this would be moot if the Court of Appeal upheld his judgment of last year that the basic patent was itself invalid and was not infringed by the ranibizumab monoclonal antibody.

It will not however be long before either Arnold J. or another Patents Court judge makes such a reference, in view of the following comment of his:

> 53. In my view, counsel for MedImmune is also correct to say that the test laid down by the Court of Justice in *Medeva* and its progeny is unclear save in its rejection of the infringement test in combination cases. In particular, it is unclear precisely what is meant by "specified (or identified) in the wording of the claims". Does this mean that it is sufficient for the product to fall within the scope of the claim on its true construction, or is something more required and if so what? For example, is it sufficient, say, for the claim to incorporate a Markush formula which covers a large number of compounds one of which is the product in respect of which an SPC is sought? Is it sufficient for the product to be defined in functional terms? Even in combination cases, it is not clear to me how the test enunciated by the Court should be applied in a case like *Gilead*. Regrettably, therefore, it is inevitable that there will have to be further references to the CJEU to obtain clarification of the test.

The *Gilead* case here referred to was a decision of the English Patents Court before the CJEU decisions and in which a patent claim to "a pharmaceutical composition comprising a compound according to any one of [certain listed claims] together with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients" had been treated as adequate to qualify the patent in which it appeared as a basic patent for a combination of an active within the scope of claims and another active.

Arnold J also went on to make an interesting observation flagging up a point that evidently troubled him but that neither side had taken; namely whether it was the purpose of the SPC Regulation to enable, as here, a patent owner to obtain an SPC for an allegedly infringing product where such patentee had not itself been delayed in getting the product to market by the need to get a marketing authorisation. This suggests that it might, in certain circumstances, be possible to challenge SPCs based on third party marketing authorisations.

In *University of Queensland* it was conceded that the effect of the CJEU's decisions was that the three patents in issue were properly to be regarded as basic patents for the four SPC applications for the individual active ingredients in the Gardasil combination vaccine. However two applications for SPCs were based on the same basis patent, although they were in respect of different actives. Thus in his judgment of 14 February 2012 the Patents Court judge, again Arnold J. on this occasion, raised the question of whether this was consistent with the observation in the *Medeva* case at [41] that "where a patent protects a product …. only one [SPC] may be granted for that basic patent." However the view of the UK Intellectual Property Office was that the CJEU was not intending to change the law as to this, its understanding of which was that there could be only one SPC per product per patent. Thus it seems unlikely that an opportunity will arise for the English courts to refer this particular question to the CJEU for clarification, and if this is to be done it will have to be left to another national court to do so.

EU: MORE DISCRETION FOR THE PAEDIATRIC COMMITTEE WHEN DECIDING ON A PAEDIATRIC INVESTIGATION PLAN (PIP) THE *'NYCOMED DECISION'*

According to Regulation (EC) 1901/2006, also known as the 'Paediatric Regulation', a pharmaceutical company is obliged to submit a Paediatric Investigation Plan (PIP) for a new medicinal product when applying for a marketing authorization. A PIP ensures that the necessary data is obtained through studies performed in children in order to support an authorisation of the medicinal product for children. Many of the medicinal products currently used to treat children have not been studied or authorised for such use. The aim of the Paediatric Regulation is therefore to facilitate the development and accessibility of medicinal products for use by children.

Submission of a PIP can be waived if the medicinal product is 'intended to' be used for the treatment of diseases when there is evidence that such diseases only occur in adults.

In this case, the medicinal product concerned was an echocardiography imaging agent (perflubutane, brand name Imagify®). The applicant, Nycomed (a Takeda company since September, 2011) stated in the application for a waiver that the product was designed to diagnose *coronary artery disease*, which only occurs in adults.

The Paediatric Committee, however, was of the opinion that the applicant had incorrectly restricted the scope of its waiver application to the diagnosis of *coronary artery disease*. According to the Paediatric Committee, the product was designed to identify *heart perfusion defects*, which can also occur in children. The Paediatric Committee therefore advised the European Medicines Agency (EMA) to reject the application for a waiver and the EMA subsequently did so.

The Nycomed Danmark vs. EMA (T52/09, 14th of December 2011) decision of the EU General Court concerns the scope of the wording of 'intended for' of Article 11(1)(b) of Regulation 1901/2006, which allows a company to apply for a waiver to the obligation to submit a PIP, and therefore not to perform studies within the paediatric population. This is the first time that the EU General Court has decided on provisions of the Paediatric Regulation.

Nycomed applied for interim measures in February 2009, but the President of the Court of First Instance (which is currently known as the EU General Court) denied these due to lack of urgency. It is settled case-law of the Court that urgency in ordering an interim measure must result from the effects produced by the contested measure and *not* from a lack of diligence on the part of the applicant. Since the applicant did not apply for a deferral and did not file a draft PIP, the urgency for ordering the interim measures sought could not be established (T52/09 R, 24th of April 2009).

