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Article

Reverse stock splits in the biotechnology industry: An effectuation approach

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ABSTRACT

Using an effectuation theory lens, we study reverse stock splits in the biotechnology industry where significant uncertainty makes specific scenarios of success difficult to predict. We conjecture and find that, in contrast to other environments where there is less uncertainty, reverse stock splits in the biotechnology industry are followed by positive abnormal returns over the subsequent 1- to 12-months. Also consistent with our effectuation-based predictions, we find that these returns are positively related to the reverse split ratio, size, cash holding, and long-term debt, and negatively related to the market-to-book ratio and firm age. We also find that liquidity improves after a reverse stock split. These results suggest that the concept of effectuation theory is better suited to analyzing reverse stock splits in the biotechnology industry.

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INTRODUCTION

According to standard, predictive signaling theory, reverse stock splits send a negative signal to the stock market. This prediction arises from the following logic. Managers are assumed to have superior predictive information about future cash flows. So, when the stock price is below the optimal range, and there are poor prospects about the arrival of good news regarding future cash flows, then the decision to undergo a reverse stock split (RSS) reveals the manager's negative private beliefs (or non-presence of positive beliefs). Studies show that in particular, expert managers in highly uncertain business environments do not use a predictive mental framework; rather, managers think in terms of their ability to effectuate change within their own firm's business environment.1 Thus, in business environments with a high degree of uncertainty, there is reason to question the explanatory relevance of traditional, predictive signaling theory.

Biotech firms operate in a highly uncertain environment. The sequential progression of products, from pre-clinical and human testing to drug approval requires relatively large sums of capital and multiple rounds of financing in order to progress through critical phases of development.[2] Obtaining financing at each stage of development is crucial for the survival and eventual success of these highly volatile biotech firms.[3-5] Also, valuation of these firms is very difficult. Traditional valuation methods, such as discounted cash flow and relative valuation practices, tend to lead to under-valuation and under-investment in earlier stage drug development projects.[6] Real-option models better capture the stochastic nature

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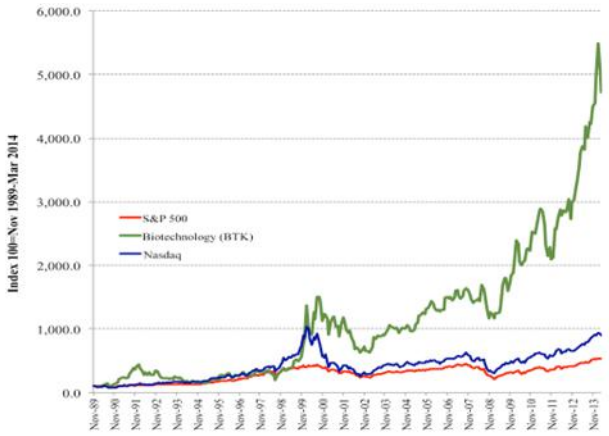

Figure 1: Biotechnology Index vs. S&P 500 and NASDAQ Indices November 1989 – March 2014

of the breakthrough potential and abandonment options for biotech firms, but these models are still very difficult to implement. To place the difficulty of valuing this uncertainty in context, the stock market index for the biotechnology sector (BTK), which has outperformed the overall market, has been 9 times more volatile than the S&P 500; and 5 times more volatile than the NASDAQ (Figure 1).

Because of these features of the biotech industry, we hypothesize that the signaling properties of reverse stock splits for biotech firms will differ from the signaling properties implied by the traditional, predictive model. Investors' ability to predict success among biotech firms does not depend on being able to predict success of specific conceivable scenarios; rather, success depends more on being able to predict how well, and how likely, firms will be successful in "taking effectual action and help[ing] stakeholders make effectual commitments" in a radically uncertain future.[7] Also, with effectual processes, the environment is not exogenous to the firm's transformative actions and, because of this endogenous relationship between stakeholder action and the environment, success depends heavily on endogenous factors, like the ability to obtain stakeholder commitments and the ability to adaptively coordinate and leverage capabilities both within and without the firm. We analyze these differences between the traditional, predictive-signaling model and an effectuation-based signaling model and hypothesize that, for biotech firms, reverse stock splits should comprise a positive signal about future prospects of success.

To empirically test our hypothesis, we utilize event study methodology and find that cumulative abnormal returns (CARs) are positive following a reverse stock split for biotech firms. We also find that this effect is stronger when the split ratio is higher. These results are consistent with our hypothesis that, in accordance with effectuation theory, a manager's commitment to keeping the firm's stock price sufficiently high, in order to avoid the risk of having to delist, is a signal that the manager has positive beliefs about his or her ability to effectively exercise control over endogenous factors important to the firm's ability to succeed in the industry.

In additional cross-sectional regression analysis, we find that abnormal returns are associated with firms that are larger, have greater cash holding, are younger, have a positive amount of long-term debt, and, albeit a less robust finding, have lower market-to-book ratios. These results are consistent with our effectuation-based model in the following ways. With regard to size, larger firms have greater control over their environment, implying that our positive abnormal return hypothesis should be greater for larger firms. With regard to cash holding, firms with more cash have more means to control their environment. With regard to firm age, firms that are older are "past their prime" in the sense of failing to signal their ability to be successful even when given a reasonable amount of time to do so. With regard to long-term debt, the presence of such debt signals an ability to get financial stakeholders to commit to the future of the firm. Finally, with regard to market-to-book ratios, value firms that have more depressed market values, relative to their book value, are able to strengthen any positive impact from the signal to the market and lead to stronger positive abnormal returns. Although not all of these results are uniquely predicted by our effectuation-based framework, these results nevertheless make good sense from an effectuation perspective.

We also study liquidity and find that liquidity measures, such as turnover ratio, the proportion of days with zero returns, and the Amivest liquidity ratio (a measure of the price impact of a trade), all point to a positive impact on liquidity following a reverse stock split by biotech firms. This result is consistent with other studies of reverse splits.[8-9] In light of the positive abnormal returns, the improved liquidity implies the positive signal of the RSS has attracted more participation and trading activity from investors and, consequently, a lower cost of equity in further rounds of financing.

The remainder of our paper is organized as follows. Section 2 analyzes the biotechnology industry and effectuation theory. Section 3 discusses forward and reverse splits, and provides motivation for our empirical hypotheses and predictions. Section 4 describes empirical methodology, data, and sample summary statistics. Section 5 presents our empirical results from analyzing stock returns and liquidity. Section 6 concludes and suggests areas for future research.

AN EFFECTUATION-BASED VIEW OF THE BIOTECH INDUSTRY

The biotech industry is heavily dependent on the research and development of new drugs. Because of the significant uncertainty and long-term nature of biotech research, which typically requires multiple rounds of new financing, the biotech industry has many of the characteristics embedded in effectuation theory. In this section, we first describe the highly uncertain, non-predictive nature of the biotech industry. Then we describe effectuation theory and argue that it provides a framework for understanding the biotech industry that is more suitable than standard predictive frameworks.

The non-predictive nature of the biotechnology industry

Biotechnology research is a highly uncertain, long-term affair. Predicting which particular research efforts will be successful is very difficult. Because of this, successful biotechnology firms typically pivot several times, from one area of research to another, before achieving any significant level of success. Moreover, new lines of promising research frequently appear only after initial research in some area is already begun.

This underlying uncertainty of the research process is compounded by a fundamental financial tension that biotechnology firms face: on the one hand, the vast majority of development-stage biotechnology firms have no revenues; on the other hand, these same firms must plan for long product development cycles (12 years on average from initial research to commercialization). Because of this tension, financing occurs in successive incremental rounds that provide resources to the next valuation inflection point (typically 1-3 years). This firm-specific financial risk is compounded by the volatile nature of market-wide "open windows" for subsequent financings. Thus, a firm could be progressing on research goals, but end up being unable to raise capital at accretive terms due either to investor skepticism or a down market. And because biotechnology firms rely so heavily on multiple rounds of financing, setbacks in achieving milestones can be devastating to development-stage biotechnology firms.[10]

The following example of Cytokinetics illustrates the compounding effects associated with the highly uncertain nature of biotechnology research, long-product cycles, and multiple rounds of financing. Cytokinetics was founded in 1998 in San Francisco to pursue therapeutics using a novel technology platform of cytoskeleton and the biology of muscle function to tackle the pursuit of new treatments for multiple disease areas. The company has completed eight different financings totaling $308 million since its IPO in 2004. First, the company experienced multiple setbacks in oncology, notably a Phase 2 trial for SB-715992 (ispinesib) platinum-sensitive and platinum-refractory non-small cell lung cancer (NSCLC) showed that ispinesib led to a disease stabilization rate which was insufficient to proceed to the next stage of the development. After share price declined, Cytokinetics effected a reverse split of 1-for-6, which increased the share price from $2 to $12 with a corresponding decrease in shares outstanding in June 2013. Subsequently, the company went on to complete a financing of $40 million in February 2014. In April 2014, the company announced that tirasemtiv (fast skeletal muscle troponin activator), its lead unpartnered compound, missed the primary endpoint in the Phase 2b trial in 711 patients to treat amyotrophic lateral sclerosis (ALS). On the news, its stock price immediately dropped from $8.40 to $4.59. Despite multiple setbacks, however Cytokinetics continues to move forward with large biotechnology partner Amgen which is evaluating an oral formulation of Cytokinetics' omecamtiv mecarbil in a Phase 2 trial in patients with chronic heart failure (CHF) and left ventricular systolic dysfunction.

A standard discounted-cash-flow framework for analyzing biotechnology firms, like Cytokinetics, has significant weaknesses which lead to under-valuation and under-investment. Although real option techniques can be used to improve valuation accuracy, these models quickly become very complex as the number of development pathways increases. On the contrary, effectuation theory provides an alternative and more suitable way to value and understand the biotechnology industry.

Effectuation theory

Effectuation theory refers to "a set of means as given and focus on selecting between possible effects that can be created with that set of means," while predictive models rely on predictable processes that "take a particular effect as given and focus on selecting between means to create that effect."[11] The original effectuation model consists of four dimensions: means, affordable loss, partnership, and expecting the unexpected.[12] In the remainder of this section, we describe how these four dimensions of effectuation theory fit the biotechnology industry.

In previous studies, effectuation has been widely explored in entrepreneurship,[13] but it has also been considered in the context of corporate R&D,[14] management,[15-16] economics,[17] finance[1] and marketing.[12] However, to our knowledge, our research is the first to explore its use specifically within the context of the biopharma industry and to apply it to analyzing reverse

stock splits for development stage companies. Also, although the concepts of effectuation theory have been empirically tested at both the individual and the firm level, surveys have been the predominant method of data collection. Dew et al.[11] study individual decision-making in exploring new venture success with data collected from surveys of expert entrepreneurs and compared to MBA student responses. Wiltbank et al.[1] surveyed angel investors and analyze how effectuation framing relates to success. Our research differs from these studies in that we look only at existing firm-level variables, a precedent suggested and supported by Brettel et al[14] who collected their data using surveys of European technology firms rather than adopting archival financial data as proxies. As such, their survey-based results are based on management perceptions.

Means

The "means" construct is a three dimensional variable: "what I know," "who I am," and "who I know." "What I know" tends to be defined as domain specific expertise as well as more general variables such as personality, gender, and management experience. In the biotechnology industry, this dimension is largely comprised of knowledge about the R&D process. "Who I am" is operationalized at both the individual level of analysis (such as propensity for risk and self-efficacy) and the firm level (such as patents, capital, and internal R&D). "Who I know" includes family and friends who are resourceful or well connected, including entrepreneurs, university personnel, scientists, or others experts in the innovation process.[17]

Because pharmaceutical firms enjoy high profit margins, most multinational biopharmaceutical companies have significant financial means or resources to deploy, including large cash balances, borrowing capacity and stock market values. These means allow them to invest heavily in R&D, among other things. However, their decisions on how much to invest and on what segments can differ significantly depending on their degree of diversification and priorities. For example, a diversified biopharma firm like Johnson and Johnson (J&J) gains about 37% of sales from its biopharma segment, but a more focused biopharma firm such as Biogen gains 100% of revenues from drug sales. While both earn about the same profit margins on their biopharma sales (24.4% for J&J and 23.5% for Biogen), in absolute terms, the internally generated cash available to a corporate giant like J&J ($15 billion total, $6.1 billion from biopharma) dwarfs the internally generated cash available to a stand-alone biotechnology firm like Biogen ($1.2 billion). However, this advantage in financial means is a disadvantage when it comes to managing affordable losses, as discussed below.

The relatively diminished means for development-stage biotechnology companies can be crippling. For example, development stage Aveo Oncology completed a Phase 3 trial for ASP4130 (tivozanib) in advanced renal cell carcinoma (RCC), and found a co-promotion partner in Japan-based multinational pharmaceutical Astellas Pharma. However, a FDA advisory committee known as Oncologic Drugs Advisory Committee (ODAC) voted 13-1 to recommend the agency reject tivozanib for RCC in June 2013. The FDA subsequently rejected the company's application which it faulted as uninterpretable and inconclusive, and requested a new trial be conducted in December 2013. Aveo restructured with the layoff of 140 staffers—62% of its workforce—following the advisory committee rejection. Its share price reduced from $7 to $2. Three weeks later, Astellas Pharma informed Aveo it would not pursue European approval for the drug candidate, and would stop funding RCC trials under their collaboration, which ended the company's programs.

Affordable Loss

Rather than using expected return as a criterion for investment, "each effectual stakeholder strives to invest only what he or she can afford to lose."[7] Although large firms have more financial resources than development-stage firms, implementing an affordable-loss approach is easier in smaller biotechnology firms. This is because multiple rounds of financing are frequently needed to keep biotechnology firms afloat, a mechanism that naturally limits losses. The pros and cons of the different ways that large versus small biotechnology firms manage investment decisions can be illustrated in the following examples.

As an example of a large multinational biopharma leveraging its resources to shift from a traditional internal R&D model to biopharmaceutical alliances to further its product pipeline, consider Bristol-Myers Squibb Company (BMY). BMY has been strategically aligning with small and mid-sized drug developers and biotechnology companies by targeting companies whose products and technologies address unmet medical needs and build on BMY's R&D strengths and/or create new areas of expertise.[18] The String of Pearls strategy, formalized in 2007, threads together a library of compounds and portfolio of technologies for the purpose of accelerating the discovery, clinical development and commercialization of new therapies across a broad range of therapeutic areas. However, BMY's acquisition of Inhibitex in Phase 3 clinical development for HCV (hepatitis C virus) for $2.5 billion or 167% premium resulted in a total failure. After

only eight months, the lead drug trial was discontinued when a patient death resulted in a $1.8 billion write-off.

While BMY withstood the Inhibitex setback, consider the smaller, development-stage Ziopharm Oncology clinical study for ZIO-201 (palifosfamide) in metastatic soft tissue sarcoma in March 2013. The DNA alkylating agent did not meet its primary endpoint of progression-free survival (PFS) in a Phase 3 trial, designed to assess the drug as a first-line treatment for metastatic soft tissue sarcoma. The setback resulted in the elimination of the company's entire oncology portfolio, the elimination of 65 positions (leaving approximately 30 employees), and the complete change in strategic focus on its synthetic biology programs being developed with Intrexon. Ziopharm Oncology survived, but the failure resulted in more drastic changes compared to post-setback changes implemented in larger firms like BMY.

Stakeholder Commitments

Because of the greater reliance on multiple rounds of financing, smaller firms depend more than larger firms on commitments from external stakeholders. Effectuation theory frames partnerships as collaborations with stakeholders and organizations willing to make a significant commitment to product and market development. Read et al.[12] distinguish the means-based "who I know" dimension from the stakeholder-commitment-based "partnerships" dimension by determining whether success depends on the firm itself ("means") or the other party ("who I know"—typically as a result of money, equity or a product changing hands).

In the biotechnology industry, the vast majority of the over 600 public and 8,000 private companies worldwide have no revenues or earnings, which means that their investment is funded through grants, public or private equity, and/or through partnerships with larger, better capitalized publicly traded firms. The small percentage of these firms that are successful in moving into later stages of clinical trials or actually receiving FDA approval to market a drug are often acquired by larger biopharma firms in these later stages.[19] Thus, for large, well-established firms, partnering with and/or later acquiring smaller biotechnology companies provides a viable option to committing a firm's R&D investment capital to internal development programs.[20] These partnerships, collaborative agreements, and joint ventures create powerful innovation network effects,[21] as well as allow both firms to learn to work together, providing an option for possible later acquisition.

Despite the greater information asymmetry associated with early stage novel technologies (e.g., stem cells, checkpoint inhibitors, gene therapy, cancer vaccines, RNAi), signaling mechanisms can help investors discriminate among firms' pipelines. The relevant data in this process includes clinical data (such as announcement of clinical results at medical conferences), publicly announced partnership deals (such as licensing, co-development, co-promotion), and institutional investment by specialist mutual and hedge funds.[22,23] For example, Agios Pharmaceuticals, an early stage drug development company which focused on cancer metabolism with a marquee research partnership with large biopharma Celgene, successfully completed an IPO at $18 which overshot the range of $14-16, raised an additional $106 million, and soared 60% on its first day of trading—sending the market capitalization to over $800 million.

External stakeholder commitments can also be critical in allowing a development stage company to survive a major setback. For example, development stage Rigel partnered R788 (fostamatinib) with multinational pharmaceutical company AstraZeneca (AZ). In June 2013, Rigel announced that R788 (oral spleen tyrosine kinase inhibitor) with methotrexate (MTX) did not show statistically significant improvement compared to placebo in the Phase 3 OSKIRA-3 clinical study. Of note, AZ was solely responsible for all costs and expenses, and subsequently recorded a $136 million pre-tax impairment charge to R&D expense. AZ announced that it would not proceed with regulatory filings, and returned its rights to the compound to Rigel which has since turned its primary focus to other programs.

Expecting the Unexpected

The "expect the unexpected" effectuation principle encourages companies to embrace surprises that arise from uncertain situations, remaining flexible rather than tethered to existing goals.[12] Wiltbank et al.[7] refer to this effectuation dimension as "leveraging contingencies" defined as a willingness to dramatically change goals, products, or strategies.

While all large biopharmaceutical companies have a pressing and ongoing need for new products, they have approached pipeline and product investment and development differentially, in the sense that some rely on internal development and research partnerships, while others rely on purchasing external R&D and/or smaller firms typically in later stages of FDA approval through mergers and acquisitions). Illustrating these different approaches, Pfizer has heavily relied on multibillion dollar acquisitions such as Warner-Lambert in 2000, Pharmacia in 2002, Wyeth in 2009, King Pharmaceuticals in 2010; and Roche has relied on internal development and partnerships (e.g., Genentech partnership to grow a pipeline of blockbuster oncology products such as Herceptin® (trastuzumab), Rituxan® (rituximab), and Avastin® (bezicuzimab) each with greater than $5 billion

in 2012 annual revenues. There is a tradeoff between the perceived risk of overpaying for late-stage products, often obtained through mergers and acquisitions, and the uncertainty of valuing internally developed earlier stage products.[24]

An example of an "unexpected" event is the emergence of an unanticipated safety signal, even after extensive clinical studies. For example, Biogen-Idec and Elan's Tysabri (natalizumab) was originally approved for all relapsing forms of multiple sclerosis (relapse-remitting, secondary-progressive, and progressive-relapsing) in 2004. However, four months after its approval in February 2005, the manufacturer withdrew natalizumab voluntarily after two fatal cases of progressive multifocal leukoencephalopathy, and the stock price fell from $66 to $38. The drug was eventually re-approved in June 2006 after an extensive safety review and heavy lobbying by patients, and Tysabri reached $5.5 billion in 2012 revenues.

REVERSE STOCK SPLIT AND EMPIRICAL HYPOTHESES

In this section, we first provide a review of the existing literature on forward and reverse stock splits, paying particular attention to standard predictions based on predictive signaling theory. Then we motivate our empirical hypotheses and predictions by analyzing reverse stock splits from the perspective of effectuation theory.

Forward and reverse stock splits

There are two types of stock splits, forward splits and reverse splits. A forward split is when one share becomes multiple shares, resulting in more shares but a lower price per share. Between 1933 and 2007 the average share price of major U.S. stocks remained remarkably constant, rarely straying far from $25 to $35. The average forward split was $50 pre-split. Anytime a stock went much higher, the company reduced it back down with a stock split. Conversely, a reverse split occurs when multiple shares are combined into one share, resulting in less shares but a higher price per share. The average reverse split is $1.21 pre-split.[25-27]

Typically, reverse splits are done from a position of weakness such as a setback of some kind (e.g., unanticipated loss of intellectual property protection, loss of market share, natural disaster, adverse regulatory action, significant market correction) which significantly reduces the share price and threatens the company's viability as an exchange traded stock.[28-31] Further, companies must maintain minimum standards to ensure continued compliance and exchange trading.

For example, to maintain a listing on the NASDAQ stock exchange, corporations are required to meet minimum standards for their share price, market value and corporate governance. Generally, stocks must have a share price of at least $1 and a minimum market value of $1 million. In addition, companies listed on the NASDAQ must adhere to federal disclosure requirements for publicly traded securities and pay annual listing fees. The exchange issues a deficiency notice to any company in violation of any of the minimum standards for 30 consecutive days—after which the company has 90 days to regain compliance. For example, if the price were under $1 a company could choose to effect a reverse split to increase its share price. Companies which are delisted from the NASDAQ can continue to trade on the over-the-counter markets and the Pink Sheets, and some can reapply to NASDAQ and regain their listing. Regardless, delisting is often hard on a company, because it can impair its access to capital (e.g., Blue Sky laws which limit retail brokerages to sell stock with a price under $5 per share can reduce the depth and breadth of investors), the ability to borrow and exemptions from various state laws.[32]

There are three main stock split theories: (1) The optimal price/tick theory posits that splits return the stock price and relative tick size to their optimal range in their industry and market; (2) signaling theory posits that splits reveal information about future performance; and (3) the procedure/structure theory explains how a particular feature/structure/rule can cause a certain phenomenon in relation to splits.[27] According to the traditional signaling model, managers have better predictive information about outcome scenarios and so, when a firm is near its delisting boundary, a reverse stock split (RSS) signals negative information about the probability distribution of specific future scenarios. As Rhee and Wu explain:

> *A broadly accepted explanation … is that RSS signals to the market that management has either lost confidence in future price increases or exhausted all other means of maintaining the listing. RSS is the last straw before a stock is delisted to less liquid and less transparent markets, which becomes especially apparent after the NASDAQ introduced the one-dollar rule.*[33]

EMPIRICAL PREDICTIONS BASED ON EFFECTUATION THEORY

Main prediction for stock returns

Relative to the traditional prediction-based signaling framework, signaling works differently in a non-predictive, "effectual" environment. When there is a large amount of uncertainty and firms have a significant amount of control over their future outcomes, then an RSS signals that the firm's manager is bullish about its own means, its stakeholders' willingness to commit to the future of the company, and that the firm will be able to successfully adapt to unexpected outcomes. Moreover, the RSS is a means by which the firm can, *ipso facto*, increase stakeholder commitments. However, because multiple rounds of financing are to be expected, this increase in commitment is done in a way that is consistent with the effectual logic of affordable losses.