In the current decision of December 2011, the EU General Court has ruled that, even though the applicant (Nycomed) had limited the indication of the medicinal product in the application for the waiver to a disease which is *not* intended for use in children, the Paediatric Committee is allowed to establish, by a reasoned opinion, based on scientifically-reasoned, objective evidence, that the product may not only be used for the disease covered by the indication proposed by the applicant, but also for other diseases which do exist in children. In such a case, the Committee is obliged to reject the application for a waiver unless the applicant can submit objective evidence to rebut this contention.

With this decision, it seems that the Paediatric Committee has been given significantly more discretion to decide for which indication the product at issue could be used. However, it was also explicitly stated that the indication used in the application for the waiver does *not* have to be identical to the indication used in the marketing authorisation application, which appears at a later stage of market authorisation application process. Determining for which indication a marketing authorisation is sought is therefore still at the discretion of the applicant. Furthermore, the EU General Court concludes that the rejection of the waiver application is in fact a commercial advantage. When the studies provided for in the PIP have been performed, there is nothing to stop the company from extending the indication of its medicinal product for use in the paediatric population.

Whether this decision on the degree of discretion that the Paediatric Committee has is final remains to be seen - Nycomed may yet appeal to the European Court of Justice.

The decision gives rise to some interesting issues. What if the medical ethical committee (MEC) would not approve of a certain study with children, because of, *for instance,* lack of relevance of the clinical trial, or safety concerns, in the paediatric population? Moreover, a clinical trial with minors may only take place when '*some direct benefit*' to the group of patients is obtained from the clinical trial. Notwithstanding possible discussion on the meaning of the wording 'some direct benefit', this requirement may also lead to concerns with regard to the methodological quality of the trial (i.e. too few eligible patients). If the MEC were not to approve the study protocol due to one of the aforementioned reasons, the clinical trial, based on Directive 2001/20/EC (Clinical Trial Directive), cannot proceed. The Paediatric Regulation provides for a procedure for modification of the PIP, but obtaining a waiver in such a case is not guaranteed. Consequently, a marketing authorisation may not be obtained, or, at least market entry would be significantly delayed.

As has become evident, the scope and boundaries of opinions of the Paediatric Committee require clarification.

EU: PROPOSALS ON NEW LEGISLATION ON "INFORMATION TO PATIENTS" AND "PHARMACOVIGILANCE" ADOPTED BY THE COMMISSION

On 10 February 2012 the Commission adopted proposals to amend Regulation (EC) No. 726/2004 and Directive 2001/83/EC in relation to Information to Patients[1] and Pharmacovigilance[2].

1 COM(2012) 49 final 2008/0255 (COD) Amended proposal for a Regulation of the European Parliament and of the Council amending Regulation (EC) No 726/2004 as regards information to the general public on medicinal products for human use subject to medical prescription.
COM(2012) 48 final 2008/0256 (COD) Amended proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards information to the general public on medicinal products for human use subject to medical prescription.

2 COM(2012) 51 final 2012/0023 (COD) Proposal for a Regulation of the European Parliament and of the Council amending Regulation (EC) No 726/2004 as regards pharmacovigilance.

The adoption of these proposals follows Commissioner Dalli' s announcement on 2 December 2011 at the Council on Employment, Social Policy, Health and Consumer Affairs (EPSCO) of the split of the amended proposals on information to patients, which were adopted on 11 October 2011, into two parts relating to "Information to Patients" and "Pharmacovigilance" respectively. The split of the proposals aims to facilitate the discussion of the proposals by the co-legislators. These proposals will be now discussed by the European Parliament and the Council of Ministers.

Information to patients

The original legislative proposal was first published in December 2008 and has been considered by the Council of Ministers and the European Parliament. The objective of the Commission's proposal remains to amend the pharmaceutical legislation to provide a clear framework for the provision of information by Marketing Authorisation holders about their prescription only medicines (POMs) to the general public while ensuring that direct-to-consumer advertising of POMs in the European Union remains prohibited. Therefore the proposal is still that POMs are prohibited from being advertised on television and radio in the European Union.

Also, it is proposed that the definition of "advertising of medicinal products" in Article 86 is amended to include actions by third parties. This is partially in line with European case law[3], although the proposed amendment is limited third parties acting on behalf of the marketing authorisation holder or following his instructions. In Case 421/07, the third party journalist had acted independently.

Information released by marketing authorisation holder to investors and employees on business developments will be considered advertisements if such announcements concern individual medicinal products (proposed Article 86(2)(d)).

Vaccination campaigns have been permitted subject to pre-approval by the competent authorities but the proposed amendment to such campaigns is to strengthen this provision to ensure that "objective, non-biased information" is provided by industry in the framework of the campaign "regarding the efficacy, the adverse reactions and contra-indications of the vaccine".

COM(2012) 52 final 2012/0025 (COD) Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards pharmacovigilance

3 Case C-421/07 Judgment of the Court (second chamber) of 2April 2009 (reference for a preliminary ruling from the Vestre Land Stret-Denmark) Criminal Proceedings against Frede Damgaard.

Under the revised proposal for the Directive, the system of self-regulation of advertising in place in several European member states, notably in the UK will continue; however if such systems were not in place on 31 December 2008, advertising cannot be made available to the general public until it has been approved by the competent authorities, unless such a system of control is not compatible with the constitutional rules of the Member State concerned. This allows the different national procedures in place to either pre-approve advertising or to operate a system of self-regulation and investigation of complaints (from other companies, physicians and consumers).

It is proposed that advertising materials relating to POMs which are authorised by the centralised route are vetted by the European Medicines Agency (EMA) with the cost of the vetting to be financed by applicants' fees. This pre-approval would include information contained on Internet websites. If there is disagreement between the EMA and a Member State whether the information on the website complies with the requirements of Title VIIIa of Directive 2001/83/EC there is the possibility in the proposal of referring the case to the Pharmaceutical Committee[4].

The proposal includes a modification under penalties such that the names of non-compliant marketing authorisation holders are published by Member States. This "name and shame" sanction already exists in some Member States e.g. the UK MHRA publishes a summary of Advertising Investigations on its website.

Pharmacovigilance

Despite adopting Directive 2010/84/EU and Regulation (EU) 1235/2010 which extensively amended the pharmacovigilance provisions which will apply from July 2012, recent events, in particular the so-called "Mediator case" have indicated to the Commission that there is still a requirement to improve the pharmacovigilance system. This conclusion was drawn from a "stress test" following analysis of the Mediator case.

The Mediator case concern a drug marketed by Laboratoires Servier containing the active ingredient benfluorex which was indicated for diabetes but was also used for weight-loss. It was supplied in France for 33 years and withdrawn in 2009 after the French regulatory authority Afssaps took action when the drug was implicated in causing serious cardiac adverse effects notably to heart valves. The medicinal product was withdrawn from sale in Portugal and Luxembourg at the same time as France, but had been withdrawn from the market in Spain and Italy several years earlier. According to the French health

4 Pharmaceutical Committee set up by Council Decision 75/320/EEC which is chaired by the Commission.

ministry, at least 500 people died following problems with their heart valves after taking benfluorex. The number of serious adverse effects only came to light with the publication of a book "Mediator 150 mg: How Many Dead?" by Dr Irene Frachon in 2010. The head of Afssaps resigned last year following an inquiry and the offices Afssaps were reported to have been searched in February 2012 in connection with the case. This case brought to light serious flaws in communicating safety concerns between the national authorities in Europe.

The pharmacovigilance amendments are aimed at improving transparency and ensuring that any voluntary action taken by a marketing authorisation holder to withdraw a product from the market is communicated to the EMA (under the regulation) and competent authorities (under the directive) two months in advance. Where the reason for withdrawal of the product is on safety grounds or lack of efficacy i.e. medicinal product is harmful or the risk:benefit ratio is not favourable) the EMA must bring this to the attention of Member States and vice versa.

THE "ADVERTISING" OF PRESCRIPTION BASED MEDICINAL PRODUCTS TO JOURNALISTS IS PROHIBITED IN SWEDEN

In a somewhat controversial decision, the Swedish Medical Products Agency (the "Agency") prohibited Boehringer Ingelheim AB ("Boehringer") in September 2011 from advertising the prescription-based product Pradaxa to the public. Interestingly, the advertising at issue consisted of a press release that was published on the Internet, and the 'public' in this case comprised journalists, as the press release was explicitly targeted at journalists.

The Agency made the assessment that the press release was deemed to be 'advertising' for the purposes of the Medicinal Products Act (1992:859) (the "Act"), which is the Swedish legislation partially implementing Directive 2001/83/EC (the "Directive"). According to the Agency, the press release disseminated positive information about the product, in order to create an increased demand before the launch of an expanded indication for the product. The Agency moreover stated that the text in the press release has clear advertising character which only describes the advantages of the product with no mention of the disadvantages.

The Agency thus concluded that the press release could not be categorised as a text that is of a purely factual and informative character, which would be exempted from the advertising prohibition. The Agency prohibited Boehringer from advertising the product to the public by means of the press release by the penalty of a fine.

By way of background to the regulatory framework in Sweden, it should be noted that the Act does not provide for an explicit definition of advertising of medicinal products, but follows the interpretation of the term "advertising" in Article 86 of the Directive. Whereas the Act provides general provisions in respect of advertising, more detailed regulations are found in the Agency's Code of Statutes (LFVS 2009:6).