Thus, in contrast to the predictive framework of traditional signaling theory where the manager and the stakeholders of the firm have relatively little control over outcomes, in an effectual environment this relationship is reversed: the firm operates in a non-predictive environment and the manager and stakeholders of firm have a relatively significant amount of control over the firm's outcomes. Because of this, an RSS strengthens commitments to the firm's future and signals the manger's confidence that the firm will be able to continue its operations in a propitious way. And because it is not possible in an effectual environment to exhaustively specify these possible scenarios, the signaling effect about the firm's confidence in its ability to control its own fate has a greater effect than any effect based on predictions about any specific future scenarios. Based on this logic and our previous argument that biotechnology firms are, in fact, in an effectual environment, we hypothesize the following:

H_1: Biotechnology firms who conduct a reverse stock split will experience a positive abnormal return.

Explanatory variables for stock returns

Our key hypothesis, that RSS-firms will have positive *ex post* abnormal stock returns, is rooted in effectuation theory. Effectuation theory can also be used to predict the sign of the coefficient for various explanatory variables. These predictions cannot be cleanly contrasted with predictions obtained using a predictive signaling model. Nevertheless, to better understand the empirical implications of effectuation theory in the context of biotechnology RSSs, below we discuss the predicted sign on the coefficient for various variables in a regression where abnormal stock returns are the dependent variable.

If a firm chooses a larger split ratio, then this comprises a stronger signal and effects a greater commitment. Thus, the effect underlying H_1 will be more significant and we predict that the estimated coefficient for the split ratio will be positive. Because of economies of scale, larger firms tend to have greater control of their own destiny. This is because larger firms have more means and resources to survive and adapt when setbacks occur. All else equal, size is also an indicator of commitment by internal and external stakeholders. Thus, in an effectual environment, measures of size should have a positive coefficient. Similarly, if a firm has a great deal of cash, the cash can be used as a means of increasing the firm's ability to prolong projects and successfully navigate or adapt in the face of setbacks. Cash thus comprises an alternate form of control and implies a positive predicted coefficient.

In a slightly different vein, research and development (R&D) spending represents an alternative indicator of means, commitment, and adaptability. This is because firms with larger R&D spending will, all else equal, have greater resources to spur innovation, a larger network of synergistic partners and potential partners, and a larger number of options to adapt in the face of setbacks. Thus, the estimated coefficient for R&D should have a positive sign. In a similar vein, but with a stronger emphasis on commitments, long-term debt signals that a firm has committed financial partners (debt holders). This comprises a positive signal with respect to the firm's commitments from existing financial investors and prospects for successfully navigating future rounds of financing. Additionally, the structure of debt more strongly parallels the logic of affordable losses than the structure of equity. Thus, the estimated coefficient for an indicator of long-term debt should be positive.

If the market is bearish about a firm's future prospects, this will lead to a lower market-to-book ratio, all else equal. If a reverse stock split sends a positive signal to investors, the reversal in investors' expectations is apt to be greater for these firms with low market-to-book ratios. This implies that the market-to-book ratio should have a negative coefficient estimate. Finally, with regard to firm age, older biotechnology firms can be understood as being less likely to face setbacks, since they should have more controls and means compared to younger firms, all else equal. So, when an older firm does experience a setback, as indicated by the need to undergo an RSS, then this is likely to comprise a negative signal about the firm's ability to successfully control its environment. Thus, we predict that the coefficient for firm age will be negative.

Liquidity

With regard to stock liquidity, reverse stock splits are known to improve liquidity due to reduced effective (percentage) bid-ask spread that captures round-trip trade execution costs.[8,9] In an effectual environment, an RSS draws attention from investors. This, in turn, leads to a stronger signaling effect. Also, because the signaling effect is positive, as we have argued above, the greater attention also leads to improved commitments from investors and other stakeholders. Also, inasmuch as an RSS increases the firm's stock price, this leads to a positive feedback effect in the form of a lower cost of capital, thus improving the firm's ability to adapt to unexpected setbacks. We thus hypothesize the following:

H_2: Biotechnology firms who conduct a reverse split following a setback will experience an improvement in liquidity.

METHODOLOGY AND DATA

In this section, we first explain our empirical methodology. We then discuss our sample, and provide basic summary statistics.

Methodology

We utilize the methodology of event study to test our hypotheses. An event study attempts to measure the valuation effects of a corporate event, such as a reverse stock split announcement, by looking at the response of the stock price around the announcement of the event and determine whether there is an abnormal return or not. One underlying assumption is that the market processes information about the event in an efficient and unbiased manner. To alleviate this assumption, we consider a number of lengths of event windows from one day to one year.

To estimate the normal return of a stock, we first use market model with CRSP value-weighted index as the proxy for the market return. We then use a four-factor model with Fama-French three factors (market, size, and book-to-market) and momentum factor.[34,35] The four-factor model has the advantage to control for risk premiums associated with size, growth, and market momentum. It is important to control for size and growth when estimating the normal return as our sample firms are relatively small and still in their early growth stage. We then calculate the abnormal return and the cumulative abnormal return (CAR) based on the estimated normal return and test the average of CAR using the methodology in Brown and Warner.[36,37]

In addition to the CAR approach, we follow Barber and Lyon[38] and analyze buy-and-hold returns using matched control firms. Barber and Lyon point out a potential bias induced by cumulating short-term abnormal returns, such as CARs, over long periods (see also Conrad and Kaul[39] and conclude that the matched control firm approach leads to unbiased test statistics. Because of this potential bias, we measure stock performance by computing holding-period returns (HPRs) for each adopting firm and its matched control firm over one-month, six-month, and one-year periods following RSS. The holding periods start on the RSS announcement day.

Following Spiess and Affleck-Graves,[40] we first choose our control firms on the basis of industry, size (market capitalization), and book-to-market ratio. We avoid look-ahead bias by using only the information available at the time of RSS announcement. For each RSS sample firm, we identify all public firms in CRSP that have not undergone a RSS in the previous three years and belong to the biotechnology industry as defined by their 2-digit NAICS. We select the first matched firm from the set of potential matches such that the sum of absolute percentage difference between the size and book-to-market ratio of the sample firm and the control firm is minimized. If the first-best matched firm is delisted, we substitute returns from the second-best matched firm, starting at the close of trading on the date of the delisting payment and including the delisting return. If the first-best matched firm subsequently undergoes a RSS, we substitute the second-best matched firm on the next trading day.

In our liquidity analysis, we use four measures of Chordia et al.[41] First, we construct a share turnover ratio, Turnover, by dividing the total number of shares traded by the number of shares outstanding for a trading day and then average the daily ratios over a sample period to have the mean share turnover ratio:

$$\text{Turnover}=\frac{1}{T}\sum_{t=0}^{T}\frac{\text{number of shares traded on day t}}{\text{number of shares outstanding on day t}}$$

Lesmond, Ogden[42] consider the proportion of days with zero returns as a proxy for liquidity. There are two key arguments that support this measure. First, stocks with lower liquidity are more likely to have days with little to no trading activity, and thus zero volume and zero return on these days. Second, stocks with higher transaction costs have less private information acquisition because of the higher transaction costs which gives traders a low incentive to obtain private information. Thus, even on positive volume days, these illiquid stocks can experience no-information-revelation and therefore zero return on these days. Thus:

$$\text{Zeros}=\frac{\text{number of days with zero returns}}{\text{total number of days in the subsample}}$$

The Amivest liquidity ratio is a measure of price impact which can be interpreted as the dollar volume of trading associated with a 1-percent change in the price of a security:

$$\text{Liquidity}=\frac{1}{T}\sum_{t=0}^{T}\frac{\text{volume}_t}{|r_t|}$$

where volume_t is the dollar volume on day t and r_t is the return on day t. The average is calculated over all non-zero-return days since the ratio is undefined for zero-return days. A larger value of Liquidity implies a lower price impact. This measure has been used by Amihud, Mendelson,[43] Berkman and Eleswarapu,[44] and others.

Finally, we define two volatility variables: Volatility_d as the standard deviation of daily returns, annualized by multiplying by the square root of 252; Volatility_m as the standard deviation of monthly returns, annualized by multiplying by the square root of 12. A reverse split reduces the relative bid-ask spread due to an increase in share price. This change in market microstructure alone may cause volatility to decrease.[26] As monthly returns are less impacted by bid-ask bounce, Volatility_m can reflect the level of volatility due to trading activities, which we intend to measure.

Sample and Summary Statistics

We use the Biocentury database to identify 40 biotechnology firms with RSS and collect split-related information. All 40 biotechnology firms were listed on NASDAQ and announced their reverse stock split during the 2011-2013 period. Table 1 summarizes the 40 reverse stock splits by split ratio and by their announcement year. Company financial data and stock return data are collected from COMPUSTAT (active and research) and CRSP tapes, respectively. The COMPUSTAT data includes "research" firms that have failed or been acquired eventually and CRSP stock data includes delisting returns if a firm's stock is delisted. Imposing that firms need to have data in all three sources leaves us with a total of 35 RSS firms. The choice of the sample period is governed by the availability of data.

We show summary statistics for our sample in Table 2. As shown in Panel A, the average (median) split ratio is 14.38 (7) with a range from 2 to 125 and an interquartile range from 6 to 15. The average (median) 30-day closing price for RSS firms prior to their reverse split event is 0.62 (0.52), with a range from 0.16 to 1.96 and interquartile range from 0.37 to 0.66. Thus, the majority of our biotechnology RSS firms have a prior price below $1. Average (median) market capitalization three days prior to the RSS event is 40.06 (28.58) million dollars.

Table 1: Biotech Reverse Splits by Split Ratio and Announcement Year

Split Ratio	Number of Splits			
	2011	2012	2013	Total
1:2	1			1
1:3		1		1
1:4		3		3
1:5		1	1	2
1:6	1	6	2	9
1:7		3		3
1:10	2	4	1	7
1:12		1	1	2
1:15		1		1
1:16		1		1
1:20		2	2	4
1:25			1	1
1:30		1		1
1:40	1			1
1:50			1	1
1:56		1		1
1:125			1	1
Total	5	25	10	40

This table summarizes the 40 reverse stock splits by split ratio for biotechnology firms during the sample period 2011-2013.

Panel B of Table 2 shows summary statistics of our key variables. Panel C shows correlations between the explanatory variables that we intend to use in subsequent analysis. The variables with absolute correlation greater than 0.40 are as follows: LogEmp, LogSales, and LogTA are all highly correlated, with correlations ranging from 0.45 to 0.77. All three variables are proxies of size. As half of our sample firms do not have any sales, we use LogTA to measure size in our regression analysis. Also, there is a high degree of negative correlation between LogSales and LogSplitRatio, LogSales and Cash/TA, and LogEmp and Cash/TA, ranging from 0.42 to 0.54.

Table 2: Summary Statistics and Correlations

Panel A: Share Characteristics									
Variable	**N**	**Mean**	**StDev**	**Min**	**25th %**	**Median**	**75th %**	**Max**	
Split Ratio	35	14.38	21.78	2.00	6.00	7.00	15.00	125.00	
Prior Avg (30-day) Price	35	0.62	0.43	0.16	0.37	0.52	0.66	1.96	
Prior Mkt Cap	35	40.06	55.94	2.89	7.62	28.58	57.89	263.05	
Panel B: Key Variables									
Variable	**N**	**Mean**	**StDev**	**Min**	**25th %**	**Median**	**75th %**	**Max**	
Total Assets (TA)	35	30.26	38.37	3.18	8.66	16.62	40.23	204.99	
LogTA	35	2.90	0.99	1.16	2.16	2.81	3.69	5.32	
Employees (Emp)	35	0.04	0.07	0.00	0.01	0.02	0.05	0.44	
LogEmp	35	-3.77	1.02	-5.81	-4.61	-4.02	-3.00	-0.82	
Sales	35	5.93	12.83	0.00	0.00	0.10	4.07	49.32	
LogSales	25	-0.28	2.69	-4.61	-2.43	-0.78	1.68	3.90	
M-B	32	6.65	10.29	0.17	1.89	2.79	6.51	49.45	
R&D	35	10.47	12.17	0.73	3.52	5.62	12.69	52.40	
Age	35	12.01	8.32	1.93	5.21	9.95	16.22	34.96	
LogAge	35	2.24	0.77	0.66	1.65	2.30	2.79	3.55	
Cash	35	18.21	31.15	0.59	6.20	10.82	17.72	187.66	
LT Debt	35	2.21	6.13	0.00	0.00	0.00	1.67	32.73	
Panel C: Correlations									
	LogTA	**LogEmp**	**LogSales**	**M-B**	**LogSplitRatio**	**R&D/TA**	**Age**	**Cash/TA**	**IndLTDebt**
LogTA	1.00								
LogEmp	0.68	1.00							
LogSales	0.45	0.77	1.00						
M-B	-0.06	-0.08	0.10	1.00					
LogSplitRatio	-0.19	-0.39	-0.42	-0.12	1.00				
R&D/TA	-0.33	-0.24	-0.03	0.00	0.11	1.00			
Age	0.02	-0.19	-0.12	-0.16	0.10	0.04	1.00		
Cash/TA	-0.19	-0.54	-0.44	0.12	0.14	0.09	-0.03	1.00	
IndLTDebt	-0.03	0.21	0.17	-0.14	0.06	0.29	0.05	-0.32	1.00

Panel A reports summary statistics of equity share characteristics for our sample of biotechnology firms that undergo a reverse stock split between 2011 and 2013. Panel B reports summary statistics of key variables. For variables with high degree of right skewness, we also show the logged version. Panel C shows correlation coefficients. Split Ratio is the reverse stock split ratio, the ratio between the number of new and old shares. Prior Avg (30-day) Price is the average closing price over 30 days prior to the announcement. Prior Mkt Cap is the market capitalization three days prior to the announcement. Total Assets is the total value of assets. Employees is the number of company workers as reported to shareholders (measured in thousands). Sales is the total sales of the firm. M-B is the market value of equity divided by the book value of equity. R&D is the research and development expenses, including all costs incurred during the year that relate to the development of new products or services. Age is the number of years between the split announcement day and the IPO day. Cash is the total amount of cash. LT Debt is the long-term debt. IndLTDebt is a dummy variable equal to one if the firm has a positive amount of long-term debt and zero otherwise. All variables, except split ratios, share prices, employees, and age, are in millions of dollars.

RESULTS

Analysis of Returns

Table 3 shows cumulative abnormal returns (CARs) for RSS biotechnology firms over the following six time windows, relative to each firm's RSS event: (1) 30 days before to 1 day before [-30, -1]; (2) the day of [0, 0]; (3) the day after [+1, +1]; (4) two days after to one month after [+2, +30]; (5) 1 month after to 6 months after [+31, +180]; (6) the day after to one year after [+1, +365]. Panel A shows CAR results using the market model with CRSP value-weighted index as the proxy for the market return whereas Panel B shows CAR results using a 4-factor model with Fama-French 3 factors (market, size, and B/M) and the momentum factor.

The results in Table 3 tell a fairly clear empirical story: biotechnology RSS firms experience positive abnormal returns prior to the RSS event, negative returns on the day of and the day after, and positive returns in 1-, 6-, and 12-month periods following the RSS event. These results are generally statistically significant, although if the Z-statistic is adjusted for both time-series and cross-sectional dependence, following Mikkelson and Partch,[37] then the day-of and month-after results are not significant. The economic significance of these results is, on average, quite large: 16% for the one-month prior; about 2.5% on the event day; 6% for the day-after; 33% for the month after; an additional 61% for the next 5 months; an additional 59% for the next 6 months, or 120% for the 1-year post-RSS window. The stock market initially reacted negatively to the announcement as shown by the negative CARs on the event day and the day after (albeit a less robust finding), and quickly reversed to strong positive returns in longer event windows.

Table 3: Cumulative Abnormal Returns

Panel A: Market Model					
Event Window	**Average (%)**	**T-Statistic**	**Z-statistic**	**25th Percentile (%)**	**75th Percentile (%)**
[-30, -1]	16.04	2.275*	1.913*	-4.74	28.94
[0, 0]	-2.48	-1.929*	-0.648	0.04	1.70
[+1, +1]	-6.25	-4.855***	-1.928*	0.90	2.55
[+2, +30]	33.04	4.765***	-0.648	10.10	47.34
[+31, +180]	61.01	3.869***	2.340**	16.63	289.35
[+1, +365]	120.34	4.892***	3.620***	95.43	581.90
Panel B: Fama-French-Momentum Four-Factor Model					
Event Window	**CAR (%)**	**T-Statistic**	**Z-statistic**	**25th Percentile (%)**	**75th Percentile (%)**
[-30, -1]	16.70	2.372**	1.917*	-9.53	47.59
[0, 0]	-2.62	-2.036*	-0.644	-8.52	3.82
[+1, +1]	-6.09	-4.739***	-1.925*	-13.56	3.02
[+2, +30]	34.03	4.917***	-0.644	-20.20	39.11
[+31, +180]	62.40	3.965***	2.770**	-2.59	112.15
[+1, +365]	120.86	4.923***	3.624***	33.28	199.96

*This table reports certain measures of the distribution of cumulative abnormal returns (CARs) for various event windows surrounding the announcement day of the reverse stock split of the biotechnology firms in our sample. Panel A shows the results based on market-model adjusted stock returns. Panel B shows the results based on Fama-French-Momentum four-factor model adjusted stock returns. The T-statistics of average CARs are based on the time-series standard deviation test in Brown and Warner (1980). The Z-statistics of average CARs are computed using the methodology of Mikkelson and Partch (1986), which considers both time-series and cross-sectional dependence, as well as unequal variances in returns. The 25th percentile and the 75th percentile of the distribution of CARs are also reported. The symbols *, **, and *** denote statistical significance at the 0.05, 0.01, and 0.001 levels, respectively, using a two-tailed test.*

Cross-sectional CAR regressions

Table 4 shows the results of cross-sectional regressions with CARs for various event windows as the dependent variable. In accordance with our effectuation-based prediction, we find that the coefficient on LogSplitRatio is positive and significant for each event window, and that the magnitude of the effect is larger for longer horizons.

LogTA, our size measure, has a positive and significant coefficient for the 6-month and 1-year post-RSS returns. This result is consistent with our effectuation-based prediction. For M-B, the coefficient is negative, in line with our prediction, but it is only significant for the one-month prior, event-day, and day-after returns. With regard to cash holding, we find that the coefficient on Cash/TA is significant only for the 1-year-after event window. The coefficient on Cash/TA is positive, in accordance with our prediction.

The coefficient on R&D/TA is positive and significant, as predicted, for the 1-month prior, 6-month after, and 1-year-after event windows. The coefficient on Age is, as predicted, negative and significant for the 1-month prior, day-after, 6-month-after, and 1-year-after event windows. The coefficient on IndLTDebt is positive and significant, as predicted, for the 6-month-after and 1-year-after event windows.

Matched returns

Table 5 shows holding-period returns (HPRs) for RSS biotechnology firms compared to a matched sample of non-RSS firms on industry, size, and book-to-market. The returns for our biotechnology RSS firms are significantly higher than our control sample. This difference is 7.5% at 1 month, 20.7% at 6 months, and 27.0% at 1 year. These results corroborate our CAR findings reported in Table 3 and strengthen our H_1 hypothesis.

Analysis of liquidity

Table 6 reports mean and median values for each liquidity measure and the corresponding difference of the measure of the same firm in the windows of 180 days before and after the effective day. We conduct the paired sample t-tests and Wilcoxon signed-rank tests of differences in means and medians respectively, and report corresponding p-values. The number of firms in this table is 34.

In accordance with H_2, we find that the share turnover ratio and the Amivest liquidity ratio are higher and Zeros is lower after the RSS by the mean and median. Both volatility measures indicate a slight increase in return volatility after the RSS despite insignificant p-values. When combining with the positive abnormal returns, these data support the idea that the reverse split draws positive attention and trading activities from investors. The improved liquidity can enhance the ability of biotechnology firms to raise capital in subsequent rounds of financing.

CONCLUSION

The highly volatile nature of the biotechnology industry possesses several features that make it an ideal fit to evaluate effectuation theory. In particular, there is significant uncertainty in developing specific product development scenarios which makes it confounding to predict results, as firm success depends on their internal means and ability to procure stakeholder commitments, limit losses, and being prepared to adapt to unexpected results (i.e., expecting the unexpected). Because this environment differs substantially from the presumed predictable environment of traditional stakeholder theory, the usual negative-signal predictions regarding reverse stock splits are not appropriate. We conjecture, instead, that reverse stock splits following a setback comprise a positive signal for biotechnology firms regarding their own competencies and commitments pertaining to operations and future rounds of financing.

In our empirical analysis, we find that biotechnology firms who conduct a reverse split following a setback experience positive abnormal returns over 1-, 6-, and 12-month periods. We also find, in accordance with the effectuation-theory perspective, that the abnormal returns are positively related to the reverse split ratio, size, cash holding and long-term debt, and negatively related to the market-to-book ratio and firm age. Moreover, we find that liquidity improves after reverse stock splits.

In sum, we believe this study contributes to the research literature by expanding and extending the use of effectuation theory as an integrative and highly relevant framework for assessing biotechnology firms, especially with regard to financial decisions. More specifically, our analysis suggests that the concept of effectuation theory is better suited to analyzing reverse stock splits in the biotechnology industry. To the best of our knowledge, this is the first effectuation research to use archival financial data as opposed to relying on surveys of management perceptions, as in prior research. Further, our integration of effectuation and stock split theories provides a lens from which to explore emerging approaches for breakthrough innovation and technology development. Future research, particularly in the biotechnology industry, should therefore, pay more careful attention to the distinct aspects of effectuation theory.

Table 4: Cross-Sectional CAR Regressions

	[-30, -1]		[0, 0]		[+1, +1]		[+2, +30]		[+31, +180]		[+1, +365]	
Variable	**Param**	**P-value**	**Param**	**P-value**	**Param**	**P-value**	**Param**	**P-value**	**Param**	**P-value**	**Param**	**P-value**
Intercept	53.17	0.258	0.83	0.730	9.86	0.039	17.30	0.845	227.49	0.477	-49.31	0.925
LogSplitRatio	27.95	0.072	1.47	0.014	1.71	0.003	61.59	0.043	233.12	0.020	410.26	0.001
LogTA	2.10	0.721	-0.06	0.882	-0.09	0.877	21.33	0.040	63.12	0.077	117.90	0.066
M-B	-1.12	0.013	-0.08	0.011	-0.06	0.046	-1.45	0.121	-1.90	0.434	-3.84	0.219
R&D/TA (%)	0.35	0.040	0.00	0.880	0.00	0.882	0.32	0.234	2.76	0.025	4.52	0.036
LogAge	-13.90	0.067	-0.26	0.213	-1.30	0.001	-21.93	0.120	-114.99	0.019	-163.32	0.027
Cash/TA (%)	0.02	0.902	0.00	0.602	0.00	0.657	-0.09	0.663	0.57	0.621	3.40	0.042
IndLTDebt	-8.60	0.431	-0.32	0.547	0.76	0.464	20.87	0.241	221.60	0.012	502.93	0.004
R^2	0.41		0.50		0.42		0.45		0.49		0.68	

This table reports coefficient estimates from the cross-sectional OLS regressions where the dependent variable is the cumulative abnormal return (CAR) in percentage for various event windows surrounding the announcement day of the reverse stock split of the biotechnology firms in our sample. Variable descriptions are provided in Table 1. P-values are adjusted for heteroskedasticity. We report the adjusted R^2 in the last row.