Before the implementation of the Directive in Sweden in 2006, the supervising function in respect of advertising was traditionally managed by the medicinal products industry itself through the Swedish Pharmaceutical Industry's Information Examiner (**"IGM"**) and the Information Practices Committee. The IGM is a scientifically qualified doctor who continuously examines information and other marketing activities for pharmaceuticals from the industry. The industry and the Agency assisted these organisations by reporting complaints and concerns about advertising of medicinal products, but the Agency had less defined powers to intervene in these matters *pre*-2006. Today the industry organisations still have an important function and participate actively in the work of maintaining fair marketing practices within the industry. The Agency monitors how the system of self-reporting is working and has the authority to intervene where companies do not abide with the industry's own regulations and systems.

Appeal of the decision

Boehringer has appealed the Agency's prohibition decision to the Administrative Court of Uppsala and contends that the press release is not to be construed as advertising for the purposes of the Directive or the Act, and that a press release is protected by the principle of freedom of speech (the criticism against the decision of the Agency has focused in large parts on the potential limitation of freedom of speech). Moreover, Boehringer states that the IGM chose not to intervene against the press release. The deciding factor in the opinion of the IGM was that the press release was targeted at journalists (and thus not at the public).

In a statement in the appeals proceedings, the Agency submits that there are two types of advertising provisions in the Directive and in the Swedish rules. On the one hand there are rules that govern advertising aimed at healthcare professionals (Articles 91-96 of the Directive) and on the other there are rules that govern the advertising to all others, i.e. the public (Articles 88-90 of the Directive). There are no categories other than or in between these two, and hence no category should deserve special treatment under the Directive or the Act. According to the Agency, journalists are not to be considered as healthcare professionals and enjoy no special status

pursuant to the Act, and thus fall into the "other", public category. In sum, the Agency reasons that there is no explicit support for exempting journalists from the general prohibition on advertising.

A judgment from the Administrative Court can be expected during the spring.

OLIVER BRÜSTLE V GREENPEACE E.V. (C-34/10)

The CJEU has handed down its decision in *Brüstle* on the interpretation of Article 6(2)(c) of the Biotechnology Directive (98/44EC), relating to the concept of a 'human embryo' and its patentability.

Background

Greenpeace applied to invalidate a German patent held by Oliver Brüstle, filed in 1997, which concerned isolated and purified neural precursor cells, processes for their production from embryonic stem cells, and the use of neural precursor cells for the treatment of neural defects.

Greenpeace asserted that Brüstle's patent was invalid on the basis that its claimed invention was contrary to TRIPS and the EPC which permit signatories to exclude an invention from being patented if its commercial exploitation would be contrary to *ordre public* or morality, and that it fell within Article 6(2)(c) of the Biotech Directive which provides that in particular this exclusion is satisfied if human embryos are used for industrial or commercial purposes. The Bundesgerichtshof stayed proceedings and referred a number of questions to the CJEU concerning the definition of a 'human embryo' and its application in these circumstances.

Stem cells

A distinction can be made between 'totipotent' and 'pluripotent' stem cells. The former arise after fertilisation and are capable of dividing and developing into a complete individual. A few days after fertilisation a blastocyst is formed consisting of the latter, which although capable to developing into any type of cell, cannot develop into a complete individual.

The CJEU's decision

The definition of a 'human embryo' in Article 6(2)(c)

The CJEU considered that although member states should have wide discretion to interpret *ordre public* and morality, Article 6(2) sets out particular exclusions from patentability. Therefore, the concept of a 'human embryo' for these purposes should be interpreted uniformly across the EU rather than leaving this to member state courts. The Biotech Directive aimed to remove obstacles to trade and smooth the functioning of the internal market. This aim would not be achieved if some member states chose a narrow interpretation which would result in a liberal patenting regime whilst others interpreted the exclusions more broadly.

The CJEU noted that although the Biotech Directive seeks to promote investment in biotechnology, the use of biological material originating from humans had to be consistent with regard to fundamental rights and, in particular, the dignity and integrity of the person. Therefore, the concept of a 'human embryo' should, for these purposes, be interpreted in a wide sense. Accordingly, the CJEU ruled that, for the purposes of Article 6(2)(c), a 'human embryo' constituted any (i) any human ovum after fertilisation, and (ii) any non-fertilised human ovum (a) into which the cell nucleus of a mature human cell has been transplanted or (b) for which further development has been stimulated by parthenogenesis. However, it would fall to the relevant national Court to ascertain whether a stem cell obtained from a human embryo at the blastocyst stage fell within this definition, in light of scientific developments.

The stem cells in question in Brüstle's patent were pluripotent cells. Advocate General Bot had recommended that these should not be regarded as a 'human embryo' as they do not have the capacity to develop into a human being, although if obtained from a blastocyst they could only be patentable if they could be obtained without detriment to the embryo (which was not the case at the priority date). However, the CJEU's broader definition of a human embryo means that pluripotent cells could fall within the concept of a 'human embryo', depending on how a member state's national Courts interpret this ruling in light of scientific developments.

Use of human embryos for scientific research

The second question referred asked whether the 'use of human embryos for industrial or commercial purposes' covered the use of human embryos for the purposes of scientific research. The CJEU noted that the purpose of the Biotech Directive was not to regulate the use of human embryos in scientific research, but to the patentability of biotechnology inventions. However, the use of a human embryo for scientific research implies its industrial or commercial application: even if the aim of scientific research was different, such use of a patent's subject matter would fall within the exclusion. This is subject to the clarification in Recital 42 of the Biotech Directive, that therapeutic or diagnostic purposes which are to be applied to the human embryo and are useful to it are patentable.

Invention requires destruction of human embryos

The third question asked whether an invention would be unpatentable if it necessitated the destruction of a human embryo, even if its purpose is not the use of human embryos. In answering this question, the CJEU reached essentially the same conclusion as the Enlarged Board of Appeal had in WARF (G 2/06) in relation to the EPC. If the implementation of the invention required the destruction of human embryos, it had to be concluded that human embryos must have been said to have been used within the meaning of Article 6(2)(c). It was irrelevant if the claimed invention was implemented at a stage long after the destruction of such embryo. Moreover, it does not matter whether the invention as claimed referred to the use of human embryos – a contrary conclusion could enable a patent to avoid the exclusion and be valid by skilful drafting, rather than because the invention itself does not fall within the exclusion.

Conclusion

On the face of it, the CJEU's decision in Brüstle is likely to be disappointing for those engaged in stem cell research in the EU. The CJEU has chosen to define a 'human embryo' broadly for the purposes of Article 6(2)(c) and given national courts discretion only to decide how this is to be interpreted in light of scientific developments.

However, the CJEU has not ruled that pluripotent cells per se must be regarded as a human embryo. Moreover, since 1997 new methods have been developed for the production of stem cell lines that do not require the use or modification of human embryos but instead rely on 'reprogramming' differentiated cells to revert to a pluripotent state. Companies will also be able to rely on confidentiality rather than the patent system to protect techniques developed in this area of research.

UK Supreme Court reverses lower courts as to the validity of HGS' "gene patent" after a thorough analysis of EPO case law on "industrial application"

On 2 November 2011 the UK Supreme Court delivered judgment in *Eli Lilly v Human Genome Sciences*, the first patent case it has heard since replacing the House of Lords as the final appellate court in the UK. It reversed the decisions of the lower English courts which had found the patent to be invalid and so in effect upheld the validity of the UK designation of Human Genome Sciences' (HGS) patent EP 0,939,804, as the other issues that remained open in the Court of Appeal and to which the case was remitted are unlikely to result in the patent being held invalid.

HGS applied for the patent in 1996 based on its work on sequencing the human genome. HGS identified a novel gene sequence which it postulated, because of its homology with certain known gene sequences, would code for a previously unknown member, designated as neutrokine-α, of a known "superfamily" of proteins. HGS also identified in the patent the tissue distribution of neutrokine-α, and its expression in T-cell and B-cell lymphomas. This suggested a wide range of potential physiological effects for neutrokine-α, the modulation of which offered scope for a wide range of therapeutic applications. The patent was granted by the European Patent Office (EPO) with claims to the gene sequence in issue and also neutrokine-α itself, but the most commercially important claims have proved to be those to monoclonal antibodies (MABs) that would modulate the effect of neutrokine-α. As a result GlaxoSmithKline, whose new MAB Benlysta (Bemilumab) for the treatment of lupus falls within such claims, has taken a licence under the HGS patent.

The underlying issue in Eli Lilly's challenge to the validity of the patent was common to the different legal grounds of objection raised against the patent; namely, had HGS, in its original application, disclosed enough to move out of the realm of mere speculation as to the possible therapeutic utility flowing from its identification of neutrokine-α and the sequence which codes for it, into a more concrete disclosure of possible applications and which merited a patent.

The Patents Court and Court of Appeal both held the patent to be invalid; the Patents Court because of lack of industrial application (Article 57 EPC) insufficient disclosure (Article 83 EPC), and lack of inventive step (Article 56 EPC) for making no technical contribution, although more specific attacks on inventive step failed. The Court of Appeal only considered the Article 57 objection and upheld the Patents Court decision. The Court of Appeal decision was controversial because it had differed from an EPO Technical Board of Appeal which, after the Patents Court decision, had upheld the validity of the patent, although the Court of Appeal had sought to explain that its reasons for so differing were that the Patents Court, whose judgment it upheld, had had different evidence before it to that which was before the Board of Appeal.