Table 5: Holding-Period Returns Following Reverse Split Matched on Industry, Size, and Book-to-Market

	1-month				6-Month				1-Year			
	Sample Firms	**Matched Firms**	**Difference**	**P-Value**	**Sample Firms**	**Matched Firms**	**Difference**	**P-Value**	**Sample Firms**	**Matched Firms**	**Difference**	**P-Value**
Mean	17.16	9.61	7.54	0.040	30.64	9.98	20.67	0.016	50.21	23.16	27.04	0.008
Median	9.05	1.93	6.12	0.054	27.39	10.51	18.81	0.024	39.65	16.95	24.19	0.013

This table shows mean and median holding-period returns (HPRs) for sample firms, matched control firms, along with paired differences over 1-month, 6-month, and 1-year horizons. HPRs are calculated as $\left[\prod_{t=1}^{T_i}(1+R_{it})-1\right]\times 100\%$ *where Rit is the return on stock i on the t-th day after the announcement day and Ti is the number of days from the announcement to the end of the holding period. Matched firms are chosen based on industry (2-digit NAICS code), size, and book-to-market ratio. If the matched firm is delisted, or undergoes a reverse split subsequently, we use the next closest matched firm's return. There are 32 sample firms that can be paired to control firms. We conduct the paired sample t-tests and Wilcoxon signed-rank tests of differences in means and medians respectively, and report corresponding p-values.*

Table 6: Liquidity Measures: Before and After the Reverse Split Announcement

	Stat	[-180, 0]	[0, 180]	Difference	P-value
Turnover (%)	Mean	0.80	4.73	-3.94	0.018
	Median	0.60	0.96	-1.52	0.023
Zeros (%)	Mean	6.26	4.21	2.05	0.010
	Median	5.88	3.36	2.46	0.002
Liquidity	Mean	30.11	172.27	-142.17	0.070
	Median	7.88	38.40	-13.30	0.002
Volatility[d] (%)	Mean	110.92	125.89	-14.97	0.044
	Median	98.00	89.69	-20.31	0.207
Volatility[m] (%)	Mean	100.55	116.86	-16.31	0.156
	Median	68.51	101.48	-32.39	0.207

This table compares liquidity of stock trading activity around the reverse split announcement day for the biotech firms in our sample. The first period is from 180 days before the announcement to the announcement day [-180, 0]. The second period is from the announcement day to 180 days after the announcement [0, 180]. Turnover is defined as the daily number of share-trading volume divided by the number of common shares outstanding, and then the daily ratios are averaged over time. Zeros is the proportion of trading days with a zero price change from the previous day over a specified time period. Liquidity is the Amivest liquidity ratio to measure price impact defined by dividing daily dollar trading volume by the absolute daily return, and then averaging over time. Volatility$_d$ is defined as the standard deviation of daily returns, multiplied by the square root of 252. Volatility$_m$ is defined as the standard deviation of monthly returns, multiplied by the square root of 12. The table reports mean and median values for each measure and the corresponding difference of the measure of the same firm before and after the announcement day. We conduct the paired sample t-tests and Wilcoxon signed-rank tests of differences in means and medians respectively, and report corresponding p-values. The number of firms in this table is 34.

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Article

Debt and taxes: Marginal tax rate changes, capital structure, and innovative activity in the biotechnology sector

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ABSTRACT

The purpose of this investigation was to examine the association between changes in corporate marginal tax rates (MTRs) and measures of both innovative activity and capital structure among publicly-traded biotechnology firms. Across a 1980-2010 time frame, a five-year distributed Almon lag model was utilized to assess the effect of annual changes in MTRs upon patenting activity, research and development (R&D) expenditures, cash and short-term investments, debt-to-asset ratios, and debt-to-equity ratios. Across the 99 biotech firms studied, results suggested that increases in MTRs were significantly associated with marked decreases in patents, R&D expenditures, and cash and other short-term investments. Additionally, large and statistically significant increases in both debt-to-asset and debt-to-equity ratios were observed with annual increases in MTRs. While this research can not necessarily discern whether capital structure changes occurred either as an *ex-ante* response to or an *ex-post* result of MTR increases, the implication of decreased patenting activity warrants continued evaluations of both internal financial decision making and external tax policy.

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INTRODUCTION

The corporate marginal tax rate (MTR) represents the present value of both current and expected future taxes based upon a firm's existing taxable income (i.e., taxes associated with an additional dollar of income currently earned).[1] Additionally, because existing tax code allows carry-forwards and carry-backs wherein negative taxable income may be used as an offset for positive taxable income in either past or future income streams, the tax implications of a current income stream remain contingent upon both past earnings and future expected earnings.[2] Overall, corporate MTRs reflect the highest rate at which a firm is taxed, therefore comprising a central tenet within quantitative financial analyses (e.g., cost of capital calculations, debt policy and corporate compensation decisions, and relative pricing between taxable and nontaxable securities).[3] Notably, corporate MTRs also parallel the federal tax code treatment of net operating losses, investment tax credits, alternative minimum tax, and tax rate expectations from management at the time that debt policy decisions are made.[3]

Considerable empirical evidence suggests that innovative and entrepreneurial activity decreases as MTRs increase.[4-11] Carroll et al. (1999, 2000) stressed that a predominant impact of taxes is placed upon the marginal return to investing, wherein an increase in MTR

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reduces the marginal return to investing and ultimately results in declined business investment.[4,5] While empirical evidence generally supports this stance, other theories purport that business investment is not substantially impacted, predominantly because effective entrepreneurs may work to effectively reduce MTRs to levels which do not impede innovative activity (e.g., by delaying decisions to incorporate).[12] In a broader context, Lee and Gordon (2005) reported that increases in corporate tax rates were associated with lower future growth rates (i.e., GDP per capita) across 70 countries from 1970-1997, with a 10% decrease in corporate tax rates being associated with higher GDP growth rates ranging from 1.0-1.8%.[13]

Beyond any potential association with R&D-intensive activities, firms with higher MTRs may additionally have greater incentives to issue debt to take advantage of interest deductibility, *ceteris paribus*.[14] Allowing interest payment deductions to occur may create a benefit for a corporation to finance external debt (e.g., in the form of a tax shield) rather than to finance internal equity. Notably, Slemrod (2000) recognized that the most empirically studied form of income shifting concerning corporate taxes involved assessments of issuing debt as a means to reduce the firm's taxable income, hence building upon the seminal Modigliani-Miller Theorem of capital structure.[16-18] According to the Modigliani-Miller Theorem, or the capital structure irrelevance principle, a firm's market value is contingent only upon the income stream generated by its assets, not by its financing mechanisms (e.g., dividends, reinvestments) or its share of debt within their financial structure.[17,18] Building upon market imperfections, however, the use of debt within a firm's capital structure has been suggested as being underutilized by corporations. While Graham (2000) initially reported that up to 33% of firms could double their debt and retain tax benefits at the top statutory rate, updated analyses by Blouin, Core, and Guay (2010) suggested that these terms are present among only 11% of companies.[2,14] Despite any potential allure, however, there is strong evidence that debt is a disfavored source of finance, particularly for R&D investment.[19]

The biotechnology sector remains one of the most research-intensive, reserving approximately 18% of sales and 38% of assets for R&D and requiring over $1.2 billion in capitalized costs per new drug approved.[20,21] The cost of capital associated with biotechnology R&D remains high, with necessary returns typically exceeding 10-15%.[22,23] Given the high costs of R&D and low marginal cost of production, the importance of patents within the biotech sector has received considerable attention in recent years particularly concerning intellectual property rights.[24] Notwithstanding, the association specifically between taxes and innovative output among biotechnology firms has received only limited empirical investigation, and overall research findings surrounding the theoretical arguments for the tax sensitivity of companies' capital structures and debt policy remains varied.[25] As such, the purpose of the current investigation was to examine the association between changes in corporate MTRs and both innovative output and capital structure among publicly-traded firms within the biotechnology sector. More specifically, a finite distributed lag approach was employed to quantify the relationship between annual changes in corporate MTRs and patenting activity, R&D expenditures, cash and short-term investments, debt:asset ratios, and debt:equity ratios. Assessments of MTRs assist in providing an understanding that extends beyond those of innovation or capital structure which involved payout policy, cost of capital and investment policy, and compensation and tax strategy. Importantly, if entrepreneurial activity remains a key contributor to economic growth as posited by Schumpeter (1942), then vital policy insight may be realized by studying the relationships between corporate taxes, capital structure, and innovative output.[26] From a broad welfare perspective, the importance of stimulating R&D rests in the assertion that its social returns also greatly exceed private returns.[27]

METHODS

This study extended the theoretical models developed by Pakes and Griliches (1984) and Grabowski and Vernon (2000) involving pharmaceutical industry R&D production functions and R&D expenditures, to include the role of changes in MTRs upon innovative activity in the biotechnology sector.[28,29] Appearing in Figure 1, the research production function developed by Pakes and Griliches (1984) involved the contributing role that R&D expenditures plays to a net accreditation of economically-valuable knowledge, which is ultimately expressed in the form of patents or indicators of expected or realized benefits from invention (e.g., profits, growth, productivity, stock market value).[28] Concerning the role of financing in drug development, Grabowski and Vernon (2000) proposed that expected returns and cash flows were major determinants of pharmaceutical R&D, also providing empirical support with R&D intensities among 11 major drug companies from 1974-1994.[29] Within their model, internal versus external financing was identified as being especially important in pharmaceutical R&D due to the large uncertainty associated with drug development, the length of time associated with new drug approvals, and asymmetric information. Therein, presented in Figure 2, an optimal level of R&D

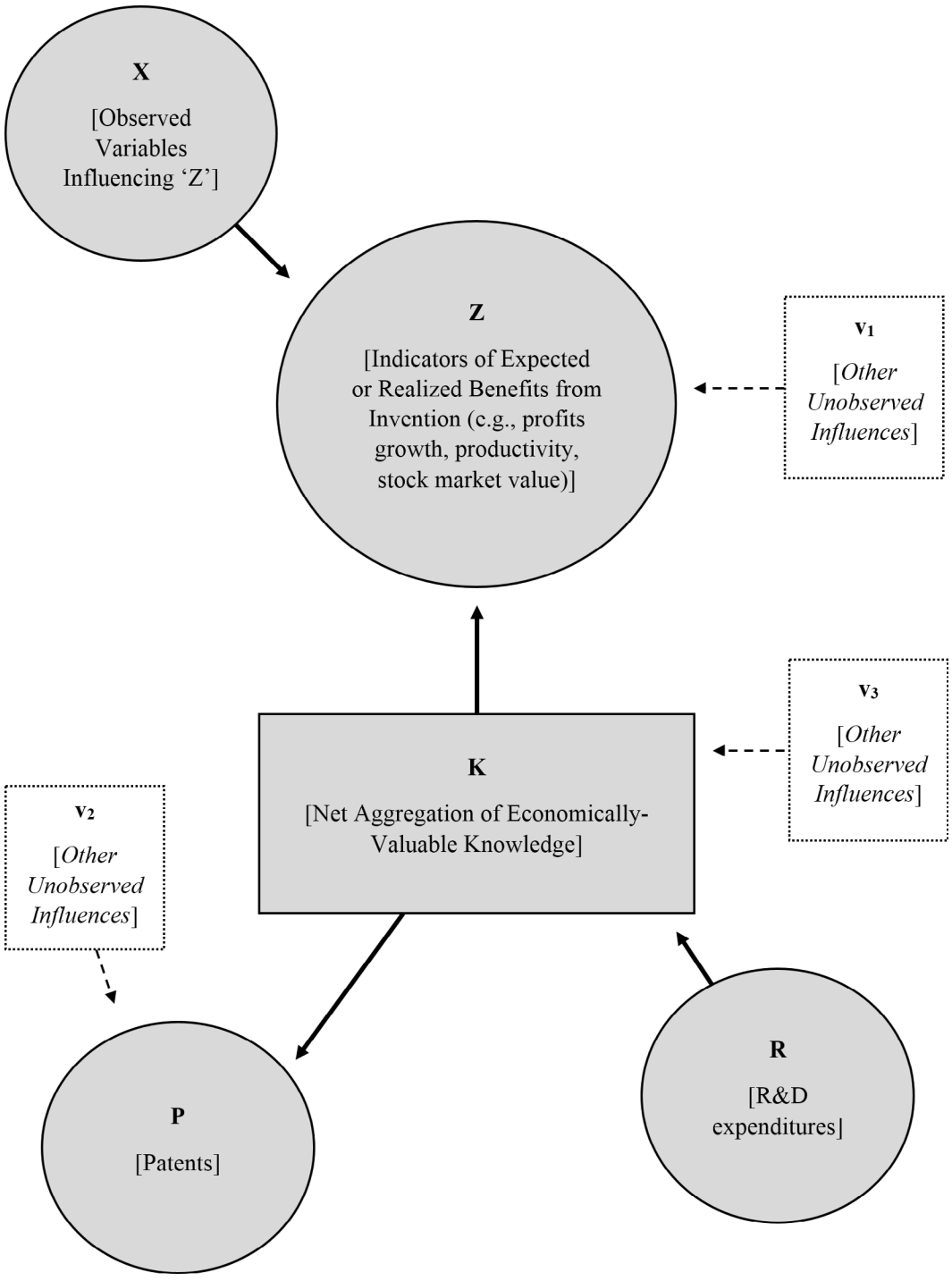

Figure 1. Simplified model of the research and development knowledge production function
R&D = research and development. Adapted from Source: Pakes A, Griliches Z. Patents and R&D at the firm level: A first look. In: Griliches Z, ed. R&D, Patents and Productivity. University of Chicago Press: Chicago; 55-72.

investment is found by obtaining the intersection of the marginal rate of return on investment (*mrr*) and its associated marginal cost of capital (*mcc*) as *mrr* = *mcc*. Summarized in Hubbard (1998) and due to numerous factors (e.g., tax advantages, agency problems, distress costs, transaction costs), the *mcc* involves a lower cost for internal financing versus higher costs to establish new equity externally, with new debt financing consisting of

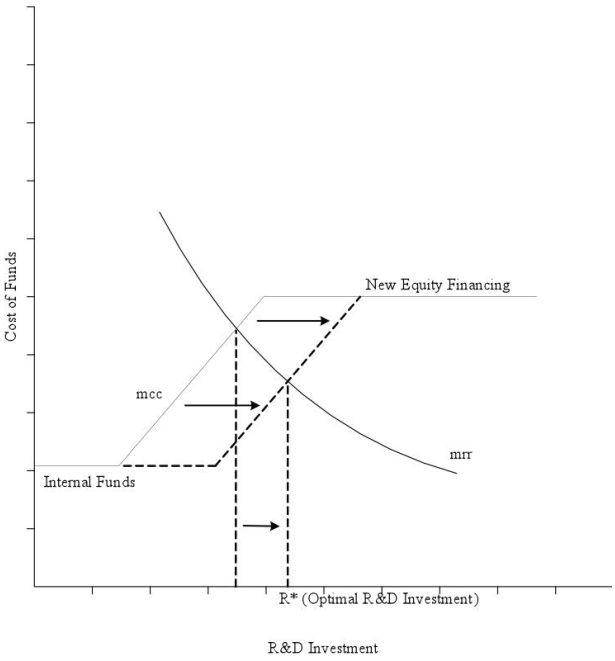

Figure 2. The effect of increased cash flow on research and development investment decisions R&D = research and development; *mcc* = marginal cost of capital; *mrr* = marginal rate of return. Adapted from Source: Grabowski HG, Vernon J. (2000) The determinants of research and development expenditures. Journal of Evolutionary Economics 10:201-215.

a rising segment between internal funds and new external equity.[6] Overall, an increase in internal funds would result in a positive effect on the optimal level of R&D investment. Importantly, Grabowski and Vernon (2000) made special note that raising R&D capital among small biotech firms (with little or no cash flow) often results in venture capital expectations for new projects to generate 25-35% annual rates of return, also fueling many of the corporate partnerships between large firms (e.g., acquisitions, strategic alliances).[29]

Given the aforementioned, an observational cross-sectional time-series study design was utilized in the current work to assess the relationship between changes in corporate marginal tax rates for biotechnology firms upon measures of innovative activity and financial valuation, including outcomes of: 1) patenting activity; 2) R&D expenditures; 3) cash and short-term investments (i.e., highly liquid assets consisting of cash and equivalents plus short-term investments in marketable securities); 4) debt:asset ratios (i.e., leverage); and 5) debt:equity ratios. The time period for this study ranged from January 1, 1980 to December 31, 2010, spanning some 31 years overall, and including all publicly-traded corporations listed on the major U.S. stock market exchanges (i.e., NYSE, AMEX, and NASDAQ) and with a primary four-digit Standard Industrial Classification (SIC) of 2836, defined as Biological Products, Except Diagnostic Substances.[30] Data were obtained from numerous sources, including: 1) U.S. Patent and Trademark Office (i.e., Patents for Classes 424 and 514: Drug, Bio-Affecting and Body Treating Compositions); 2) Standard & Poor's Compustat (i.e., R&D expenditures, cash and short-term equivalents, short- and long-term debt, total assets, total equity); 3) The University of Chicago's Center of Research in Security Prices (CRSP) database (i.e., monthly security-level stock market prices); and 4) Standard & Poor's Capital IQ (marginal tax rate calculations).

MTRs used in this study were based upon the approach developed by Blouin, Core, and Guay (2010), employing non-parametric methods to provide improved estimates that forecast future taxable incomes more closely to future income stream.[2] Building upon both Shevlin (1990) and Graham (1996a,1996b), this non-parametric method employed approaches from Barber and Lyon (1996) that improved upon error and bias associated with income estimation via random walk models, while recognizing that MTR is fundamentally dependent upon both expectations of future taxable income and an accurate modeling of tax codes.[1,3,31,32] As empirical and theoretical arguments also suggest that stock market returns may follow random walks, mean reversion is known to occur with income, principally due to various accounting and economic factors (e.g., transitory components in income, entry and exit).[33,34] Additionally, prior research also suggests that mean-reversion is greatest during negative income years and among extreme income amounts.[35]

A distributed lag model analyzed each of the study's outcome measures based upon absolute changes in MTRs via the Almon approach (i.e., a structured and finite method) across a five-year time horizon, specified in the following general form:

$$y_j = \alpha + \beta(L)x_j + \mu_j = \alpha + \sum_{s=-1}^{-5} \beta_s \cdot x_{j,s} + \quad _j$$

where: y_j = outcome of interest for firm j; α = model intercept; β = lag weights comprising the lag operator, L; x_j = marginal tax rate for firm j; μj = stationary error term for firm j.; and s = lag time period (i.e., $year_{t-1}$ to $year_{t-5}$).[36] Therein, at least 3 years of consecutive annual financial data were required for inclusion into the study's analytic framework. Overall, these cross-sectional time-series (i.e., panel) data were analyzed to control for firm-specific characteristics via a generalized estimating equations (GEE) with a: 1) negative binomial distribution with log link for patenting activity and debt:equity ratios; 2) gamma distribution with log link for R&D

expenditures and cash and short-term equivalents; and 3) Poisson distribution with log link for debt:asset ratios (i.e., leverage).[37] All regressions utilized maximum likelihood estimation and employed an independent correlation structure with robust correlation matrix calculation to allow for correct statistical inference even under potential conditions of misspecification; alternate correlation structures, distributional families, and link designations were selected based upon assessments of residuals and deviance (i.e., quasilikelihood information criteria, QIC).[37-39] Results were reported as various relative risk measures (e.g., exponentiated beta coefficients/*exp(b)*, incidence rate ratios/IRRs), and an *a priori* alpha level of 0.05 was used for statistical significance.[37]

RESULTS

Appearing in Table 1, some 99 biotech firms met the study's inclusion criteria, representing 1,290 year-level observations. The average corporate MTR after interest deductions across the study's time horizon was $MTR_{Biotech,231980\text{-}2010}$ = 11.48±10.61% ($MTR_{1980\text{-}1989}$ = 22.14 ± 14.62%, $MTR_{1990\text{-}1999}$ = 11.53 ± 9.57%, and $MTR_{2000\text{-}2009}$ = 9.99±9.40%). Comparatively, across all sectors, the overall $MTR_{All\ Sectors,\ 1980\text{-}2010}$ = 24.30 ± 13.73% ($MTR_{1980\text{-}1989}$ = 30.76 ± 14.67%, $MTR_{1990\text{-}1999}$ = 22.71 ± 11.81%, and $MTR_{2000\text{-}2009}$ = 20.41 ± 12.65%). A total of 2,166 patents were represented in the sample, averaging 1.68±3.58 per firm per year. Overall, $108 billion in total was expensed as R&D ($86.53±318.59 million per firm per year), and the sum of each biotech company's market capitalization was $187 billion ($1.89 ± 7.74 billion per firm). Full descriptive statistics are presented in Table 2, and Figure 3 graphically depicts the annual changes in MTR for the study's biotech sample from 1980-2010 relative to all other sectors combined.

Results of the distributed lag analysis of MTRs are presented in Table 3. Over varying years, increases in marginal tax rates were significantly associated with large decreases in patenting activity, R&D financing, and cash and short-term investments. More specifically, patents decreased at year two following a change in MTR of a full percentage point by −88.9% (IRR_{t-2} = 0.111, p<0.05). At the fifth year following a MTR increase, a −81.1% (IRR_{t-5} = 0.189, p<0.05) decrease in patents was noted. R&D expenditures declined throughout the entire lag period, significant exceeding −90% for each lagged year (p<0.05). Similarly, cash and short-term investments significantly decreased over −96% or more across each of the five years following a similar increase in MTR (p<0.001).

These aforementioned decreases in patenting, R&D, and cash and short-term investments were paralleled with large and significant (p<0.05) increases in debt-to-asset ratios and debt-to-equity ratios. In the year following increases in marginal tax rates, leverage increased over 25-fold (IRR = 26.985, p<0.01), while debt-to-equity increased by a factor of almost 150-fold (IRR = 146.922, p<0.001). Significant increases across the remaining five-year time horizon were additionally noted for leverage at year two (IRR_{t-2} = 14.058, p<0.01) and year four (IRR_{t-4} = 19.879, p<0.01).