The Supreme Court accepted that the Court of Appeal would have been entitled to come to a different conclusion to the Board of Appeal if there had indeed been such a difference. However it saw no difference between the central findings of fact of the Board of Appeal and the Patents Court and held, after close analysis, that the reason for the Court of Appeal differing from the Board of Appeal was that it, and the Patents Court, had incorrectly applied the accepted principles established by the

EPO case law as to Article 57 EPC to the findings of the Patents Court. There were two reasoned speeches in the Supreme Court, from Lord Neuberger and Lord Hope, both of whom recognised the difficult nature of the case and identified their marked reluctance, which they had only with difficulty overcome, to reverse the judgments below. Of the three concurring speeches that from Lord Walker summarised the policy arguments for allowing the appeal which to his mind justified the Court in taking what would otherwise to him be a questionable course - the one was to reduce the risk of a chilling effect on investment in bioscience (though here he noted that the arguments are certainly not all one way), and the other was to align the UK interpretation of the European Patent Convention (EPC) more closely with that of the other EPC contracting states.

As to the policy issues, Lord Hope and Lord Neuberger both referred to an intervention that the Supreme Court had allowed in an amicus brief from the BioIndustry Association, the trade association for innovative enterprises in the UK biosciences sector. Although it had not set out to support either of the two parties to the appeal it did suggest that if the reasoning of the Court of Appeal were upheld there was at least a risk that it would "make it appreciably harder for patentees to satisfy the requirement of industrial applicability in future cases" and that if that were so, this "would cause UK bioscience companies great difficulty in attracting investment at an early stage in the research and development process". This was a consequence of the reasoning of the lower courts that there would normally be a need to conduct tests to provide experimental data to establish to the requisite standard that a protein (or its antagonists) have a therapeutic use, which would be expensive, when funding would be hard to obtain for a project of this sort which had no existing protection in the form of a patent application. It had however also accepted that it would be wrong in principle to enable applications for patents to be made when the applicant can reveal no more than "a vague indication of possible objectives that might or might not be achievable by carrying out further research", given that the purpose of the patents system is not "to reserve an unexplored field of research for the applicant nor to give the patentee unjustified control over others who are actively investigating in that area and who might eventually find ways actually to exploit it."

Lord Neuberger started his speech by observing that although the present case could be said to raise an important question of principle, its resolution was inevitably fact-sensitive, and therefore its answer might be of limited wider application. He analysed the relevant EPO case law on Article 57 EPC in detail, an exercise which the lower courts had also undertaken, there being no relevant UK case law, but went further and extracted from this, at paragraph 107, a set of principles which he derived from such case law – four general principles, six to be applied where a patent discloses a new protein and its encoding gene, and five where the protein is said to be a member of a known family or superfamily of proteins. Applying these principles to the conclusions of the Patent Court as to what the patent disclosed, namely the existence and structure of neutrokine-α and its gene sequence, and its membership of a particular ligand superfamily, this should to him have sufficed, taking into account the common general knowledge, to hold that the patent did indeed satisfy the Article 57 EPC threshold. He went on to consider, and dispose of, various specific arguments to the contrary, one of which lay in the suggestion that the "extravagant and wordy" assertions in the patent would have diverted the notional addressee from what their search of the literature, coupled with common general knowledge, would otherwise have led them to understand represented the teaching of the Patent. The argument failed as there was no finding from the Patents Court to this effect and the Technical Board of Appeal had held this was not the case. Having held that the patent did satisfy Article 57 EPC, Lord Neuberger went on, relatively briefly, the matter not having been addressed by the Court of Appeal, to consider the generalised Article 83 EPC objection (insufficiency), which had succeeded at first instance but which he rejected, having noted the close connection in EPO case law between the two grounds of objection in situations such as this, and having construed the product claims as not being in any sense functionally limited.

Lord Hope in his speech identified indications in the decision of the Court of Appeal that the standard which it set for Article 57 EPC was a more exacting one than that used by the Board of Appeal in that it had been looking for a description that showed that a particular use for the product had actually been demonstrated rather than that the product had plausibly been shown to be "usable".

So the first judgment of the Supreme Court in the field of patents establishes no new legal principles (although it does provide a most useful summary of ones extracted from the EPO case law and it does adopt the standard for Article 57 EPC set by the EPO) and may be of limited wider application. It does however show the importance of policy considerations to the thinking of the Supreme Court in areas such as patents, and the increasing relevance to such policy considerations of amicus briefs filed by third party interveners.