DISCUSSION

This study investigated time-dependent associations between changes in marginal tax rates (MTRs) and measures of technological change within the biotech sector, suggesting that increases in MTRs were inversely related to measures of innovative activity. The order of magnitude of these changes was pronounced. When the annual change in MTR increased by one percentage point, reductions of −81.1%, −99.3%, and −98.6% at year five were noted for patents, R&D expenditures, and cash and short-term equivalents, respectively. Conversely, increases in MTRs were also associated with large increases in debt relative to assets and equity, reaching an almost 150-fold increase for debt:assets (i.e., leverage) and 25-fold increase for debt:equity in the immediate year following MTR increases. Temporally, these findings suggest that there may be potential trade-offs that occur in the biotech sector, wherein increases in MTRs might either be voluntarily acquiring debt (*ex-ante*) or incurring debt as a result (*ex-post*), ultimately at an expense of decreased innovative activity. While prior work has sought to quantify the relationship between MTRs and cash flow, debt, or R&D expenditures, the current study expands this empirical framework to include patents as a key proxy measure for innovative activity in the sector. As an important precursor to this, Alti (2003) validated the key associations between lagged cash flows and a firm's future investment opportunities (i.e., R&D) by finding that cash flow provides distinct information relating to project quality that is not captured in other financial measures.[40]

Overall, findings of the present investigation provide insight into the relationship between MTRs and both the capital structure and innovative output of biotechnology firms. The observation that large and significant reductions in patenting activity are associated with increases in MTRs may initially appear to run contradictory to economic principles. To illustrate, under most circumstances an increase in MTR would appear to signal that the firm was improving in its financial position. Findings from this study, among others, provide support that the fiscal impact of these increased rate changes

Table 1. List of companies analyzed under primary SIC 2836, 1980-2010

Abgenix Inc.	Curis Inc.	Maxim Pharmaceuticals Inc.
Advanced Tissue Sciences	CV Therapeutics Inc.	Maxygen Inc.
Alexion Pharmaceuticals Inc.	Cypress Bioscience Inc.	Medarex Inc.
Amgen Inc.	Cytrx Corp.	Medimmune Inc.
Anergen Inc.	Dendreon Corp.	Nabi Biopharmaceuticals
Antex Biologics Inc.	Diacrin Inc.	Neopharm Inc.
Aphton Corp.	Diadexus Inc.	Neurocrine Biosciences Inc.
Ardea Biosciences Inc.	Dyax Corp.	Northfield Laboratories Inc.
Ariad Pharmaceuticals Inc.	Dynavax Technologies Corp.	Novavax Inc.
Arqule Inc.	Encysive Pharmaceuticals Inc.	NPS Pharmaceuticals Inc.
Array Biopharma Inc.	Enzon Pharmaceuticals Inc.	Organogenesis Inc.
Astex Pharmaceuticals Inc.	Exelixis Inc.	Progenics Pharmaceutical Inc.
Autoimmune Inc.	Genaera Corp.	Repligen Corp.
Avigen Inc.	Genetics Institute Inc.	Ribi Immunochem Research Inc.
Baxter International Inc.	Genta Inc.	Sangamo Biosciences Inc.
Biocryst Pharmaceuticals Inc.	Genzyme Corp.	Sangstat Medical Corp.
Biogen Idec Inc.	Geron Corp.	Seattle Genetics Inc.
Biogen Inc.	Gilead Sciences Inc.	Siga Technologies Inc.
Biomarin Pharmaceutical Inc.	Helix Biomedix Inc.	Sirna Therapeutics Inc.
Biomatrix Inc.	Hemispherx Biopharma Inc.	Somatogen Inc.
Biopure Corp.	Idenix Pharmaceuticals Inc.	Spectrum Pharmaceuticals Inc.
Biotime Inc.	Idera Pharmaceuticals Inc.	Stem Cells Inc.
Cel-Sci Corp.	Imclone Systems Inc.	Symbollon Pharma Inc.
Cell Genesys Inc.	Immtech Pharmaceuticals Inc.	Synaptic Pharmaceutical Corp.
Cell Therapeutics Inc.	Immunex Corp.	Syntro Corp.
Centocor Inc.	Imreg Inc.	Telik Inc.
Cerus Corp.	Insmed Inc.	Transkaryotic Therapies Inc.
Cetus Corp.	Intermune Inc.	Trimeris Inc.
Connetics Corp.	La Jolla Pharmaceutical Co.	Vical Inc.
Corixa Corp.	Life Sciences Research Inc.	Vion Pharmaceuticals Inc.
Corvas International Inc.	Life Technologies Inc.	Xechem International Inc.
Creative Biomolecules Inc.	Lipid Sciences Inc.	Xenoport Inc.
Curagen Corp.	Liposome Co. Inc.	Zymogenetics Inc.

Standard Industrial Code (SIC) 2836 defined as Biological Products, Except Diagnostic Substances

Table 2. Descriptive statistics by decade and overall, primary SIC 2836, 1980-2010

Variable	1980-1989	1990-1999	2000-2009	Overall 1980-2010
Marginal Tax Rate, % (average ± standard deviation)	22.14 ± 14.62	11.53 ± 9.57	9.99 ± 9.40	11.48 ± 10.61
Annual Change in Marginal Tax Rate (absolute Δ), % (average ± standard deviation)	+1.26 ± 7.02	−1.81 ± 4.20	+0.55 ± 5.21	+0.30 ± 5.15
Patents, count (average ± standard deviation)	0.74 ± 1.47	1.36 ± 2.68	1.90 ± 3.66	1.68 ± 3.57
R&D, $ mil (average ± standard deviation)	24.91 ± 49.85	37.67 ± 94.65	119.25 ± 399.10	86.53 ± 318.59
Cash and Short-Term Investments, $ mil (average ± standard deviation)	45.25 ± 62.99	71.18 ± 164.37	251.44 ± 867.78	184.22 ± 813.31
Total Current Assets, $ mil (average ± standard deviation)	223.63 ± 639.41	170.85 ± 604.86	422.47 ± 1520.50	338.21 ± 1374.60
Total Assets, $ mil (average ± standard deviation)	522.20 ± 1685.02	338.37 ± 1410.93	978.24 ± 3950.58	753.19 ± 3340.67
Year-End Security Price Close, $ (average ± standard deviation)	13.07 ± 12.19	15.87 ± 20.58	13.33 ± 17.19	14.22 ± 18.29
Market Capitalization, $ mil (average ± standard deviation)	481.74 ± 1139.52	1032.56 ± 4029.45	2556.82 ± 9685.01	1887.39 ± 7739.14
Debt, $ mil (average ± standard deviation)	147.59 ± 520.40	78.53 ± 416.84	208.34 ± 947.03	167.74 ± 847.97
Debt:Asset Ratio (Leverage) (average ± standard deviation)	0.17 ± 0.18	0.11 ± 0.21	0.20 ± 0.40	0.17 ± 0.33
Debt:Equity Ratio (average ± standard deviation)	0.18 ± 0.28	0.07 ± 0.26	0.17 ± 0.79	0.13 ± 0.61
Number of Observations	103	453	693	1290
Number of Companies	21	80	87	99

Standard Industrial Code (SIC) 2836 defined as Biological Products, Except Diagnostic Substances

appears as an increase in debt, whether voluntarily as a tax shield or unintended as a consequence of decreased cash flow.[4-11] In the biotech sector, an inverse relationship between MTR increases and R&D, cash and short-term equivalents, and patents suggest more complex dynamics concerning capital structure and the financing of innovative activity. While firms may decide to issue debt rather than equity to potentially benefit from tax shields in the form of interest deductions, debt may ultimately provide a poor substitute to finance R&D (i.e., subsequently reducing patenting activity).[19] Providing an alternative interpretation, existing MTR policy might not be optimized for innovative activity within the biotech sector. The current study, in these regards, sought to provide empirical evidence to better understand the complexities associated with tax policy and any potential association with corporate R&D and innovative output.

Both theoretically and empirically, the MTR plays an important role in corporate financial decision making, including determinations of cost of capital, debt allocation, compensation, and relative pricing between taxable and nontaxable securities.[3] Hines (2001) stated that taxation of corporate income inherently encourages entrepreneurs and managers to structure and conduct

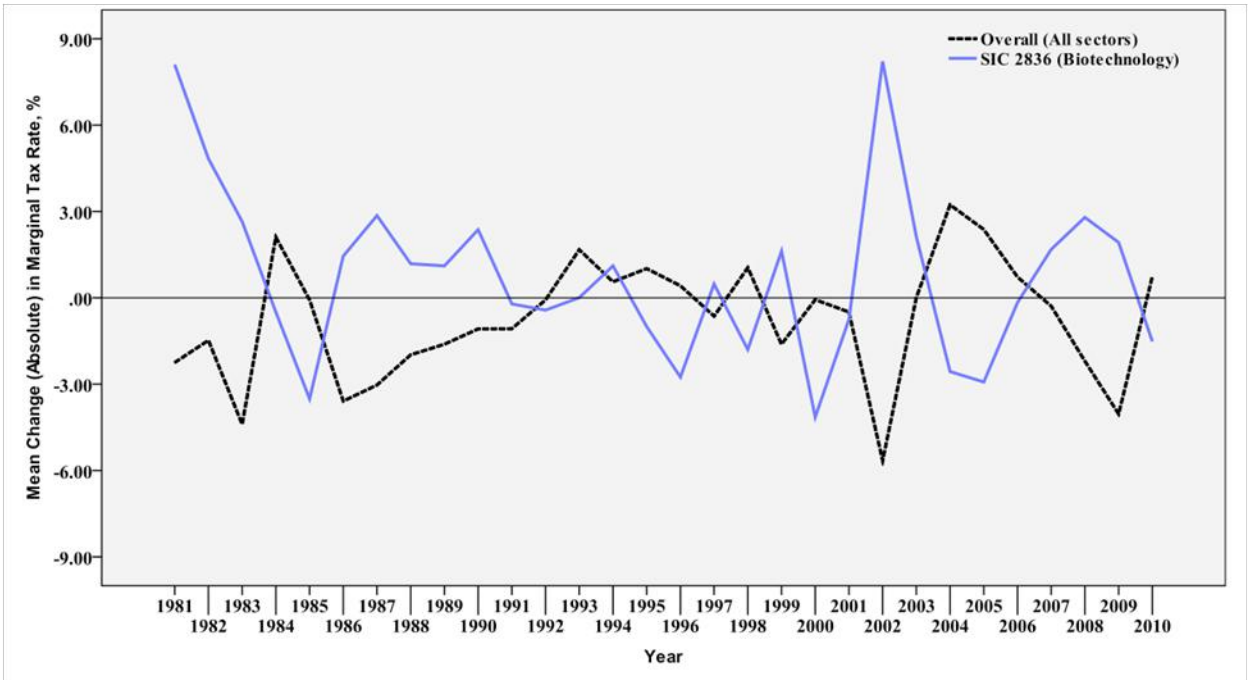

Figure 3. annual change in marginal tax rate by year, primary SIC 2836 and across all sectors, 1980-2010

business operations in ways designed to avoid taxation.[41] A major tax consideration in corporate finance is that interest payments to bondholders are deductible from taxable income, while dividend payments to corporate shareholders are not deductible. Therefore, corporations may generally have tax incentives to issue more debt than typical, and debt:equity ratios increase as a result. Similar findings were reported in Bartholdy and Mateus (2011), in that the introduction of deductibility of interest payments entails benefits to debt financing (versus equity financing) in the form of a tax shield and therefore the capital structure becomes important for the value of the firm.[15] This may lead to investments in assets more readily financed by debt rather than investments financed by stock. According to Brown et al. (2009), firms in the U.S. finance R&D often with internal or external equity such as cash flow or stock.[42]

While a general recognition exists that external debt is often a less desirable substitute than internal finance, particularly among smaller firms, this is an important consideration among R&D-intensive industries for several reasons.[43] Especially within the pharmaceutical and biotechnology sectors, returns associated with high-technology R&D programs are often highly-skewed and characterized with marked uncertainty and low probabilities of success.[44,45] Early-stage R&D projects typically have variable expected future revenue patterns that provide insufficient capital to cover interest payments associated with external debt instruments.[43,45] Supported empirically particularly during early-stage drug development, financial constraints may exist particularly among smaller biotech companies with limited ability to generate sufficient profit from existing sales to finance R&D internally.[46] Additionally, innovative activity predominantly generates assets that are intangible in nature which remain largely insufficient as loan collateral to secure borrowing, despite the availability of appropriate valuation methods.[45,47,48] Although not investigated in the current work, external funds raised through venture capital generally reduces the firms' financial constraints and increase R&D, often leading to joint ventures or other strategic alliances.[46]

The determinants of pharmaceutical R&D spending have been investigated particularly by Grabowski and Vernon (1981), Grabowski and Vernon (2000), and Vernon (2005).[29,49,50] By similarly investigating the R&D intensity as measured by the ratio of R&D expenses to sales, each consistently finding that companies with low levels of internal cash indeed invested less in R&D, *ceteris paribus*. In general, a firm's financial commitment to R&D would intuitively be based upon both the expected return that may be generated from that investment and the upon presence of fiscal constraints (e.g., cash flow).[46] Alti (2003) reported that, even if lagged by only a single year, cash flow was strongly related to a firm's future investment opportunities and R&D spending.[40]

Though the current study measured overall cash and short-term equivalents without explicitly assessing internal versus external financing, the Modigliani-Miller theorem purports that various corporate

Table 3. Relative risk measures of lagged change in marginal tax rate, primary SIC 2836, 1980-2010

Independent (Predictor) Variables[D]	Dependent (Outcome) Variables				
	Patents[A] *IRR (95th CI)*	**R&D Expenditures[B]** *exp(b) (95th CI)*	**Cash and Short-Term Investments[B]** *exp(b) (95th CI)*	**Debt:Asset Ratio[C] (Leverage)** *IRR (95th CI)*	**Debt:Equity Ratio[A]** *IRR (95th CI)*
Lag ΔMarginal Tax$_{t-1}$	1.075 (0.090-12.833)	0.045*** (0.010-0.205)	0.016*** (0.003-0.101)	26.985** (2.626-277.319)	146.922** (6.438-3353.056)
Lag ΔMarginal Tax$_{t-2}$	0.111* (0.013-0.962)	0.025*** (0.003-0.181)	0.034*** (0.007-0.166)	14.058** (2.016-98.054)	3.576 (0.099-128.828)
Lag ΔMarginal Tax$_{t-3}$	0.533 (0.045-6.310)	0.081* (0.011-0.608)	0.019*** (0.003-0.130)	9.274 (0.681-126.370)	2.254 (0.044-114.501)
Lag ΔMarginal Tax$_{t-4}$	0.382 (0.052-2.794)	0.020*** (0.003-0.137)	0.024*** (0.003-0.164)	19.879** (2.068-191.085)	0.742 (0.001-565.389)
Lag ΔMarginal Tax$_{t-5}$	0.189* (0.037-0.976)	0.007*** (0.001-0.088)	0.014*** (0.001-0.135)	3.998 (0.343-46.562)	46.050 (0.784-2705.590)
Constant	2.203*** (1.437-3.378)	138.028*** (66.066-288.375)	287.329*** (122.771-672.457)	0.201*** (0.156-0.259)	0.158*** (0.104-0.241)
Number of Observations	697	671	696	696	693
Number of Companies	99	96	98	98	96

** Statistically significant at p<0.05; ** Statistically significant at p<0.01; *** Statistically significant at p<0.001*
[A]Generalized Estimating Equation (GEE) Negative Binomial regression with log link, independent correlation structure, robust correlation matrix
[B]Generalized Estimating Equation (GEE) Gamma regression with log link, independent correlation structure, robust correlation matrix
[C]Generalized Estimating Equation (GEE) Poisson regression with log link, independent correlation structure, robust correlation matrix
[D]Independent variables = Five-year lagged marginal tax rate with interest, absolute change [Blouin, Core, and Guay (2010)]
IRR = Incidence Rate Ratio; exp(b) = exponentiated beta coefficient estimate; CI = confidence interval
Standard Industrial Code (SIC) 2836 defined as 'Biological Products, Except Diagnostic Substances'

financing mechanisms should be perfect substitutes at the margin.[17,18] In theoretical terms, a firm's valuation or levels of investment should not necessarily be related to the method through which it was financed, be it by issuing stock in the securities exchanges or by leveraging through debt. Due in part to capital market imperfections, growing empirical work has found that preferences in financing do exist with firms financing new projects internally, only seeking external financing after no other means of internal support exist.[51,52] As such, private internal equity or retained earnings most often appear to be the main source of funding for most small-to-medium sized enterprises under 500 employees.[43,53,54] In allocating R&D funds, pharmaceutical or biotechnology firms may typically utilize internally-retained earnings based upon sales of existing products and rely less upon more costly external forms of financing, the findings of the current work remain important – increased MTRs were associated with marked increases in debt measures (debt:assets and debt:equity) and decreases in R&D and cash and short-term equivalents beginning within the first year following MTR increases, also accompanied by decreases in patenting activity. As R&D activities in the biotech sector are typically characterized by high costs and low marginal costs of production, a high degree of importance surrounds patent protection to enable for innovators to recoup investment.[46] Even in the presence of patent protection, however, underinvestment may still occur if insufficient internal funds are not present to finance all economically-viable investments, or if the cost of external funds exceeds those internally.

Despite incorporating marginal tax information with financial and patent data, several potential limitations should be considered in interpreting results of

the current investigation. Foremost, the inclusion criteria was limited to publicly-listed biotech companies within SIC 2836 and, thus, cannot generalize to private biotech firms or other companies that may be engaged in R&D-intensive biotech endeavors. Assessing the impact of tax policy on investment based solely upon the link between tax parameters, capital structure, and innovative activity is also likely to be incomplete. Both Cummings et al. (1994) and Hassett and Hubbard (1997) noted that both measurement error and simultaneity make investment assessments involving technology, cost of capital, and entrepreneurial ability are difficult to estimate.[55,56] Additionally, the current work did not explicitly include a "kink" analysis to measure an optimal debt level similar to Graham (2000) or Blouin, Core, and Guay (2010).[2,14] Finally, given the nature of the available data and analytic framework employed, causation cannot be determined whether changes in capital structure was undertaken in response to, or as a result of, MTR increases.

CONCLUSION

This investigation of corporate marginal tax rates within publicly-traded biotechnology firms from 1980-2010 found that annual increases in tax rates were associated with: 1) large decreases in patents, R&D expenditures, and cash and other short-term investments; and 2) large increases in debt-to-asset and debt-to-equity ratios. Given these findings' implications on overall technology policy, continued work is required to optimize tax policy and capital structures within the biotech sector to stimulate innovation in the most impactful and economically-efficient manner possible.

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Article

Industrial application of biological self-healing concrete: Challenges and economical feasibility

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ABSTRACT

Self-healing concrete has been scrutinized by several researchers and some industrial concrete producers in relation to the remediation of the occurrence of micro-cracks. Such cracks are a quite well known problem that can lead to corrosion of the steel reinforcement and thus to the possible failure of the entire concrete structure. The need to repair these cracks as soon as possible leads to maintenance costs which can be of the order of €130 (direct costs) per m^3 of concrete. Recent scientific studies indicate that a Microbial Induced Carbonate Precipitation (MICP), using microbial spores as active agent, can be an alternative for the actual repair methods. However, the production of bacterial spores is yet imposing considerable costs. According to some concrete producers they would be willing to pay about €15 to €20 per m^3 of concrete for a bio-based self-healing product. However, the actual cost of spores production and encapsulation represent a total cost which is orders of magnitude higher. This article analyzes the costs for the biological self-healing in concrete and evaluates the industrial challenges it faces. There is an urgent need to develop the production of a bio-additive at much lower costs to make the biological self-healing industrial applicable. Axenic production and a possible non-axenic process to obtain ureolytic spores were analyzed and the costs calculations are presented in this paper.

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INTRODUCTION

Concrete is a composite construction material made primarily with aggregates, cement and water. It is the most widely used construction material in the world with a usage, worldwide, twice as much as steel, wood, plastics and aluminum combined.[1]

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Due to its wide usage, concrete represents the basis of a large commercial industry. In the United States alone, concrete industry represents a €23.3 billion of sales per year, considering only the value of the ready-mixed concrete sold each year.[2] Despite of its high compressive strength, the tensile strength is low, making it necessary for most applications to add a material (often steel) to allow the structure to maintain its correct form and performance. Reinforced concrete is obtained by adding steel reinforcement bars, steel fibers or glass or plastic fibers to carry the tensile loads. The most widely used reinforcement are the steel bars, forming a net inside the concrete structure.

Due to the intrinsic heterogeneity in concrete, cracks are almost unavoidable. Cracking in concrete structures is a well-known and studied phenomenon. Cracks can have many causes such as drying shrinkage, thermal stress, weathering, externally applied loads or corrosion of reinforcement.[3] When a crack opens, aggressive compounds such as chloride ions (Cl^-) or carbon dioxide (CO_2) can penetrate the concrete cover, getting to the reinforcement and causing corrosion. The rusting process leads, with time, to the loss of tensile strength, which can cause irreparable damages in the structure. Due to this, it is quite important to fill these cracks avoiding the increase of permeability thus protecting the reinforcement. Moreover, since, on the one hand, cracks in concrete structures can lead to the premature failure of the structure and on the other hand, sustainability is one of the main issues in the modern world,[4] the repair of such cracks is also becoming important from an environmental point of view.

Until now, applying some compounds either to fill the cracks, such as epoxy resins, or to prevent the formation of these cracks, such as plastic polymers applied on the surface of the concrete (repairing and curing compounds, respectively), are the common ways to improve and/or extend the life of concrete structures. However, for both processes, human interventions are required leading to an added cost in labor work. The cost for crack injection in tunnel elements can be estimated to be of the order of €130 per m^3 of concrete (COWI, personal communication). Furthermore, sometimes it is not possible to get to the damaged areas for repairing because of their location and/or environmental conditions. Examples of difficult accessible structures are underground constructions, water tunnels and radioactive waste storage tanks among others.

Due to these facts, self-healing of cracked concrete has been examined for some years. In fact, concrete has always some self-healing ability. The hydration of unhydrated cement particles causes the filling of small cracks. However, this autogenous healing is limited to small cracks (<200 μm) and requires the presence of water.[5] The self-healing concept is quite interesting. It is comparable to the phenomenon occurring when a plant or an animal has a small cut. The latter can be self-healed by the natural biologic repair mechanisms that are pre-existent in these organisms. Hence, the intriguing question for this field of study is "Can we achieve a similar process in concrete?" Several studies have been pointing to an affirmative answer. However, the costs are yet too high to be considered in industrial applications.

It is not our purpose to provide full information about the biological self-healing process in concrete due to its wide spectrum. This paper describes the actual challenges to bring an efficient biological self-healing product to the concrete market with the guaranty that this product can attain legislative requirements and also be cost-effective.

Biological self-healing concrete

The phenomenon of self-healing in general is already under study since 1970[6] starting with the investigation of this phenomenon in cracks of polymers. However, only after 2001 with the article of White et al.,[7] the topic of self-healing attracted the attention of several investigators. Three main definitions of self-healing and self-repairing have already been provided.[4,8-9] However, the central issue is that for concrete to be considered as self-healing, the concrete should not require any treatment to improve the action of the self-healing agents.

Several authors have dealt with microbial induced carbonate precipitation as being a possible approach for the treatment (self-healing/repairing) of concrete structures.[5,10-16] The microbial hydrolysis of urea ($CO(NH_2)_2$) can be used as a way to place a restoring and protective layer of calcium carbonate ($CaCO_3$) on degraded limestone.[17] The hydrolysis of urea is catalyzed by an urease enzyme and in the process carbonate (CO_3^{2-}) and ammonium (NH_4^+) ions are produced (equations 1 to 4). For each mole of urea two moles of ammonium ions and one mole of carbonate ions are formed (global reaction of hydrolysis of the urea – equation 5).

$$CO(NH_2)_2 + H_2O \rightarrow NH_2COOH + NH_3 \quad (1)$$

$$NH_2COOH + H_2O \rightarrow NH_3 + H_2CO_3 \quad (2)$$

$$2NH_3 + 2H_2O \rightarrow 2NH_4^+ + 2OH^- \quad (3)$$

$$2OH^- + H_2CO_3 \rightarrow CO_3^{2-} + 2H_2O \quad (4)$$

$$CO(NH_2)_2 + 2H_2O \rightarrow 2NH_4^+ + CO_3^{2-} \quad (5)$$

The calcium carbonate precipitation process becomes complete when calcium ions are present and the chemical reaction between carbonate ions and calcium ions results in the deposition of a white precipitate (equation 6).

$$CO_3^{2-} + Ca^{2+w} \rightarrow CaCO_3 \quad (6)$$

It was also described that for a proper deposition of calcium carbonate it is necessary to have what is called sites of crystal nucleation.[18] Due to the negative charge on the bacterial cell wall, calcium ions can be bound to it. This fact, allied to the release of carbonate ions from

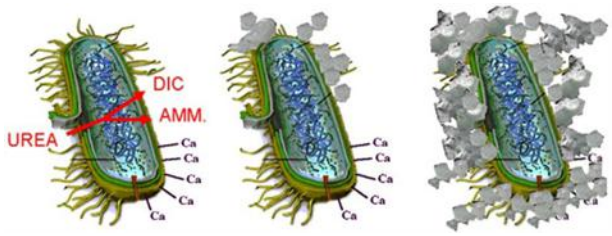

Figure 1: Schematic overview of the ureolytic carbonate precipitation occurring at the microbial cell wall. DIC: Dissolved Inorganic Carbon; AMM: Ammonia[10]

the hydrolysis of the urea, results in the formation of calcium carbonate crystals on the cell wall (Figure 1). Biodeposition of calcium carbonate using bacterial strains can thus be taken as a process to provide a larger and faster calcium carbonate precipitation when compared with the natural precipitation of this compound.

Several micro-organisms have the capacity to rapidly hydrolyze urea with rates of 16,5 grams of urea consumed per gram cell dry weight per hour.[14] Despite the good ureolytic activity of several microorganisms, it was found that the ones closely related to *Bacillus sphaericus* show a greater ability to hydrolyze urea leading to precipitation of a larger amount of calcium carbonate.[19-20] Two of the best performers regarding the ureolytic activity and precipitation of calcium carbonate are *Bacillus sphaericus* LMG22557 and *Sporosarcina pasteurii* DSM33 (previous called *Bacillus pasteurii* DSM33).[10,21] They can produce up to 0,4 grams of $CaCO_3$ per gram cell dry weight per hour.[22]

However, to bring such self-healing agent to the market, some practical aspects should be taken in consideration. The use of pure bacterial cultures with high specific ureolytic activities has considerable importance when related to fundamental research but, generally, these axenic pure cultures, represent a high cost for industrial application. For this specific case, despite of the high ureolytic activity and good calcium carbonate precipitation, production costs are of a very high importance. Thus, there is an urgent need to develop the production of a bio-additive at much lower costs. A possible approach would be the production of a mixed and non-axenic bacterial culture that could perform as well, or even better, than the pure strains regarding urea hydrolysis and calcium carbonate precipitation.

ECONOMIC EVALUATION OF SELF-HEALING BACTERIAL CONCRETE

Bacillus sphaericus axenic production

One of the major problems to apply the bacterial induced calcium carbonate precipitation to achieve self-healing in concrete is the total cost of the product used to incorporate in the concrete. Since concrete itself is relatively inexpensive, costing around €60 to €75 per m^3 of applied concrete at the Belgian market, any product that is added to the concrete with a price above €15 to €20 per m^3 of applied concrete is considered too expensive to be taken in consideration in the normal market (Coeck NV, Belgium, personal communication). Moreover, at industrial scale, besides the price, it is necessary to look also for the warranty provided for such product. According to the European Standard EN206-1:2000,[23] any concrete structure well applied, should fulfill a service life of, at least, 50 years. However, the warranty period in which the contractor is responsible for defects in the concrete structure, is normally 10 years and cracks are not included. Nowadays correct properties of the concrete structure are achieved by means of maintenance using some repairing agents (Coeck NV, Belgium, personal communication). If a bio-based product could give the warranty of a longer life for the concrete, the benefits will overcome the costs and new market can be established. The latter will be enhanced if the bio-based approach is also environmental friendly, thus winning support in the eco-tuned market.

Actually, the bio-based additive for concrete, consisting of encapsulated spores to mix in the concrete before the casting process, results in prices of €5760 per m^3 of applied concrete, making this approach unlikely to be applied (see Box 1). This price is mainly due to the need of aseptic conditions to produce the microbial spores, due to the use of expensive growth media and to the necessary labor. Moreover, the encapsulation process of microbial spores is expensive. Depending on the capsules used, but also on the yield of the encapsulation process and even on the percentage of capsules needed, this step to obtain encapsulated spores can cost between €30 and €50 per kg of spores, contributing significantly to the total price of the final product.

For some applications when there is urgency for the healing/repairing of the structure when a crack appears, the cost of such a product could be acceptable. For example, in an underground museum or library, the quick healing/repairing of cracks is crucial to the maintenance of the right conditions to preserve the highly valuable objects inside. In such instances, the price of such a product is of secondary importance since it provides guaranties that the cracks will be repaired in a matter of days to

Box 1: Estimated total costs to produce a microbial based additive capable to bring about self-healing of micro-cracks in concrete under optimal (submerged) conditions. Estimates based on in house price calculations

1. Costs to produce 1 kg of the effective *Bacillus sphaericus* spores:
   To calculate the cost to produce 1 kg of *Bacillus sphaericus* spores one should take in consideration:

   - MBS sporulation medium used for spores culture[22]
   - Required labor work to assembly and maintain the axenic process
   - Sterilization and energy requirements
   - Production yield of each batch (grams of cell dry weight produced per L)

   Considering the following, one can calculate:

   - Production scale of $1m^3$
   - A labor work cost at 50 €/h
   - 3 hours of required labor work
   - An industrial standard steam sterilization process
   - The electricity cost at 0,09 €/kWh
   - A maximum yield of 3,5 kg CDW/m^3

MBS medium cost	1370	€/m^3
Labor work cost	150	€/m^3
Sterilization cost	5	€/m^3
Total cost	435	€/kg

2. Costs to produce 1 kg of self-healing agent:
   To calculate the cost to produce 1 kg of self-healing agent one should take into consideration:

   - The encapsulation process
   - The addition of the required nutrients
   - The required amount of self-healing agent per m^3 of concrete

   Considering the following, one can calculate::

   - An encapsulation cost of 40 €/kg
   - The capsules do not increase the total weight of the final product
   - The addition of urea (20 g/kg) and $CaCl_2$ (35 g/kg)
   - The addition of 0,5% (w/w) of self-healing agent
   - An average concrete density of 2400 kg/m^3

Encapsulated spores	475	€/kg
Self-healing product (encapsulated spores + nutrients)	480	€/kg
Quantity of self-healing agent	12	kg/m^3
Total cost	5760	€/m^3

3. An important value is the cost per activity unit. Considering the best result of 16,5 grams of urea consumed per gram cell dry weight per hour[14] one can calculate the total cost of spores that can be expressed as about 350 €/g urea hydrolyzed/g CDW.h

crete from the outside will be the treatment of choice. The use of epoxy resins in the case of smaller cracks times less expensive when compared with the application

Table 1. Direct cost in Euro for axenic production of *Bacillus sphaericus* and non-axenic production of an ureolytic bacterial mixed culture

	Axenic pure culture production	Non-axenic mixed culture production	Factor
Spores cost per kg	435	145	30
Self-healing agent cost per kg	480	595	8
Cost per activity unit (i.e. g urea hydrolyzed per g CDW per h)	350	43	8

of bio-based technology (Denys NV, Belgium, personal communication).

To achieve prices of about €15 to €20 per m^3 of applied concrete, one must work with cultures produced under less expensive (non-sterile) environmental conditions. The process must furthermore be optimized to obtain viable spores that maintain ureolytic activity over long storage time to perform the hydrolysis of the urea and provoke a massive calcium carbonate precipitation. It is also necessary to find an inexpensive encapsulation process, providing the necessary protection to the spores, maintaining or slightly altering the concrete proprieties.

Summarizing, from the economical point of view, for a bio-based product for self-healing and/or self-repairing in concrete structures, prices of about €15 to €20 per m^3 of applied concrete are warranted. Even at such levels of costs, for this type of product to be added to concrete, the markets will require that it will be guaranteed to be effective over a certain period, depending on the type of cracks to be healed. This period may range from weeks to months in case of early age cracks due to autogenous or drying shrinkage up to several decades due to the aging of the structure.

Non-axenic ureolytic spores production

As indicated before, the main problem of using axenic pure cultures is the high production cost of such bio-material. Thus, a possible solution would be the development of a less costly process to obtain ureolytic sporulating bacteria. It must be possible to select an ureolytic sporulating bacterial community starting from soil, wastewaters, activated sludge or any kind of material rich in active microbial activity.

Ureolytic bacteria can be found almost everywhere. Under the right stimulus, one can select the sporulating strains in order to obtain an ureolytic non-axenic mixed culture able to perform as well, or even better, than the pure cultures.

Considering that such non-axenic production is possible and that the main stimulus are the presence of considerable amounts of urea and a thermal shock to induce sporulation one can estimate some costs to produce a non-axenic ureolytic mixed culture. One can consider activated sludge as raw material and a feed containing an easy degradable carbon source (such as sucrose) and urea (in considerable amounts). Considering also a regular activated sludge one can easily get about 12 kg/m^3 of dry organic matter after drying. This value can be assumed as the production yield of such non-axenic process (see Box 2).

Making then a direct comparison between the axenic production of *Bacillus sphaericus* spores and the production of such mixed culture of ureolytic spores (Table 1) one can easily conclude that further studies should be performed using the mixed culture. Furthermore, the development of this new technology might contribute to decrease the production cost.

CONCLUDING REMARKS

In order to use the MICP technology under real applications on concrete structures, the following three points should be taken in consideration:

i. Despite of the lower costs estimated for the non-axenic production process, active ureolytic bacterial spores are still too costly for practical application and prices below €2 per kg of spores dry weight should be strived for.
ii. The encapsulation process of the spores or of vegetative cells should be achieved by means of inexpensive methods so that the overall extra costs per kg of spores decrease from the current €40 to a maximum of €15.
iii. There are at present two markets for the application of the "submersed" MICP technology available i.e. pillar bridges respectively tunnels. Indeed the right conditions to provide the proper microbial activity which depends on ample water supply are, for these two environments, provided.

Box 2: Estimated total costs to produce a non-axenic microbial based additive capable to bring about self-healing of micro-cracks in concrete under optimal (submerged) conditions. Estimates based on in house price calculations

1. Costs to produce 1 kg of the effective ureolytic mixed culture of bacterial spores:
   To calculate the cost to produce 1 kg of such mixed culture one should take in consideration:

   - Culture medium used for spores production
   - Required labor work to assembly and maintain the process
   - Energy requirements
   - Production yield of each batch (grams of cell dry weight produced per L)

   Considering the following, one can calculate:

   - Production scale of 1m^3
   - A labor work cost at 50 €/h
   - 3 hours of required labor work
   - Industrial standard equipment
   - The electricity cost at 0,09 €/kWh
   - A maximum yield of 12 kg CDW/m^3

Medium cost	9	€/m^3
Labor work cost	150	€/m^3
Energy cost	15	€/m^3
Total cost	145	€/kg

2. Costs to produce 1 kg of self-healing agent:
   To calculate the cost to produce 1 kg of self-healing agent one should take into consideration:

   - The encapsulation process
   - The addition of the required nutrients
   - The required amount of self-healing agent per m^3 of concrete

   Considering the following, one can calculate:

   - An encapsulation cost of 40 €/kg
   - The capsules do not increase the total weight of the final product
   - The addition of urea (20 g/kg) and CaCl2 (35 g/kg)
   - The addition of 0,5% (w/w) of self-healing agent
   - An average concrete density of 2400 kg/m^3

Encapsulated spores	545	€/kg
Self-healing product (encapsulated spores + nutrients)	595	€/kg
Quantity of self-healing agent	12	kg/m^3
Total cost	714	€/m^3

3. An important value is the cost per activity unit. Considering the best result obtained with these non-axenic cultures is the same obtained for the axenic ones (16,5 grams of urea consumed per gram cell dry weight per hour) [14] one can conclude that the total cost of spores can be expressed as about 43 €/g urea hydrolyzed/g CDW.h

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Article

Differentiating public policy for technology startups — essential for biotech?

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ABSTRACT

The paper presents the limited quantitative and qualitative analysis of the biotechnology and ICT industries in Lithuania and Estonia, as well as public policy instruments aimed at supporting the development of these industries. In depth analysis of the employment and revenue profile and correlations of the selected biotechnology and ICT enterprises are provided. The paper suggests that existing public policy instruments designed to promote enterprise and innovation fail to differentiate among technological fields. This and other factors cause preference to the short cycle technological fields, such as ICT. Very few instruments are available for the needs of the biotechnology industry, and the long cycles and return horizons of biotechnology development are not recognized. These oversights are detrimental to the biotechnology sector and high-tech local employment. Suggestions on the policy reform are made.

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Keywords: entrepreneurship; technology; ICT; biotechnology; startups; business cycle

INTRODUCTION

Entrepreneurship and startups are desirable phenomena in all aspiring economies. Most developed and emerging economies implement public policies to facilitate startup creation and entrepreneurship, especially in the highly innovative technological fields, such as biotechnology.

Huge economic potential, inherently international and highly developed marked, as well as national success stories make biotechnology entrepreneurship and startups a public policy priority area across Europe and the Baltics.

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Unfortunately, public policy initiatives may miss the differences of biotechnology field and its business processes. Most existing support schemes and policies do not differentiate technology fields, and treat all young enterprises from different emerging technologies, such as information/communication technology (ICT) and biotechnology, alike. With few exceptions the existing public financial support and public policy measures are not technology field specific. Few instruments aimed specifically at biotechnology startups are in place and even these instruments do not present a realistic understanding of the biotechnology business cycles and startup needs in this field. The paper provides an empirical analysis of the public policy measures in order to investigate the level of understanding of the different business cycles that govern the field of biotechnology in pertinent public policies.

The paper argues that biotechnology and other long-business cycle fields have been suffering due to the oversights in the public policy. As a result, the numbers of the new biotechnology startups are underwhelming

especially compared to startups in the ICT technological field. At the policy level this disparity is often written off as the supply side problem — that is, insufficient numbers of university graduates and PhDs in the field of biotechnology, as well as brain drain. However, different levels of available support may be a more important reason. Thus, startup public policies instead of alleviating the biotechnology enterprise creation difficulties, may have added to these difficulties, that is — have become an obstacle for startup activity in the field of biotechnology.

The main purpose of the paper is to provide empirical analysis of the biotechnology business profile and suitability of the public policy instruments with respect to the biotechnology enterprise development. Additional purpose is to identify and analyze main differences of the startups in the biotechnology business field compared to the ICT field. Difference analysis provides the basis for the empirical analysis of the public policy instruments. Suggestion is made and supported by the findings that the specifics of biotechnology business are disregarded in the public policy, hence policy reforms or targeted policies are needed. Finally the paper suggests instrument recommendations for facilitating the biotechnology development and business through public policy.

Statistical analysis, comparative empirical analysis, phenomenological, quantitative and qualitative analysis methods are used for the research presented in this paper.

BIOTECHNOLOGY STARTUP CONTEXT

With any biotechnology, the development time between lab idea and a tangible product is far longer than in the field of ICT technology. A normal product development cycle in biotechnology generally lasts at least 7 to 10 years. Some studies suggest the time to market for drug development of 12-15 years. Moreover, biotechnology research is very costly and fixed to infrastructure. The main costs are fixed and sunk costs — infrastructure and biotech consumables. In biotechnology, a startup phase can last for up to 10 years. Based on empirical studies of the US biotechnology industry, it costs from $250 million to $300 million to create, develop, test and prepare a drug/product for market.[1] In biotechnology startup is generally any company, which is in the process of developing a product — that is for up to 10 years.[2]

The above is very different in the ICT field, where product development terms are notoriously short and rarely exceed 18 months. Also, in the ICT startups the principal costs are variable and entirely dependent on available human resources. In the ICT field the company which was not able to deliver a competitive product to market in less than 3 years is widely recognized as a failure.[3]

Differences between the fields are summarized in Table 1.

The above summary highlights substantive differences between the business enterprises in these two technological fields.

Infrastructure fixation of the biotechnology startups also means that jobs created (and also taxes paid) by such startups are fixed a specific location.

To demonstrate this effect, it is appropriate to look into the case studies of the most successful ICT and biotechnology startup in the Baltics over the last 20 years. Note that the term startup is used in this context to refer to the enterprises, which are not necessary startups in the traditional sense, since most of them have been successfully operating for more than a decade. Rather the term is used in order to stress the technological background of these enterprises and the fact that all of them emerged over the last 20 years. Also, only enterprises, which engage and invest in the real R&D activities (within the meaning of the OECD Frascati Manual) are investigated.

The most prominent ICT success cases in the Baltics are Skype, as well as GetJar and Pixelmator in Lithuania. An emerging ICT startup FitsMe from Estonia is also included. Joint commonality for these enterprises is the quick international success or more specifically very scalable technology which was aimed at international market from the outset. In biotechnology this is a non-issue, since any biotechnology is inherently international and scalable, as long as it is scientifically sound. Studied examples

Table 1. Comparison of biotechnology and ICT startup features

Biotechnology	ICT
• Development time between lab idea and a tangible product is generally 7 to 10 years; • Biotechnology development is fixed to infrastructure (universities, etc.); • The main costs in biotechnology are fixed and sunk costs; • In biotechnology, a startup phase can last for up to 10 years — that is no sales for 10 years.	• Development time generally 12-18 months; • Very fluid and not fixed to any infrastructure; • Mainly variable costs; • ICT startup which does not have final product/ sales for 3 years is generally considered a failure.

in biotechnology are Lithuanian enterprises Fermentas and Sicor Biotech, as well as Quattromed from Estonia. A general observation must be mentioned that biotechnology sector is much more developed in Lithuania compared to Estonia. Bioseka — an emerging biotechnology startup from Lithuania is also included. Most of the studied companies, with the exception of Pixelmator and Bioseka, have attracted significant international investment and/or were sold to multinational players (Ebay/Microsoft, Accel Partners, ThermoFisher, Teva, etc.).

Fermentas is genuinely Lithuanian biotechnology company, established in 1994 by the employees of the Lithuanian Biotechnology Institute and developing instruments (enzymes — restriction endonucleases) for molecular biology and biotechnology. All development and manufacturing of Fermentas products is performed in the Fermentas site in Vilnius, while sales are carried by the international staff abroad. 99.5% of all Fermentas products are exported. In 2010 Thermo Fisher Scientific acquired Fermentas and assumed most of the sales functions and staff. The development and manufacturing of the products, remain unaffected by the Thermo Fisher acquisition. Thus, Fermentas as a wholly owned subsidiary of Thermo Fisher Scientific is the biggest biotechnology employer in Lithuania, which has little development employment abroad, and is also involved in major collaborations with the life sciences universities in Lithuania. Fermentas has all telltale features of the classical biotechnology enterprise (cf. Table 1), especially its local employment very significantly outsizes foreign employment.

SicorBiotech is another Lithuanian biotechnology company, established in 1991 by the employees of the Lithuanian Biotechnology Institute and focused on the recombinant biotechnology for production of human recombinant proteins. Initially known as Biofa, subsequently as Biotechna and now Sicor Biotech. In 2001 the company became a part of a group of companies owned by Sicor Inc., an international pharma company and in 2004 it became part of Teva Pharmaceutical Industries Ltd. Regardless of the changing ownership, the development and manufacturing in the company remains concentrated in Lithuania, with mainly sales and marketing staff abroad. Thus, SicorBiotech fully fits the features of the biotechnology enterprise model outlined above.

Quattromed is the Estonian medical diagnostics startup, established in 1995 as a spin-off of the Estonian Oncology Centre of the Tartu University. In 2008, the major Baltic venture fund BaltCap acquired a majority stake in Quattromed and in 2013 the company was acquired by the German company Synlab. Quattromed is, employing more than 150 people in Estonia, including in cities where there are few other good job opportunities. Insignificant employment abroad is maintained for marketing purposes. Although, not a development company, Quattromed maintains the features of the biotechnology company, especially fixation to infrastructure and mainly local employment.

Bioseka is a Lithuanian biotechnology company established in 2011 by three PhDs, working in the fields of microbiology, bioinformatics and antisense technology. Bioseka collaborates closely with the Faculty of Medicine of the Vilnius University. In 2013 Bioseka employs 7 people, all in Lithuania.

One noteworthy additional finding is that all of the analyzed biotechnology companies are profitable (based on 2012 financial accounts).

Skype is the biggest of all analyzed companies and an unquestionable ICT success story. Although not a genuinely Estonian startup, it is widely promoted as Estonian by the Estonian government.[4] Skype was founded in 2003 by two Danish and Swedish entrepreneurs, although the Skype software was developed by the four Estonian nationals. Estonian nationals have only been a minority shareholders at Skype — when Skype was sold to eBay in 2005 for a little over 2 billion EUR, about 100 million EUR was paid to the Estonian owners. From the outset Skype was headquartered in Luxembourg, and only development office is maintained in Estonia. From Skype's rapid growth period of 2005-2006 until 2009, its Estonia office remained its main development center. After 2009 the Silicon Valley branch has grown much more, followed by the London branch — previously the business end of the operation. Skype has also established development branches in Stockholm, New York, Moscow and Prague. Although Skype has somewhat increased the development headcount in Estonia, the Skype Estonian team is increasingly outsized by employees located elsewhere. As of July 2012 only about a third of Skype's 800 developers were located in Estonia. The Skype situation is a classic example of the fluid ICT startup, which although retains sizable local employment is increasingly developing abroad.

Other analyzed ICT startups are much smaller compared to Skype. GetJar is an independent mobile phone application store founded in Lithuania in 2004, with offices in Vilnius, Lithuania and San Mateo, CA, USA. In 2007 Accell Partners acquired a stake in the company. Prior to 2007 the company had a development office of 10 people in Lithuania and a small marketing office in the UK. After 2007 the development of the company has increasingly moved to the Silicon Valley. Although the Lithuanian development office of 10 people remains in Lithuania in 2013, the Silicon Valley office has grown to 70 people (September 2013). The fluidity of jobs in GetJar is even more evident than in Skype. Even though GetJar was founded by the Lithuanian locals, it is much

less related to Lithuania and has very small employment impact.

Pixelmator was founded in 2007 by two Lithuanian nationals. Pixelmator develops the image editing software for Mac OS platform. The company has development office in Lithuania, as well as marketing and development office in the UK. In 2013 (September 2013) the Lithuanian development office employed 19 people, while the UK office was 15 people. The foreign part of the company has been growing faster lately, but has not outsized local employment in Lithuania yet. Being one of the younger analyzed companies Pixelmator will be a very interesting case study for the follow-up research.