NEW TRANSPARENCY RULES ON THE PUBLICATION OF FINANCIAL RELATIONS BETWEEN HEALTHCARE PROFESSIONALS AND THE PHARMACEUTICAL INDUSTRY

In the Netherlands, the advertising of medicinal products is governed by the Medicines Act, which implemented Directive 2001/83/EC on the community code relating to medicinal products for human use, as amended. In addition, the Foundation for the Code for Pharmaceutical Advertising (the "Foundation CGR") has set out, within the legal framework of the Medicines Act, detailed advertising rules in its self-regulatory Code of Conduct for Advertising of Medicinal Products.

The Foundation CGR has now drawn up rules of conduct relating to the publication of financial relations between healthcare professionals and the pharmaceutical industry in the Code of Conduct Publication: Financial Relations (the "Code"). The Code contains obligations for the pharmaceutical industry to disclose any service agreements (such as consultancy activities, participation on an advisory body, participation as a speaker or research which is not subject to the Research Involving Human Subjects Act (WMO)) and sponsor agreements with healthcare professionals in a central transparency register. Financial relations below EUR 500 a year are excluded. The nature of the financial relation, the name and address of the pharmaceutical company, information on the healthcare professional or the institution along with the amount paid must be placed on the register. The publication will remain on the public record for three years after which the information will be removed from the register.

The Code will come into force on 1 January 2012. The independent central register for the publication of the information will become operational in the course of 2012. However, the first actual publication in the register will take place in the first quarter of 2013, as the financial information will be updated once a year within three months following the calendar year in which the relation between the healthcare professional and the pharmaceutical industry is carried out.

Conference Review

Drug discovery & development landscape: New trends in academia-industry partnerships

Vasu Pestonjamasp

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INTRODUCTION

The Association of University Technology Managers (AUTM) held its 2012 Annual Meeting in Anaheim, CA. This event was attended by about 1700 professionals that represented biotechnology and pharmaceutical companies, startup ventures, academic technology transfer offices, service providers and law firms. The goal of academic technology transfer is to assist the commercialization of research for public benefit. In accordance with this mission, and in addition to various other sessions, the AUTM Meeting focused on the aspect of academia-industry partnerships with respect to commercialization of scientific discoveries. Some representative highlights are described below.

A two-part panel discussion entitled, "Any Port in a Storm or How to Survive and Thrive Partnering with Industry!" featured Christopher Yochim (AstraZeneca), Louisa Daniels, JD (Pfizer Inc.), Muz Mansuri, Ph.D. (Gilead Sciences Inc.), Thomas Marron, Ph.D. (Eli Lilly & Co), Sunita Rajdev, Ph.D. (University of California San Francisco), Malcolm Skingle, Ph.D. (GlaxoSmith-Kline) and Jon Soderstrom, Ph.D. (Yale University). The panel reiterated the facts that the drug development process can involve spending a billion dollars, may take 10+ years, and remains a risky endeavor. However, the quest for new therapeutics goes on. While biotechnology companies have inventories available for pharma companies, the products are predominantly early stage (phase I or II). The number of preclinical compounds in Top 10 pharma pipelines has dropped during year 2003 to September 2011 [Source: DefinedHealth]. The presence of fewer programs in preclinical trials indicates that down the road, there will be fewer programs also in clinical development phases. Venture capital (VC) peaked in 2007 ($39.5 billion) from that in 2003 ($10.4 billion); however, has remained at a lower level since then. It stood at $16.2 billion in 2011, which was only moderately higher than the VC funding in 2010 ($15.5 billion) [Dow Jones Venture Source]. The investments and deal flow also appear to be static, although the time and cost involved in drug development continue to grow. The demands regarding restoration of pipeline growth while meeting commercialization and regulatory hurdles, avoiding me-too programs and enabling risk-sharing also persist.

The panelists discussed novel ways via which the industry and academia could benefit and thrive together. Gilead for example, has acquired Arresto Biosciences (a cancer biologics company), a manufacturing facility, and Calistoga Pharmaceuticals (a small molecules oncology company) to move into oncology space. Gilead reached out to Yale University for its stellar investigators, clinical oncologists, track record of forming companies, and ongoing genomics and drug discovery efforts. Gilead and Yale have a 10-year deal, which is renewable after 4, and 7 years. This deal structure provides Gilead the time to strategize and grow organically, and also a right to terminate the deal if the key people within Yale leave. Gilead is not only looking at the specific tangible outcomes such as to discover and complete projects, but also the intangibles, such as the way in which Yale could affect Gilead's thinking that would in turn help the company's own biologics program. On the other hand, Yale investigators get to work in an exciting area and enhance their understanding of a very good and practical drug discovery program.