Finally FitsMe is Estonian technology startup developing software and hardware for virtual fitting of apparel — a "virtual fitting room." The company was established in 2006 and is known as Massi Miliano, although the company started marketing its main product in 2010. The company has 48 employee development office in Estonia, however the company has foreign offices in several countries, including the UK, Germany, France, Spain, Australia and the US. Local (Estonia) employment by the company has expanded twofold in two latest years, however foreign employment by the company expanded even more significantly in 2010-2013 and comprises 45 employees. Assuming the launch in 2010 FitsMe is a very young undertaking and rather atypical in terms of development and employment profiles.[5] FitsMe is a major recipient of public support. Over 3.7 million EUR of public support and public venture fund investment was put into the company even before it had any sales, hence the local employment may be a regulatory requirement, rather the business need. Due to this FitsMe data distorts the general picture of the ICT technology startup employment, as explained further on.

Out of the analyzed ICT enterprises, Skype and Pixelmator are profitable ventures, the profitability information for GetJar is private, while FitsMe has not been profitable over its history.

For the additional analysis of these enterprises publicly available employment data on them was gathered and analyzed. Based on empirical employment data, regression analysis was done in order to establish determination coefficient and non-parametric correlation coefficients was calculated based Kendall's tau-c. Use of Kendall's tau-c is justified due to small data sample. Kendall's tau-c calculations were made using IBM SPSS Statistics 21.0 software.

The provided analysis if sufficient to establish the differences between the two business sectors analyzed in this article, although it may also justify gathering of additional data (data on more enterprises) and further correlation analysis in the future research.

Results of the analysis, which are summarized in Figure 1 demonstrate that ICT companies preference for foreign employment at the expense of local employment. Further substantiation of this analysis is presented in Figure 2 and Table 2, as well as Figure 3 and Table 3. Regression analysis is justified since the coefficient is >0.25. Regression analysis results in different equations and significantly different correlation coefficients (R^2), what substantiates different models of employment in biotechnology and ICT sectors.

Based on this analysis, it may be concluded that ICT enterprises produce more foreign employment than the biotechnology companies. Thus, ICT startups seem to be at a disadvantage, when it comes to retention of the local jobs at the national level.

The reasons for this may be several. First, it is caused by the highly fluid nature of the ICT technology, which is not fixed to any infrastructure, as well as due to the need to be close to the main markets, customers, large talent

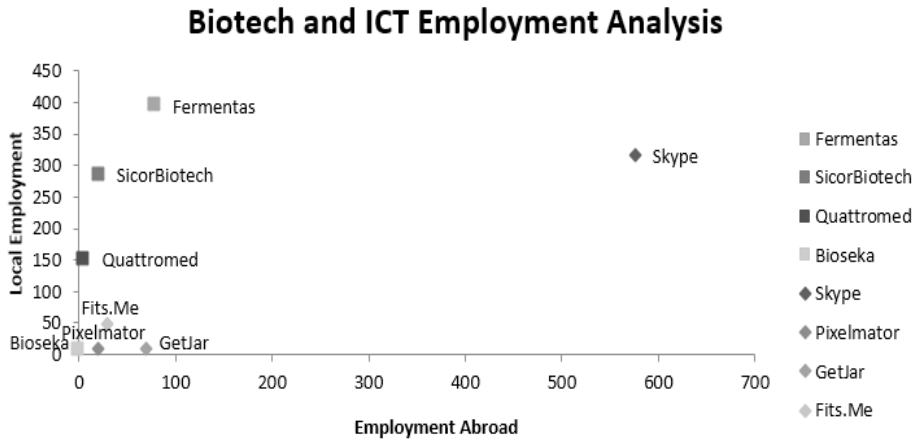

Figure 1: Employment profile analysis in the studied biotechnology and ICT startups in Lithuania and Estonia

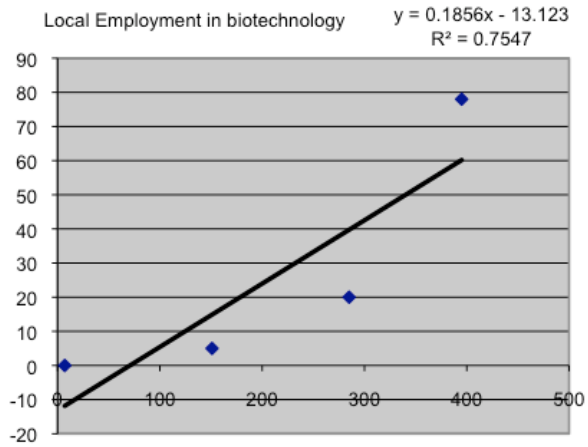

Figure 2: Regression analysis of the employment in biotechnology enterprises

Table 2. Non-parametric correlation coefficient for the employment in the analyzed biotechnology enterprises

Symmetric Measures

		Value	Asymp. Std. Error[a]
Ordinal by Ordinal	Kendall's tau-c	1.000	.000
N of Valid Cases		4	

[a]Not assuming the null hypothesis.

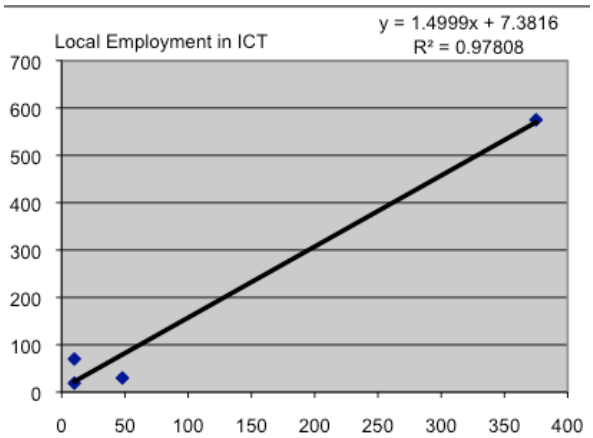

Figure 3: Regression analysis of the employment in the analyzed ICT enterprises

pools and sources of capital. Unfortunately, neither Estonia, nor Lithuania has a deep talent pool and several successful companies exhaust it very rapidly. ICT sector is in need of talent worldwide, therefore there is also a problem of the brain drain. Previous research points out the fact that it is very difficult to import employment from outside of the EU in the field of ICT.[5] Clusterization effects are also very strong in the field of ICT, which explains such unique phenomena as the Silicon Valley in the US and relocation of startups to such areas.

It must be acknowledged that the employment case of FitsMe is very likely distorted by the very substantial government intervention for the company to maintain employment in Estonia. Other analyzed enterprises have also received various support from the national governments, however it was much lesser compared to the size of the company. If it was not for this distortion it is likely that the observed effects would have been even greater.

Contrary to the ICT startups, biotechnology industry is much more rooted and productive in terms of retaining local high-tech jobs. As it was identified in the feature analysis — biotechnology entrepreneurship needs access to the significant and expensive infrastructure, which is commonly shared with the public research institutions (universities, research institutes). Relocation of such infrastructure is not possible, hence the biotechnology enterprise sticks around. It is not uncommon for biotechnology enterprises to develop a very close relationship with the higher education institutions for mutual benefit.[1]

For the additional analysis of the examples of analyzed Estonian and Lithuanian biotechnology (Fermentas, Sicor Biotech, Bioseka, Quattromed) and ICT (GetJar, Pixelmator, FitsMe) enterprises publicly available employment data was analyzed in the context of publicly available revenue data. Data about Lithuanian enterprises (Fermentas, Sicor Biotech, Bioseka, GetJar, Pixelmator) employement and revenue was taken from Public register of Lithuanian companies,[6] data about Estonian enterprises (Quattromed, FitsMe) was taken from official presentations about companies.[7,8]

Regression analysis and non-parametric correlation coefficient of the employment and revenue in the studied biotechnology startups in Lithuania and Estonia are presented in Figure 4 and Table 4. Regression analysis is justified since the coefficient is >0.25. Regression analysis results shows that there is a strong correlation between employment and revenue.

Regression analysis and non-parametric correlation coefficient of the employment and revenue were also calculated in the studied ICT startups in Lithuania and Estonia. The results are presented in Figure 5 and Table 5. Regression analysis is justified since the coefficient is >0.25, however in this case it demonstrates a very weak correlation between employment and revenue in ICT startups.

Results of analysis of ICT and biotechnology startup data, which are summarized in Figures 4, 5 and Tables 4, 5 demonstrate that there is a strong positive correlation between employment and revenue in biotechnology startups, which means that the more employee enterprise

Table 3. Non-parametric correlation coefficient for the employment in the analyzed biotechnology enterprises

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-c	.563	.419	1.342	.180
N of Valid Cases		4			

[a]Not assuming the null hypothesis.
[b]Using the asymptotic standard error assuming the null hypothesis.

Figure 4: Regression analysis of the employment and revenue in the studied biotechnology startups in Lithuania and Estonia

Table 4. Non-parametric correlation coefficient for the employment and revenue in the analyzed biotechnology enterprises

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-c	.938	.188	5.000	.000
N of Valid Cases		4			

[a]Not assuming the null hypothesis.
[b]Using the asymptotic standard error assuming the null hypothesis.

has, the more revenue it generates. But the results may be different in ICT startups — the analyzed data suggests only a very weak correlation between employment and revenue in ICT startups, which means that revenue does not depend on number of employees.

Building on the analysis of employment and revenue correlations, it is further useful to investigate average revenue per employee in biotechnology and ICT enterprises. Revenue data was obtained from Public register of Lithuanian companies,[6] data about Estonian enterprises (Quattromed, FitsMe) was taken from official presentations about companies.[7,8] Revenue arithmetic averages for the target enterprises per employee are as follows: Quattromed revenue per employee is 106 666 EUR, Sicor Biotech — 131 752 EUR, Fermentas — 64 127 EUR, Bioseka — 1242 EUR meanwhile in ICT enterprises: Pixelmator revenue per employee is 12 787 EUR, GetJar — 1 449 EUR, FitsMe — 476 EUR. Graphical representation is provided in the Figure 6 below.

Results of the analysis, which are summarized in Figure 6 demonstrate that analyzed ICT startups (Pixelmator, GetJar, FitsMe) have less revenue per employee compared to biotechnology enterprises (Quattromed, Sicor Biotech, Fermentas).

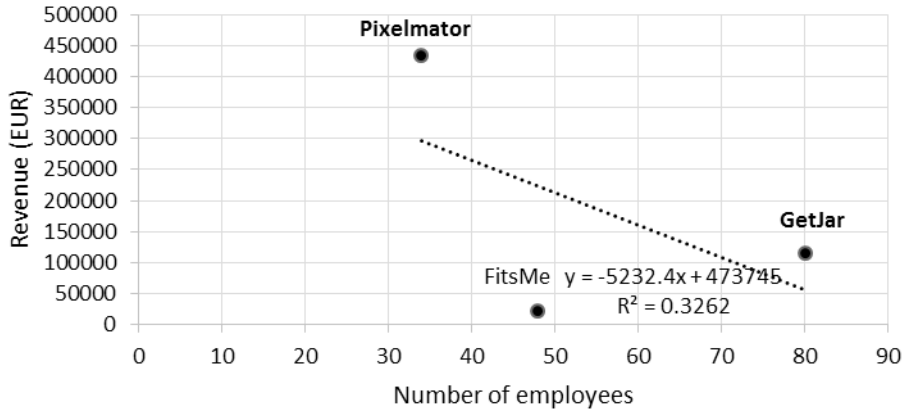

Figure 5: Regression analysis of the employment and revenue in the studied ICT startups in Lithuania and Estonia

Table 5. Non-parametric correlation coefficient for the employment and revenue in the analyzed ICT enterprises

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Ordinal by Ordinal	Kendall's tau-c	-.333	.544	-.612	.540
N of Valid Cases		3			

[a]Not assuming the null hypothesis.
[b]Using the asymptotic standard error assuming the null hypothesis.

Further scrutiny of the biotechnology enterprise case analyses also suggests that biotechnology entrepreneurship carries secondary social benefits. Since biotechnology sector is always fixed to the research infrastructure and startups are generally born as the spin-offs of the universities. Biotechnology startups tend to retain close collaborations with the universities, which also means that biotechnology startups cause indirect benefits for employment — employment in the academia and peripheral fields. Case studies of Lithuanian biotechnology giants Fermentas and Sicor Biotech highlighted not only job creation and retention potential, but also the said secondary benefits. Fermentas example demonstrates this best of all. Fermentas was essentially a spin-off of the Biotechnology (Enzymology) Research Institute and for the whole existence of the company shares the same premises. Fermentas has very close relationship with the Vilnius University as well as the Lithuanian Health Sciences University, this includes both mutual infrastructure access, close collaborations on research and study programs. From 2003 Fermentas also collaborates with the Vilnius College, which trains undergraduate biotechnology graduates specifically for Fermentas. Fermentas also provides free supplies for biology classes in the Lithuanian secondary schools. Existing research suggests that such university-industry collaborations are beneficial both for business development and for innovation processes, including diffusion of innovation.[9]

Close industry-university collaborations in the ICT sector are rarer and relatively modest. Only Skype relatively recently gave back — in 2012 Skype and Estonian Information Technology Foundation signed the sponsor agreement which allows IT Academy to use Skype name and sets 100 000 EUR annual grant from Skype for 3 years.

Additional spill over benefits of biotechnology enterprise are scientific advancement, as well as spin-off biotechnology startups created by the former employees. The latter effect is also notable in the ICT field, however the scientific advancement is much more prominent in biotechnology.

Previous case studies in the Canadian provinces (e.g., Kingston area in Ontario) suggest that biotechnology sector is able to retain key staff even in relatively less affluent communities throughout the product development cycle (5-10 years), as long as there is efficient access to the research infrastructure and critical mass of people working in the field.[10] Also, even if the startup is not an economic success case it leaves behind the trail of the scientific achievement and academic output. Biotech teams sticking together in one geographic area and collaborating with the universities for at least 36 months

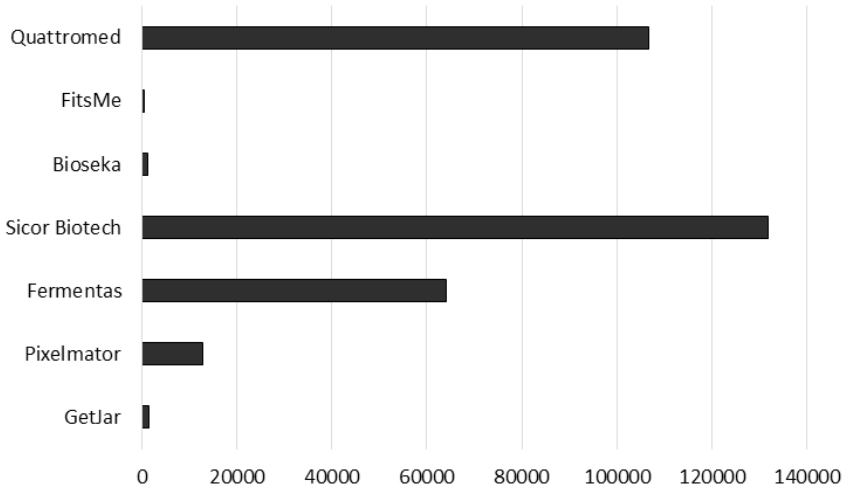

Figure 6: Revenue per employee in biotechnology and ICT startups in Lithuania and Estonia

tend to attract younger talent (especially master and PhD students), thus increasing the overall socio-economic effect of the enterprise. As it was noted — these effects are independent of the eventual economic success of the biotechnology enterprise. Based on the length of time observed in the surveyed research a correlation of the secondary socio-economic effects and long business cycles can be observed.[11]

ICT enterprises have lesser secondary socio-economic effects. One of the reasons is that ICT entrepreneurs tend to be younger and not uncommonly lack full university education and involvement in the academic pursuits. The secondary socio-economic effects produced by the ICT enterprises are moderate, mainly focused on highlighting the social profile of the ICT sector, career and economic opportunities in this sector for the young people. Spin-off creation is also the case in the ICT field among the former employees (alumni). One of the reasons justifying the weaker secondary socio-economic effects is the short business development cycles. Short business cycles contribute to the fluidity of the ICT enterprise and consequently less fixed employment within such enterprise.

Summarizing the analysis it must be noted that entrepreneurial ventures in biotechnology have much longer business cycles compared to ICT enterprises. On the other hand such longer business cycles contribute to the increased positive socio-economic effects of the biotechnology business ventures both directly (through local employment), and indirectly (through scientific and academic virtues). Thus, from the point of view of creating local hi-tech and high-value-added employment for the longer term and maximizing secondary socio-economic biotechnology startups may be more desirable than the fast-cycling ICT startups.

PUBLIC POLICY AND PROMOTION OF BIOTECHNOLOGY INDUSTRY

Public policies have important role in the innovation systems. Intervention into the markets are justified by the market and system failures, which are a commonplace phenomena in small emerging markets, as well as technological fields. The public policies may promote innovation and development in a specific sector, where it is desirable, by adopting various policy instruments.[12]

In general innovation and knowledge economy support public policies are supportive of the technology based businesses, such as biotechnology and ICT. Unfortunately the different lengths of the business cycle and different employment profiles of biotechnology and ICT sectors are not reflected in the public policy programming, design and implementation. To demonstrate this, the basic analysis of the EU context and specific analysis of the pertinent public policy measures in Lithuania and Estonia was done.

Based on existing academic research most countries implement various business support policies and instruments.[12] Grounded on the availability of the EU Structural funds main support instruments in Lithuania and Estonia are financial grants for the enterprises. Also, both countries have adopted Strategic and framework documents and indirect measures supporting technology-based businesses and technology-based activities inside of the existing traditional and not technology intensive businesses.[13]

Both biotechnology and ICT are the sectors of smart specialization in Lithuania and Estonia. Both sectors are also priority development areas in the EU strategic documents and instruments, such as the existing COST, FP6 and FP7 and forthcoming Europe 2020 and Horizon

2020 framework programmes. The EU instruments tend to be relatively selective. FP6, FP7, COST instruments have separate parts and budgets designated for life sciences and biotechnology, and separately for ICT. The separate parts designated for life sciences and biotechnology, and separately for ICT in FP6, FP7, COST instruments can be seen in Table 6.[14-16]

Forthcoming Europe 2020 and Horizon 2020 framework programmes also include fields of ICT and biotechnology. Europe 2020 is a strategy for smart, sustainable and inclusive growth, which presents 7 initiatives. One initiative is called "Digital agenda for Europe", which covers area of ICT. "Innovation Union" initiative includes area of biotechnology, because it seeks to ensure that innovative ideas can be turned into products and services that create growth and jobs.[17]

Horizon 2020 — The EU framework Programme for Research and Innovation introduces 3 main sections — Excellent Science, Industrial Leadership, Societal Challenges. Industrial Leadership section includes Information and Communication Technologies and Nanotechnologies, Advanced Materials, Advanced Manufacturing and Processing, and Biotechnology as a separate areas.[18]

There are also horizontal instruments embracing all different areas. In that the EU framework instruments are reasonably accommodative to the different profiles and business cycles of the biotechnology and ICT sectors. On top of the framework instruments there are also dedicated instruments for biotechnology, such as the IMI (Innovative Medicines Initiative), which is specifically crafted to meet the needs and profile of the biotechnology business. Nevertheless, IMI is not designed to be the primary support instrument, but it is rather a gap-filler, aiding the industry (including big and established pharma companies) in the long development cycles and dealing with under-financed problems of public health concern. Thus, IMI is a relatively short cycle (up to 3-4 years) instrument, which was never supposed to be a primary business support instrument. It is important to note that framework instruments as well as IMI recognize long development cycles in biotechnology as one of the key problems of the sector, limiting availability of risk capital and other financial investments, also necessitating public-private collaborations (such as industry-university collaborations). These collaborations are recognized as one of the advantages and social benefits of the field.

Public policies at the national level in general shall adjust for the EU framework instruments and focus on the national priorities — such as creating sustainable long term knowledge economy, creating employment or promoting the field of business that has national importance.

Estonian Research and Development and Innovation Strategy 2007-2013 directs the growing support from the state on the basis of the following principles:

(1) preference given to R&D with internationally competitive high quality;
(2) creation of preconditions for the RD&I system to grow and be oriented towards efficiency, first at all creating a sustainable community of researchers and entrepreneurs and creating an attractive environment for research and development, and technological innovation;
(3) preference is given to innovation projects creating high economic added value.

The same is generally laid down in the Lithuanian Innovation Strategy 2010-2020 and it is difficult to disagree with the above. Unfortunately both said documents do not differentiate technological fields that provide high added value and the growth potential — that is, biotechnology is recited next to the information and communication technologies, and the different profiles and contexts of these fields are not even mentioned. This position is translated into the implementing measures of both countries so that funding instruments for innovative technologies are the same and based on the same premises and horizons for all sectors of technology.

Based on said foundations, the analysis of the specific measures in both countries suggests unsurprising similarities. Both Estonia and Lithuania have only one biotechnology targeted measure — 2009 State Biotechnology Programme in Estonia and 2011-2013 Industrial Biotechnology Development Programme In Lithuania. This biotechnology specific instrument was not preceded by other targeted measures in Estonia, however, in Lithuania there were earlier measures specifically supporting biotechnology. On the other hand, the Lithuanian measure is a strictly 3-year measure with uncertain continuity, while the Estonian one is open ended. Unfortunately neither is accommodative to the longer development cycles typical to the biotechnology industry and unable to support longer term projects. Description, priority areas and expected outcomes of 2009 State Biotechnology Programme in Estonia and 2011-2013 Industrial Biotechnology Development Programme In Lithuania are defined in Table 7.[19,20]

Both programs — 2009 State Biotechnology Programme in Estonia and 2011-2013 Industrial Biotechnology Development Programme In Lithuania seek to develop field of biotechnology. But the priority areas of both programs are not the same: 2009 State Biotechnology Programme in Estonia focuses on food processing, molecular diagnostics and 2011-2013

Table 6: Thematic areas of COST, FP6, FP7 documents

Document	Description	Thematic areas, fields of research
COST	European Cooperation in Science and Technology, was founded in 1971. It is European framework for the transnational coordination of nationally funded research activities.	COST scientific organization is based on 9 fields of research: • **Biomedicine and Molecular Biosciences;** • Chemistry and Molecular Sciences and Technologies; • Earth System Science and Environmental Management; • Food and Agriculture; • Forests, their Products and Services; • Individuals, Societies, Cultures and Health; • **Information and Communication Technologies;** • Materials, Physics and Nanosciences; • Transport and Urban Development.
FP6	European Community Framework Programme for Research and Technological Development 2002-2006	7 thematic areas: • **Life sciences, genomics and biotechnology for health;** • **Information society technologies;** • Aeronautics and Space; • Food quality and safety • Sustainable development, global change and ecosystems • Citizens and governance in a knowledge-based society • Nano-technologies and nano-sciences, knowledge-based multifunctional materials, new production processes and devices.
FP7	European Community Framework Programme for Research and Technological Development 2007-2013	Research will be carried out in ten key thematic areas: • Health • **Food, agriculture and fisheries, and biotechnology** • **Information and communication technologies** • Nanosciences, nanotechnologies, materials and new production technologies • Energy • Environment (including climate change) • Transport (including aeronautics) • Socio-economic sciences and the humanities • Space • Security

Industrial Biotechnology Development Programme In Lithuania pays attention to creation of materials, products, bioplastics from renewable raw materials. Also, there is one priority area in both programmes — pharmacy. There are expected various developments in biotechnology sector, a high value-added products from both programs in Estonia and Lithuania. But 2009 State Biotechnology Programme in Estonia added export of high value products as an expected outcome and 2011-2013 Industrial Biotechnology Development Programme in Lithuania defines closer cooperation between business and science, creation of new "spin-off" companies as an important outcome.

At the operative level the public policy in both countries is dominated by fiscal instruments. Overall, after 2007 there is increasing focus in both Lithuania and Estonia to focus on fiscal instruments,[21] but neither country has adopted instruments focused on long time and financial return horizons.

The operative level instruments are dominated by the short cycle and short return focus. Out of 23 instruments aimed at supporting technological research and development in Lithuania, over the 2007-2013 programming period none was designed to accommodate projects longer than 4 years. Similar situation can be noted in Estonia. All reviewed instruments were able to provide financial support for no longer than 4 years and demand specific results (such as sales of the product and export growth) over the short period. The existing support instruments are either specifically designed to the needs

Table 7: Description, priority areas and expected outcomes of Lithuanian and Estonian Biotechnology Programmes

Document	2009 State Biotechnology Programme in Estonia	2011-2013 Industrial Biotechnology Development Programme In Lithuania
Description	The Estonian biotechnology programme is a part of the operational plan for the Estonian research, development and innovation (RDI) strategy "Knowledge-Based Estonia 2007-2013" and is the national research and development programme in the field of biotechnology.	2011-2013 Industrial Biotechnology Development Programme In Lithuania aims to facilitate the development of the biotechnology industry in Lithuania order to increase the high-tech industry.
Priority areas	• Functional food; • Food processing - transform raw material into food; • Molecular diagnostics – create tests and methods used on the molecular level to establish disease or propensity for disease; • Drug discovery technologies.	• Creation of materials and products from renewable raw materials; • Creation of bioplastics from renewable raw materials; • Creation of a new biocatalyst; • Pharmaceutical and veterinary products.
Expected outcomes	• In the priority development areas in the biotechnology sector, a critical mass of financing and people with the requisite skills has been achieved; • In the priority development areas of the biotechnology programme, Estonia has become one of the Baltic Sea region's most attractive centres and cooperation partners; • Increased use of biotechnology applications for producing and developing products, services and technologies with higher value added and export potential.	• Techniques have been developed to help get a high value-added products from local renewable materials, which will help increase biofuel plants in Lithuania; • Added value of industrial biotechnology firms created products will rise 30%; • Created a culture of innovation, encouraging closer cooperation between business and science, creation of new "spin-off" companies.

of the ICT sector (in Lithuania at least 8 instruments are specifically designed for ICT sector), or inadvertedly prefer the short business cycles of the ICT sector.

Study of the Estonian government efforts to support early stage innovative ventures overwhelmingly indicated support to short business cycle companies, mainly in the ICT field.[5]

It is noteworthy that short-cycle instruments are inherently preferred by the policy makers, since they allow the possibility to demonstrate quick results during the political and electoral cycles,[19] which coincidentally are 4 to 5 years.

This bias towards short cycles in the innovation support instruments is an obvious obstruction for the development of the biotechnology sector, putting it at a disadvantage to the short-cycle sectors, such as ICT. Moreover, none of the reviewed public policy instruments in Lithuania or Estonia, not even the sole biotechnology targeted instruments, recognize the employment profile of the biotechnology industry. This observation is unfortunate at the time when employment is in short supply all across the Baltic and the European Union.

The short cycle problem is increasingly recognized by the scholarly work in Estonia, but not yet in Lithuania. The 2010 Feasibility study for an Estonian biotechnology programme[23] has emphasized the "lack of financial investment able to support product development" in biotechnology business, also suggested that "long-term characteristics of this field reinforce the crucial need to secure <…> a long-term and strong support". One of the key recommendations for Estonia is "dedicated specialized seed funding (with good understanding of the correlated timelines and ROI) to support the innovation financing gap".[23] Lack of long term support is also identified by the Estonian scholars, who recognize that "only a small proportion of innovative enterprises in Estonia receive financial support for innovation from the public sector (including support from the EU), and universities and public sector agencies in Estonia only cooperate with firms in innovation activities to a small degree".[13] It is important to create platform to support developments

in the specific technologies and to facilitate cooperative mechanisms between scientific institutions and business at the industrial level in Estonia.[24]

In Lithuania the short cycle problem for biotechnology has not been acknowledged as of yet. The 2007 Feasibility study of the biotechnology sector in Lithuania[25] notes general need for substantial investment, however failed to recognize the short cycle problem of the public support instruments and venture capital. These oversights may be explained by the fact the study was done by the public research institute and tends to promote investment into the biotechnology research infrastructure at the public universities. Another reason for the slow recognition is the fact that Lithuania has relatively more developed biotechnology sector and several prominent national champions in biotechnology (such as Fermentas), which fared the 2007-2010 recession very well, maintained strong export growth and have been subject to high-profile acquisitions. Recent growth of the biggest biotechnology enterprises in Lithuania is underscored by the fact that these companies are >15 years old and hence are at the peak of the cycle, where they are able to reap the benefits of the research and development done long time ago. At the same time this success masks the difficulties in obtaining research and development aid for young biotechnology companies, which may be unable to take advantage of the short term instruments, since the long development timelines do not allow for the tangible results.

The above review of the fiscal support instruments (based on the EU Structural Funds), as well as innovation public policy programs demonstrates failure to differentiate between the startups in the different technological fields. Very few policy instruments are designed for the needs of the biotechnology industry, and even these instruments fail to recognize extra-long business cycles, financial needs and return horizons of biotechnology business development.[23]

The focus and benchmarks of the existing measures are short term sales growth and short term exports, thus preferring services over products. Planning horizons do not exceed 4 years and require significant financial results in the short term.

The above is consistent through fully public measures and even public-private partnership measures, such as venture funds focused on technology sector. General lack of investment as well as lack of understanding of the biotechnology timelines and return horizons is increasingly recognized in Estonia, but not yet in Lithuania. Feasibility Study for an Estonian Biotechnology program in 2009 stresses how it is important to create a financing chain for the companies' complete life cycle in Estonia. Investment system should cover all stages with incentives and grants, advances and loans, equities, guarantees.[23]

The short-cycle bias of the public support instruments is also reflected in the rick capital market in both Estonia and Lithuania. Portfolio reviews of the most prominent venture funds, such as BaltCap (pan-Baltic), Verslo Angelu Fondas 1 (Lithuania), Practica Capital (Lithuania), LitCapital (Lithuania) suggest preference to short term investments. Occasionally the venture capitalists invest into biotechnology companies (one of the companies reviewed in this research — Quattromed — was part of the BaltCap portfolio), but only at the stage of mature product and services and positive cash flow. None of the existing venture funds in the Baltics is in position to accept the investment horizon of at least 7 years. Some funds (Venture.lt) openly declare preference only to the ICT projects with the goal of positive cash flow during the first year. The only possible exception may be Ambient Sound Investments, an Estonian venture capital firm, which has made substantial investment into Estonian biotechnology company Celecure in 2007. Unfortunately, based on the public information available the company has moved into healthcare services and the status of its innovative development is unclear.

The lack of understanding of the biotechnology business and its timelines and consequently the lack of venture capital is identified as the universal weakness in the Estonian feasibility study[23] and in the broader region of Central and Eastern Europe.[26]

Most of the said funds are also involved in redistribution of the EU support through initiatives such as JEREMIE (Joint European Resources for Micro to Medium Enterprises), thus making them public-private instruments. The research was unable to identify whether JEREMIE funds were invested into any of the biotechnology companies, however ICT companies have received significant part of JEREMIE investment (preliminary account of >50% in Lithuania).

Overall characteristic of all existing public and public-private instruments is a bias sector to the detriment of long-cycle sectors such as biotechnology. Another staring feature is the lack of differentiation of the technological sectors in these instruments. This suggests both lack of understanding of the sectorial differences, as well as lack of appreciation of the strengths and weaknesses of the different sectors.

Based on the analysis in the paper it is likely that the policies which put all innovative technological fields into one basket, are detrimental to the development of the biotechnology startups, due to inappropriately short horizons and return expectations. Although biotechnology startups are desirable for the local economy from the job creation perspective this is not even acknowledged in the current public policy instruments.

CONCLUSIONS AND RECOMMENDATIONS

Biotechnology industry has inherent differences from the ICT industry. Among such differences are very much slower business cycles, different infrastructure and capital requirements.

Most existing public policy instruments designed to promote enterprise and innovation fail to differentiate among technological fields. Very few policy instruments are designed for the needs of the biotechnology industry, and even these instruments fail to accommodate for the long cycles and return horizons of biotechnology development to the detriment thereof. This alone represents a lost opportunity to appreciate and harvest the strengths of the different technological sectors. Biotechnology sector specific needs are only recently being recognized in Estonia and not yet recognized in Lithuania, but they have not made into the operative public policy instruments as of yet. 2009 State Biotechnology Programme in Estonia and 2011-2013 Industrial Biotechnology Development Programme In Lithuania are the most important public policy documents in the area of biotechnology. But the public policy in both countries is dominated by fiscal instruments and neither country has adopted instruments focused on long time and financial return horizons. It should be done in short term period in order to increase the development of biotechnology industry.

As it was demonstrated in this paper biotechnology industry has unique job and value creation and retention profile, which remains even if the venture is not an economic success. Analysis of the revenue data for the biotechnology and ICT startup sample suggests that ICT startups have less revenue per employee than biotechnology startups. Moreover, empirical data from Lithuania and Estonia suggests positive correlation between employment and revenue in biotechnology startups, while no such correlation was seen in the ICT sector.

Further research with larger data samples may be needed to fully validate these findings, however the analysis clearly enough demonstrates the huge potential in the biotechnology sector, which may be unleashed with properly designed public policies. Thus, biotechnology sector may deserve and justify designated long-cycle friendly public policy support measures. Same may also be applicable to other long-cycle technological fields.

Specific instruments, which may be considered in order to support biotechnology enterprises may be support for university-industry collaborations, long term support for researcher employment, long term development grants, discouragement or dismissal of short term criteria in the assessment of the projects and innovation potential (such as short term sales and export gains).

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From the Boardroom

Access to medical innovation: Obstacles & opportunities

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EXECUTIVE SUMMARY

Healthcare innovation saves lives, saves money, promotes economic growth, and provides hope for hundreds of millions of people (both patients and care-givers) in the United States and around the world. But innovation isn't easy.

There are many roadblocks beyond those of discovery and development. The complicated and conflicting dynamics of politics, perspectives on healthcare economics, of friction between payers, providers, manufacturers, and regulators, the battle for better patient education, and the need for a more forceful and factual debate over the value of innovation all create the need for a more balanced and robust debate.

The public policy essays in this paper present some of the key obstructions to maximizing healthcare innovation. The Center for Medicine in the Public Interest is dedicated to addressing these problems head-on and providing practical opportunities to overcome them. Specifically:

- The importance of understanding and rewarding incremental innovation.
- The price/value debate. Rather than focusing on the short-term costs of healthcare, what are the long-term benefits to both patients and society? We will examine this issue through the lens of the Solvadi debate.
- Value-based insurance design. How a more personalized approach to reimbursement matches up well with advances in personalized medicine.
- The dynamic and distressing link between co-pays and outcomes and how this relationship must be understood and recalibrated.
- The urgent need for transparency in insurance choices within the Affordable Care Act in order to provide the right medicine to the right patient at the right time in a transparent and affordable manner.
- How to reach best clinical practice more swiftly through electronic pre-authorization and the increasing empowerment of physicians.
- Addressing the problem of medication compliance through innovative approaches such as apps and more user-friendly patient education.
- How "the story of innovation" can be more clearly and powerfully communicated to various constituencies so that we can narrow the "misperception gap."
- Rather than playing the "blame game," how we can advance healthcare innovation by working together to advance the public good.

Shortly before his death, I had the privilege of a private meeting with Nobel laureate Joshua Lederberg. We talked about the state of applied science, the prioritization of development science, biomarkers, and a host of other future-oriented issues. At the end of the meeting he put everything into perspective in a single sentence. He leaned over the table and said, "The real question should be, is innovation feasible?" Let's hope so. Innovation equals hope.

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INNOVATION NATION

In 1950, Americans spent about 5 percent of their income on health care. Today the share is about 16 percent.[1] According to Harvard University economist N. Gregory Mankiw, "many pundits take the increasing cost as evidence that the system is too expensive. But increasing expenditures could just as well be a symptom of success."[2]

And he hits a homerun with a clear, concise, and common sense explanation. "The reason Americans spend more than their grandparents did is not waste, fraud and abuse, but advances in medical technology and growth in incomes. Medical science has consistently found new ways to extend and improve lives. Wonderful as they are, they do not come cheap."

Change is not required," wrote marketing guru W. Edwards Deming. "Survival is not mandatory." If we learn nothing else from BP's recent unpleasantness, it is that being able to identify an obvious problem (e.g., when oil is gushing uncontrolled into the Gulf of Mexico) is one thing. Identifying a potential problem is tougher. Toughest of all, however, is designing a solution that addresses a need early in the curve. Consider Alzheimer disease, a health care oil spill of draconian proportion. As Gina Kolata wrote in the *New York Times*, "The failure of a promising Alzheimer's drug in clinical trials highlights the gap between diagnosis—where real progress has recently been made—and treatment of the disease."[3] Recent significant steps forward in early diagnosis of the disease are important, and also frustrating, because there is still precious little that can be done when this devastating condition is identified either late in the game or in its nascent stages.

There are some tough but important basic principles when it comes to innovation in health care technologies.

Innovation is slow. As any medical scientist will tell you, there are few "Eureka!" moments in health research. Progress comes step by step, one incremental innovation at a time. Biopharmaceutical companies more often profit by improving existing molecules and making processes more efficient than by revolutionizing the whole field with new miracle products. Discontinuous innovation is the wonderful exception to the rule.

Innovation is hard. Today it takes about 10,000 new molecules to produce one FDA-approved medicine. This observation itself is disconcerting, but, further, only 3 out of 10 new medicines earn back their R&D costs. Moreover, unlike other R&D-intensive industries, biopharmaceutical investments generally must be sustained for over 2 decades before the few that make it can generate any profit. And the most recent estimate (as of December 2014) has risen to almost $2.6 billion.[4]

Innovation is expensive. The costs of development also continue to escalate. In 2003, researchers at Tufts Center for the Study of Drug Development (CSDD) estimated the costs to bring a new medicine to market to be $802 million. More recent authoritative estimates are well over the $1 billion mark, going as high as $1.7 billion.[5]

Innovation is under attack. From accusations of the "me-too" variety, to questionable schemes to replace pharmaceutical patents with a prize system, life for innovator pharmaceutical companies is rough and tough. Israel Makov (formerly the Big Abba of generics giant Teva) once told me that he wasn't really in the pharmaceutical business, but rather "in the litigation business," and he made this comment before the reality of biosimilars.

Nonetheless, innovation is important. This is true for more than just biopharmaceutical industry profits. In the United States, increases in life expectancy resulting from better treatment of cardiovascular disease from 1970 to 1990 have been conservatively estimated as bringing benefits worth more than $500 billion a year. In 1974, cardiovascular disease was the cause of 39% of all deaths. Today it is about 25%. Cerebrovascular diseases were responsible for 11% of deaths back then. In 2004 they caused 6.3% of deaths. Kidney diseases were linked to 10.4% of deaths and now are associated with 1.8%.[6]

As Harvard University health economist (and health care advisor to President Obama) David Cutler has noted: "The average person aged 45 will live three years longer than he used to solely because medical care for cardiovascular disease has improved. Virtually every study of medical innovation suggests that changes in the nature of medical care over time are clearly worth the cost."[7] Innovation must not be only about medicines. We have to embrace innovative technologies for medical records and prescribing. We need innovative clinical trial designs and molecular diagnostics so that we can develop better, more personalized medicines faster and for far less then the current $1 billion-plus delivery charge. We need innovation in access and reimbursement policies that

1 http://visualeconomics.creditloan.com/100-years-of-consumer-spending/
2 http://economistsview.typepad.com/economistsview/2007/11/mankiw-beyond-t.html
3 http://www.nytimes.com/2010/08/19/health/19alzheimers.html?_r=0
4 http://www.innovation.org/index.cfm/insidedrugdiscovery
5 http://csdd.tufts.edu/
6 http://www.washingtontimes.com/news/2008/may/12/health-care-realities/
7 Ibid

rewards speed to best treatment rather than lower-cost patients per hour.

Do we want a health care system that is cost-based or patient-centric? Should end-of-life care be rationed? If so, by whom and by what measure? And if we decide not to pay for new medicines, the clear signal to the pharmaceutical industry is "cease research and development for new treatments for killer diseases."

These considerations lead to the conclusion that we must start taking innovation, both incremental and discontinuous, seriously, which means spending more on harder developmental R&D (with concomitant higher investment risks). Currently, lip service is being paid to the need for more robust comparative effectiveness—although this is a battle yet to be either defined (comparative effectiveness, cost effectiveness, or clinical effectiveness?) or fought (do we need a US version of NICE?). It will indeed be a battle royale. In the words of Frederick the Great, "L'audace, l'audace, toujours l'audace."

According to Yale economist William Nordhaus, "The social productivity of health care spending might be many times that of other spending. If this is anywhere near the case, it would suggest that the image of a stupendously wasteful health care system is far off the mark."[8]

When it comes to health care reform, this is not even the end of the beginning. We need to keep our eye on the prize, that is, innovation that focuses on creating a chronic health care culture that embraces prevention and prophylactic care. We will not survive as a nation of obese, hypertensive diabetics. Rather than wasting time on Beltway spin, redoubling our efforts on innovation is far preferable.

SOVALDI AND THE PRICE/VALUE DEBATE

Expensive new drugs often get fingered as the culprit to rising US health-care costs. The truth is closer to the reverse.

First off, it's hard to see how pharmaceuticals can be a major driver of costs when they're just over 11 percent of the total US health-care budget.[9]

But more important is that even extremely pricey drugs still save money if used right.

Consider Sovaldi, which has a 90 percent cure rate for Hepatitis C, a disease affecting over 3 million Americans. A three-month treatment cycle of the new drug costs upward of $84,000. On the market for just a few months, Sovaldi has already clocked in a record-shattering $2.3 billion in sales.[10]

Some are calling foul, accusing the drug's developer — Gilead Sciences Inc. — of exploitative pricing. "The company in this case is asking for a blank check," says Karen Ignagni, president of America's Health Insurance Plans. "It will blow up family budgets, state Medicaid budgets, employer costs and wreak havoc on the federal debt."[11]

That's 100 percent wrong — the exact opposite of reality. New, better medications are actually the best and swiftest way for this country to cut down on our health-care expenses. By more effectively combating disease and improving patients' lives, drugs reduce long-term medical costs and bolster the overall economy.

Consider one pre-Sovaldi "best practice" treatment for Hepatitis C, the drug Pegasys. This requires one injection a week for 48 weeks — and very few patients see the treatment through to completion, so much of that treatment, both physician time and drug cost, is wasted. Nor is it that much cheaper: At about $7,000/month, the full course of treatment is over $70,000 — barely less than cost of the three months needed for Sovaldi to work a cure.[12]

And the price of not using Sovaldi is very high. One in three patients with the Hepatitis C virus eventually develops liver cirrhosis, and managing these patients is costly. A "routine" liver transplant (where the liver is from a cadaver) costs close to $300,000; a "living donor" transplant is even more expensive.[13]

Thanks to Sovaldi, a pill that cures the disease when taken once a day over 12 weeks will eradicate the need, the risks and the costs of liver transplantation. Such radical innovation deserves to be both lauded and rewarded.

And Sovaldi's costs will come down. The initial price of such breakthrough medications reflects the huge R&D costs required to bring the drug to market, not avarice.

As Food and Drug Administration official Dr. Janet Woodcock noted of the Sovaldi controversy: "We may

8 www.econ.yale.edu/~nordhaus/homepage/health_nber_1.doc

9 http://www.ashpmedia.org/AJHP/DrugExpenditures-2014.pdf

10 http://www.nytimes.com/2014/07/24/business/sales-of-hepatitis-c-drug-sovaldi-soar.html

11 http://www.reuters.com/article/2014/05/28/us-usa-healthcare-hepatitisc-insight-idUSKBN0E80AZ20140528

12 http://www.drugs.com/clinical_trials/pegasys-proven-effective-hepatitis-c-latino-patients-according-article-new-england-journal-medicine-6620.html

13 http://www.healio.com/gastroenterology/curbside-consultation/%7Ba8b9ec89-2c79-4696-a702-84e9fad15233%7D/what-is-the-likelihood-t

have to put a big down payment down now to get something really good."[14]

It's remarkable that some large insurers have the chutzpah to complain that curing 3 million Americans of hepatitis C will bankrupt health-care systems. Data recently published by the PwC Health Research Institute suggests the reverse. The study shows that the use of Sovaldi will actually drive down overall spending within a decade. According to the authors, "The challenge may lie in targeting the patient most in need of the more expensive course of therapy."[15]

In short, drugs aren't the cause of rising health-care costs — they're the solution. Demonizing new treatments distracts from the real problem in the US biopharmaceutical industry: top-down cost-centric policies that focus on the near-term, short-changing long-term patient outcomes, and so endanger "sustainable innovation" by denying fair reimbursement for high-risk investment in R&D. (Research and development costs big even if a drug never makes it to market — and most don't.)

New treatments are a bargain. Disease is always much more costly.

Unfortunately, under ObamaCare health plans are sticking more people with a bigger share of drug costs — a strategy designed to discourage use by the people in greatest need and direct outrage away from insurers to drug companies.

Breakthrough drugs could generate huge new savings in the US economy — but only if federal regulators don't smother them in the womb with expensive and unnecessary legal hurdles. Left unencumbered, domestic medical innovation will generate the new treatments to improve lives, stave off disease and cut down on long-term health-care costs.

If we don't reward risk-taking on behalf of human health, both will shrink.

WHAT ABOUT "VALUE-BASED INSURANCE DESIGN?"