Pfizer's Centers for Therapeutic Innovation (CTI) model includes a focus on biologics and proof-of-mechanism (POM), and is not limited to any particular disease indication. Some additional aspects that were pondered with respect to enhancing the drug discovery and development efforts include: Shared funding and risk, joint ventures, shared access to clinical samples housed at a single place that pharma companies could reach, transparency regarding clinical trials, and non-exclusivity for research tools (e.g., cell lines, transgenic mice). With re-

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spect to the last aspect, Pfizer has made its proprietary, diverse antibody library available to the academic partners whose proposals are accepted by Pfizer. University of California San Francisco (UCSF) is one of the universities Pfizer is working with, under the CTI program. Pfizer and UCSF have a joint steering committee that evaluates and selects submitted proposals that are to be considered under the CTI program. The partnership includes equity in core provisions (e.g., publications and intellectual property), pre-negotiated milestones and royalty ranges, cross-licenses to disclosed know-how, standard form licensing agreement and post doctoral fellows support along with specific go-no go points for the projects.

The panel also discussed the concept of "Pre-competitive alliances." What this idea embodies is that although companies are competing with each other, they also need greater cooperation in the early/validation stage so that they will not duplicate each other's efforts and not suffer the same failures.

University of Dundee's Division of Signal Transduction Therapy (DSTT) aims to assist participating companies enhance the development of the modulators of protein and lipid kinases and phosphatases that could potentially become therapeutics. DSTT; founded in 1998, is a premier collaboration between industry and academia in Europe. Several big pharma companies are part of the DSTT consortium. DSTT uses 60% of its funding for fundamental research and 40% on services consisting of lipid kinase profiling, mass spectrometry, DNA cloning, protein production, and assay development. The consortia companies tap into these services at cost. For example, GlaxoSmithKline (GSK) has been delivered various DNA clones, kinases, substrates, antibodies, and transgenic mouse lines. Consortia companies share the unpublished research, the know-how generated by the participating Dundee laboratories, and have the first right to license the IP that arises from the research. However, the information that a particular company introduces into the DSTT is not shared with others, and is sent back only to that company. The quality and cost-effectiveness of reagents provided by DSTT, protection of proprietary compounds and access to DSTT's scientists are attractive to the industry, whereas the funding, obtaining knowledge regarding how industry works, and gaining new ideas as suggested by the consortium companies, are of benefit to DSTT.

GSK-AstraZeneca-University of Manchester Inflammation Center was announced in 2011. It is slated to work on similar lines as DSTT and involves an initial investment of £5 million from each partner over a span of 3 years.

Winning an academia-industry deal and making it work involves careful discussions on valuation and who will own the joint IP. In addition, a company may opt for an intermediate deal if the target that they are interested in, is many years away from market. Also, some deals may be killed altogether, in case there is a mismatch with respect to the expectations of the parties involved; despite the underlying science being good. In summary, the field of drug discovery and development is a dynamic environment and features innovative trends for the industry and academia to partner and flourish together.

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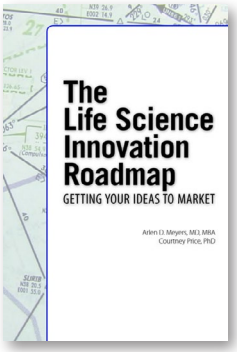

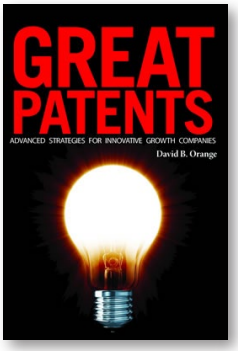

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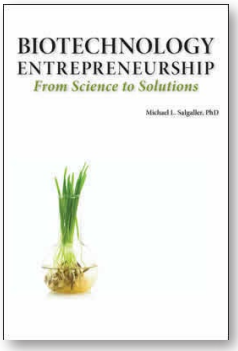

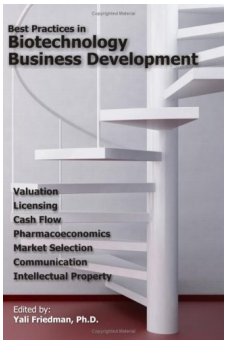

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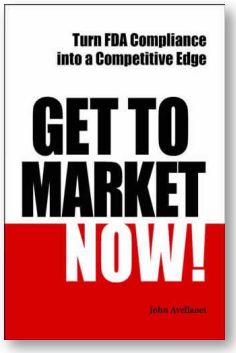

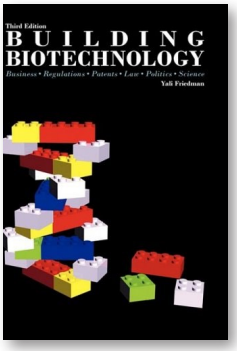

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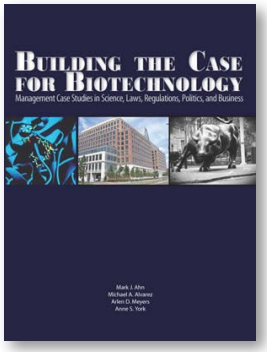

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