Consider value-based insurance design, and then consider Section 224 (c) of HR3200, "Encouraging the Use of High Value Services." The public health insurance option may modify cost sharing and payment rates to encourage the use of services that promote health and value."[16]

The Pink Sheet points out a recent paper sponsored by the National Pharmaceutical Council as "adjust[ing] out-of-pocket costs based on an assessment of the clinical benefit value — not simply the cost — to a specific patient population." The overall goal is "getting more health out of every health care dollar."[17]

And they continue:

> *A shift to value-based insurance would provide some interesting opportunities for drug manufacturers to develop and present evidence of their products' value. A permanent comparative effectiveness research program, which is being considered as part of health care reform legislation, also could become an important source of information on value.*

It's important to consider VBID in the broader conversation of clinical effectiveness and more specifically HTA modeling a la QALY – because that brings you into the direct path of VSLY – the value of a statistical life year. According to Dr. Frank Lichtenberg of Columbia University, for a healthcare technology assessment scheme (such as the NICE model) to yield valid decisions in practice, it is necessary to have reliable estimates of:

> *ΔCOST*
> *ΔQALY*
> *and VSLY (Value of a Statistical Life Year)*
>
> *and his main point is that the devil is in the details.*

Lichtenberg believes that incorrect estimates of some or all of these key inputs are often used:

> *ΔCOST is frequently overestimated*
> *ΔQALY and VSLY are frequently underestimated*

And due to these estimation biases, health technologies that are truly cost-effective may often be rejected as cost-ineffective.[18]

Per the recent debate over the utility of new cancer treatments, he makes a very interesting point — that even though, over the past 30 years, the U.S. Mortality Age-Adjusted Rates for cancer have remained relatively constant — (leading to such mainstream media headlines as Fortune Magazine's "*Why have we made so little*

14 http://www.focr.org/news/inside-health-policy-fda-drug-chief-drug-cures-progress-could-require-down-payment

15 http://www.pwc.com/us/en/health-industries/behind-the-numbers/specialty-drugs.jhtml

16 http://thomas.loc.gov/cgi-bin/query/z?c111:H.R.3200:

17 http://www.sph.umich.edu/vbidcenter/registry/pdfs/NPC_VBIDreport_7-22-09.pdf

18 http://www.stockholm-network.org/downloads/events/Lichtenberg.pdf

progress in the War on Cancer?"[19] and NEJM articles like "The effect of new treatments for cancer on mortality has been largely disappointing"[20] — the often ignored reality is that *5-year relative survival rates, for all cancer sites, have increased from 50.1% in 1975 to 65.9% in 2000.*[21]

Lichtenberg cites two crucial studies, pointing out how health care economists must seriously reconsider the outdated estimates of a QALY:

> *Viscusi and Aldy: The value of a statistical life for prime-aged workers has a median value of about $7 million in the United States*
>
> *Viscusi, W. Kip and Joseph E. Aldy, "The Value of a Statistical Life: A Critical Review of Market Estimates Throughout the World," The Journal of Risk and Uncertainty, 27:1; 5–76, 2003.*

and

> *Murphy and Topel: The value of a life year is $373,000.*
>
> *Murphy, Kevin M., and Robert H. Topel, "The value of health and longevity," Journal of Political Economy, 2006.*

Attention must be paid.

THE CO-PAY CATASTROPHE

In the current national health care debate, let's hope we never hear the words, "As Georgia goes, so goes the nation."

Since 2005, Georgia politicians have been conducting a dangerous penny-wise, pound-foolish experiment with its state health program by hiking co-pays for brand-name prescription medications.

The results of that policy have been sicker, less productive state employees. These Georgians end up consuming more and costlier health care during the course of their lives, as their neglected conditions worsen.

The lesson here is that higher co-pays discourage patients from getting the treatment they need — especially when they reach upwards of $100.

Just consider what Daniel M. Hartung of Oregon Health & Science University calls the "co-pay effect."

Professor Hartung and his colleagues analyzed the effect of even a small co-payment — $2 for generic drugs and $3 for brand-name drugs — for those pharmaceuticals that were available to Oregon Medicaid enrollees in 2003.[22]

The co-pay fees were not required for patients who were unable to pay. The researchers examined pharmacy claims data on about 117,000 Medicare enrollees with conditions like depression, schizophrenia, respiratory disease, cardiovascular disease and diabetes.

They found that the patients' overall use of prescription drugs decreased by about 17 percent after the introduction of the co-pay policy.

It should come as no surprise that any policy that encourages patients to stop taking their prescription drugs is a recipe for disaster.

There is already a growing national trend of Americans not adhering to their prescribed drug regimens.

A study by Wolter Kluwer Health found that fewer and fewer Americans are even bothering to fill their prescriptions.[23]

In fact, during the fourth quarter of 2008, American patients neglected to fill 6.8 percent of their brand-name prescriptions — a 22 percent increase when compared to the previous quarter.

This practice — often known as prescription drug "non-adherence" — can have serious repercussions on a patient's health.

For example, hypertensive patients who do not take their prescribed medicines as directed suffer 5.4 times as many poor clinical outcomes as those who do.

And poor outcomes are 1.5 times more common for heart disease patients who do not take their meds regularly. This adds an additional $100 billion to $300 billion in health care costs each year.

The trend has been perpetuated by the fact the Americans with private health insurance have found themselves paying more for prescription drugs in recent years.

19 http://fortune.com/?s=why-were-losing-the-war-on-cancer%2F

20 http://www.nejm.org/doi/full/10.1056/NEJM199705293362206

21 http://www.researchgate.net/publication/46555895_Are_Increasing_5-Year_Survival_Rates_Evidence_of_Success_Against_Cancer_A_Reexamination_Using_Data_from_the_U.S._and_Australia/file/e0b49521388f04d272.pdf

22 Hartung DM, Ketchum KL and Haxby DG. (2006) An evaluation of Oregon's evidence-based Practitioner-Managed Prescription Drug Plan.*Health Affairs* 25: 1423-1432.

23 http://www.wolterskluwerhealth.com/News/Pages/Symposium-Focuses-on-Disparities-in-Cardiovascular-Disease.aspx

Why? Because insurance companies are paying less. In 2000, people under 65 with private health insurance paid 37.2 percent of their prescription drugs costs out of their own pockets.

Many Americans mistakenly believe that this increase in out-of-pocket expenses is the result of higher drug costs. The data reveal otherwise.

In fact, the growth in prescription drug co-payments outpaced the growth rate of prescription drug prices four to one.

It's easy to see why plans to increase the co-pays for Medicare beneficiaries will also have serious adverse effects on the health of our seniors, as well as on our health care system as a whole.

Unable to afford their prescriptions, many Medicare enrollees will begin treating strict obedience to their drug regimen as a luxury, not a necessity.

As more and more seniors choose to abandon their treatment, health care outcomes will suffer, as prices soar even higher.

Making health care decisions based solely on cost is a losing strategy over the long term for both the state and for the health of its residents.

But maybe those are the kind of shortsighted, budget-driven results you get when cost-over-care bureaucrats run your health plan.

THERAPEUTIC INNOVATION IS THE GREAT EMANCIPATOR

Referring to the Model T, Henry Ford famously said, "Any customer can have a car painted any color that he wants so long as it is black." That worked out fine – until there was competition. Choice is the great emancipator. The same is true when it comes to healthcare – and a lot more important.

When it comes to the Affordable Care Act, patients can access any medicine they need — as long as it's on the exchange formulary. Sure, the ACA limits the degree to which insurers can charge higher premiums for sicker patients, but ObamaCare plans found a way around these rules: impose higher out-of-pocket costs for all or most specialty drugs. High co-pays effectively remove choice from the system for many patients.

The breakdown of Silver plans (the most popular category) is particularly revealing. In seven classes of drugs for conditions from cancer to bipolar disorder, more than a fifth of these plans require patients to shoulder 40 percent of the medicine's cost. And 60 percent of Silver plans place all drugs for illnesses like multiple sclerosis and rheumatoid arthritis in the "formulary tier" with the highest level of cost-sharing.[24]

Nearly every Silver plan across the country, in fact, puts at least one class of drug exclusively in the top cost-sharing tier. In effect, this leaves patients with a given condition — whether HIV or Crohn's disease — without a single affordable treatment option. Silver is the new Black.

And those signing up for Silver plans don't know what's going to hit them until they access the healthcare system. It's time, at least, for that to change. It's time for exchange transparency.

The American Legislative Exchange Council (a forum for state legislators and private sector members to collaborate on model legislation that members can customize and introduce for debate in their own state legislatures) has drafted the "Exchange Transparency Act." Whatever your position on ObamaCare (or, if you prefer, the Affordable Care Act), it makes a lot of sense. If there's nothing to hide then there shouldn't be a problem.

Exchange Transparency Act

Summary

Requires health plans offered through a state-based health exchange to provide specific information in order for consumers to draw meaningful comparisons between plans.

Model Policy

Section 1. Title. This Act shall be known as the "Exchange Transparency Act."

Section 2. Form of Information Available to the Public and Disclosures Required of Health

Insurers. The following information about each health plan offered for sale to consumers shall be available to consumers on {insert state-based exchange website} in a clear and understandable form for use in comparing plans, plan coverage, and plan premiums:

(1) The ability to determine whether specific types of specialists are in network and to determine whether a named physician, hospital or other health care provider is in network;
(2) Any exclusions from coverage and any restrictions on use or quantity of covered items and services in each category of benefits;

24 http://www.healthpocket.com/healthcare-research/infostat/prescription-drug-coverage-and-affordable-care-act#.U_sp9UgQGiw

(3) A description of how medications will specifically be included in or excluded from the deductible, including a description of out-of-pocket costs that may not apply to the deductible for a medication;
(4) The specific dollar amount of any copay or percentage coinsurance for each item or service;
(5) The ability to determine whether a specific drug is available on formulary, the applicable cost-sharing requirement, whether a specific drug is covered when furnished by a physician or clinic, and any clinical prerequisites or authorization requirements for coverage of a drug;
(6) The process for a patient to obtain reversal of a health plan decision where an item or service prescribed or ordered by the treating physician has been denied; and
(7) An explanation of the amount of coverage for out of network providers or non-covered services, and any rights of appeal that exist when out of network providers or non-covered services are medically necessary.

Section 3. Enforcement. The {insert state insurance commissioner} may impose fines on any entity failing to meet the requirements of this act.

What's the ETA of the ETA? Stay tuned.

PREAUTHORIZATION: PRESCRIPTIONS AND PROSCRIPTIONS

News that Blue Shield of California will no longer pay for Avastin to treat breast cancer, though "exceptions may be considered on a case-by-case basis," makes a nationwide survey by the Coalition of State Rheumatology Organizations (CSRO) big news. The survey shows broad dissatisfaction with the insidious practices of preauthorization and step therapy – specifically the ways in which it impacts the ability of physicians to treat patients.[25]

(Prior authorization, also known as pre-authorization, pre-certification or prior notification, is an extra set of steps some insurance carriers require before determining whether they will pay for a medical service or prescription medication. The physician, or other medical provider, is required to obtain approval from the insurance carrier before the carrier will agree to cover the cost of the medical service or prescription medication. Step therapy, also referred to as "fail-first," requires patients to "fail" on one or more less costly medications before the health insurance carrier will agree to cover a more expensive medication, even if a physician thinks it is a better option for the patient.)

"Rheumatologists around the country have increasingly voiced their concerns about the impact of health insurance protocols such as prior authorization and step therapy on patient care," said Reuben Allen, CSRO Executive Director. "These practices are stripping rheumatologists of the ability to direct the most appropriate and effective courses of treatment, which causes patients to suffer delays or outright denials of proper medical care. Individualized treatment plans that can restore, enhance, and preserve quality-of-life over time are essential to rheumatology patients and their struggle against autoimmune and destructive arthritic disorders."

Specific findings of the CSRO survey include:

Nearly 99% of rheumatologists surveyed say they have had to alter treatment plans including changing prescription medications to accommodate restrictions imposed by patient health insurance carriers;

91.5% of survey respondents say prior authorization has a "negative" to "very negative" effect on their ability to treat patients;

Nearly 97% of rheumatologists surveyed agree, "There should be enforceable legislation to regulate restrictions that insurance companies place on health care providers in regards to treatment modalities they prescribe for their patients;"

Nearly 98% of survey respondents agree that decisions about what medications are best for a patient should be made by the patient's own health care provider and not by the health plan or insurance company;

Nearly 73% of respondents say they are only "sometimes" or "rarely" able to easily determine what procedures will be covered by a patient's health plan at point-of-service;

52.2% of rheumatologists surveyed say they have considered re-establishing their practices as fee-for-service only because of prior authorization constraints.

Currently, prior authorization and fail-first protocols are primarily paper-based, and non-standardized. Each insurance carrier has its own set of requirements, which can vary among plans, even within the same

25 http://www.csro.info/

carrier's portfolio of coverage options. To meet prior authorization requirements physicians must complete a time-consuming series of faxes, phone calls, emails, input of data into insurance carrier web sites and, in some cases, letters.

In response to the survey, CSRO also announced its recommendations to policymakers in addressing prior authorization protocols by ensuring that:

Prior authorization should be standardized and improvements in the current process can be made by the adoption of a universal prior authorization form;

Electronic prescribing platforms are provided on neutral and open platforms that do not advance the commercial interests of any particular participant (e.g., health insurers, hospitals, pharmacy benefits managers, pharmaceutical companies, etc.) to the potential detriment of the patient;

Adjudication of prior authorization requests occurs within a reasonable time frame (hours as opposed to days or weeks); and communication between physicians and payers should be on a peer to peer basis;

Electronic prescribing platforms include access to information about all FDA-approved medications and medical services without restrictions;

Complete, up-to-date information about prior authorization and fail-first criteria is available through electronic prescribing platforms at point-of-service;

Prior authorizations should not be required on a repeated basis. It should only be necessary with a change in medication dictated by a change in clinical status;

Prior authorization should not be necessary for low cost medications; for example, prednisone and methotrexate.

"Physicians are responsible for the administrative costs associated with meeting prior authorization and fail first requirements.

"Prompt diagnosis and specially tailored treatment can improve the long-term outcomes of patients with rheumatologic diseases," said CSRO's Allen. "State legislatures and insurance commissioners should take appropriate steps to ensure that patients suffering from chronic rheumatic diseases and chronic pain do not have to needlessly suffer."

WHAT ABOUT ADHERENCE?

Advancing adherence requires innovation of a different kind

When it comes to medication adherence, is knowledge power? Or is that even the right question. Perhaps patients, and healthcare professionals (and payers and regulators) also need to learn how to share knowledge. When it comes to medication adherence in the 21st century, the medium is the medicine.

Are package inserts, hard copy med guides, brochures and "starter packages" still the best way to make important healthcare information "sticky?" Were they ever?

Zig Ziglar once said, "If what you're doing isn't working, try something else. If what you're doing *is* working, try anything else." While there are certainly success stories and validated methodologies in the battle for better adherence/compliance, we're losing the war. It's time to reconsider what we're doing.

Consider the National Council on Patient Information and Education's report, Accelerating Progress in Prescription Medicine Adherence: The Adherence Action Agenda: A National Action Plan to Address America's "Other Drug Problem."[26]

The report advocates for an expanded investment in patient/provider education and engagement tools to help clinicians implement best practices for medication adherence and counsel their patients on the importance of following treatment plans.

Will the tried-and-true ways enhance safe use or drive positive therapeutic outcomes? Or do today's patients (also known as consumers) want their healthcare intelligence the same way they're getting enlightenment and orientation on all the other things they want and need to know about the daily details of their lives? In short, on tablets and smart phones.

"Human action can be modified to some extent, but human nature cannot be changed." Those are the words of Abraham Lincoln and they pretty well sum up a major issue in American healthcare – adherence/compliance. There's a lot to be done. There are a lot of good ideas. There seems to be a lot of commitment. But more than the better angels of our nature are required.

What are the issues we are trying to impact? There are six and they are linked: Sub-optimal patient outcomes (The Big Kahuna), sub-optimal physician metrics (pay-for-performance), lower healthcare costs (for payers), sub-optimal profits (for pharmaceutical companies), impact on safe use programs – specifically in reducing medical errors and, lower healthcare costs for society.

Some think that (as with REMS), the FDA should insist that new drugs have adherence/compliance plans that can be monitored and improved through iterative learning. Should sales reps (or, better yet, MSLs) "detail adherence/compliance programs and share validated tools for adherence/compliance "triage?" The only thing that's currently on the table is that the FDA has promised

26 http://www.bemedicinesmart.org/Medication_Adherence_Fact%20Sheet.pdf

to make MedGuides more user-friendly. (We can do better.)

All these are important, but what we really need are solutions that impact social conditioning … and that means using innovative platforms such as social media — and specifically apps.

Not apps that are medical devices (although they too play an important role), but apps that remind, cajole, educate, praise, and assist patients in their quest for better health. Apps are at the nexus of safe use, treatment outcomes and patient satisfaction. And it's not science fiction. And as Philip K. Dick wrote, "Reality is that which, when you stop believing in it, doesn't go away."

At present, there are some 17,828 healthcare and fitness apps and 14,558 that can be deemed "medical."[27] Dr. Janet Woodcock, the director of FDA's Center for Drug Evaluation and Research said that the use of social media by healthcare companies is important because social media "is where the people are." And that's not just Facebook and Twitter and YouTube — also true when it comes to apps.

According to a national survey by Adherent Health Strategies of 2,216 patients (age 18+ who take at least one prescription medication per day) show that whether you're a Millennial or a member of the Greatest Generation, you're using apps via a smart phone or a tablet.[28]

And when it comes to medication management, only 4% of the sample preferred a web site that was brand specific and only 8% want manufacturers' programs sent to them via e-mail.

Will our socio-economic "technology gap" lead to a more pronounced "adherence/compliance gap?" It's an important question. That's why it's crucial we remember there is no one-size-fits all solution. But that's mustn't mean we disregard the reality of the growth and pervasiveness of apps, *mobile* apps. Let's face it, when it comes to mobile phones, any gap is rather narrow.

Apps for adherence/compliance are "safe use" apps. Apps that can be "prescribed" by physicians to their patients are the wave of the present. Adherence/compliance "app-ens" and patients, physicians, payers, pharmaceutical companies – and society benefit.

As Walter O'Malley (the man who moved the Brooklyn Dodgers to Los Angeles) once opined, "The future is just one damned thing after another."

COMMUNICATING INNOVATION

Ian Read (Chairman and CEO of Pfizer and the current Chairman of PhRMA) recently published a piece on LinkedIn under the title, *Why Society Needs a Vibrant Pharmaceutical Industry: Improving Patients' Lives.*[29]

Towards the end, Read writes:

> *I recognize that there are differing views when it comes to society's perception of the pharmaceutical industry. Many believe we are more focused on making profits rather than finding cures for patients, even though the industry has a long-standing commitment to providing patients access to needed medicines through many different programs globally. There is also a perception that we do not operate in an open and transparent manner when it comes to our clinical data and financial relationships with healthcare providers. This view lingers despite the significant steps that have been taken to increase transparency, even in the face of the current debate that rages over an individual's right to privacy.*
>
> *As an industry we are working diligently to improve our standing in society. We understand that we have a great responsibility. We are at the center of society's desire and expectation for delivering potential cures and new lifesaving treatments. We will continue to fulfill that vital purpose.*
>
> *Patients are waiting and we are working hard every day to earn their trust.*

Fine sentiments and well-crafted words – but working hard alone isn't enough to earn trust. Pharma must work hard *to do the right thing.* What does that mean?

Mr. Read offers the following:

> *Over the course of the past 50 years, this industry has tackled some of the leading causes of disease and life-threatening illnesses.*
>
> *For example, today the number of people who have died from heart attacks and strokes has declined. In 2008 around 16 percent of the U.S. adult population was taking a statin to reduce cholesterol. This translated into 60,000 fewer heart*

27 http://www.burrillreport.com/printer_article-facing_an_adherence_and_compliance_gap.html

28 http://www.adherenthealth.com/whatsnew/index.php

29 https://www.linkedin.com/pulse/article/20140612143605-322581966-why-society-needs-a-vibrant-pharmaceutical-industry-improving-patients-lives

attacks, 22,000 fewer strokes and 40,000 fewer deaths.

An article published in 2010 by the Journal of Health Economics found that from 1988 to 2000, improvements in cancer survival created an estimated 23 million additional life-years over this period.

And according to the World Health Organization, immunizations save an estimated 2.5 million lives every year. For every $1 the U.S. spends on childhood vaccinations, we save $10.20 in disease treatment costs.

Consider that pharmaceutical innovation has accounted for 73 percent of the total increase in life expectancy between 2000 and 2009 across 30 developing and high-income countries.

Those are, by any measure, extraordinary accomplishments. Why then is the biopharmaceutical industry so roundly pilloried in the press and so low in the general view of public opinion? *Working hard*, it seems, is not enough.

The genesis of Mr. Read's philosophy began (at least publically) this past April (2014), PhRMA held its 14th annual meeting in Washington DC.

During his inaugural remarks as incoming PhRMA board chair Read shared his concern about the industry's failure in getting the message out about "the value we generate." His key message, "We need to fix the misperception gap."

Specifically he talked about the industry's need to broaden the conversation from the economic performance of biopharmaceutical companies to the value that accrues to society and called for a "dialogue with society." Bravo.

He asked, "Where are the headlines?" They're not about societal value – and they need to be. There's a strong story to tell. It's not happening. And it needs to, because minus that narrative, nothing the industry wants to make happen (with government being a focus since the meeting was in Washington, DC) will be possible.

Read called for "industry speaking for itself." After all, if you can't be your own best advocate, you're suspect in the minds of many – and rightfully so. He spoke to "better ideas and clarity" versus "more tactics."

They were the right words – but what's happened since that fine oration? One thing that comes to mind is the debate over the price of Sovaldi. Another is ASCO's decision to get into the comparative effectiveness game. Both of these issues are tailor-made for a Read-led discussion on price vs. value. And neither has generated a regular and robust response from either industry or it's trade association.

That's not to say there hasn't been a debate. The Center for Medicine in the Public Interest (www.cmpi.org) has been writing and speaking with both force and frequency on these issues as have other public policy institutes (aka, "think tanks") and thought leaders across the healthcare policy spectrum.

But there has been precious little in terms of by-lined commentary from pharmaceutical executives – especially of the C-suite variety.

To achieve Ian Read's noble goal of "dialogue with society," there needs to be a… dialogue. And it can't only be via third party groups – as worthy and invested in the debate as they are. Pharma must speak for itself. Can you quote any useful answers from the folks at Gilead relative to Sovaldi pricing?

Pharma must embrace a new paradigm. Rather than focusing on traditional ROI (Return on Investment), they must now also consider Return on Integrity.

Integrity comes in many forms. Honesty. Virtue. Morality. But it also means (in more common parlance) "doing the right thing." It means not waiting to be told to do it or waiting to see what others do first. Integrity means being principled and, as my father used to say, "A principle doesn't count until it hurts."

The current risk-averse position of many in pharma does nothing if not reinforce the general perception that the industry only cares about profit. Mr. Read's words hit the nail on the head – *change is required and we must drive it!* But the gearbox has remained firmly in neutral.

For there to be Return on Integrity, integrity must first be demonstrated – publically demonstrated with names attached. This is especially true in the age of social media where the public is watching and commenting. And nature abhors a vacuum.

Read called for "industry speaking for itself." After all, if you can't be your own best advocate, you're suspect in the minds of many – and rightfully so. He spoke to "better ideas and clarity" versus "more tactics." That's a foundational shift and a timely one. Innovators win when the discussion is about the future.

INNOVATION: KEEPING OUR EYES ON THE PRIZE

The US healthcare system may be broken, as such sages as Michael Moore suggest, but it's not likely to be fixed as long as our domestic debate remains stuck on the cost of prescription drugs. Meanwhile, Alzheimer's Disease, obesity and diabetes are becoming national epidemics. Talk about sicko.

Imagine American healthcare spending as a dollar bill divided into 100 pennies. How many pennies do you think represent spending on prescription drugs? Sixty? Eighty? Wrong. The answer is 11.5 (with just under 9% being spent on innovative, on-patent medicines). The other 88.5 represent everything else—from doctor visits and hospitalization to administrative charges and insurance.[30] (If this is news to industry professionals, imagine how enlightening civilians might find it.)

Put another way, which is the bargain: a hospital stay at about $7,500 a day, or innovative medicines that help keep you healthy and productive? Clearly, fewer cents make more sense.

Yet these and many other facts backing pharmaceuticals as a sound healthcare investment have been twisted to suit the agendas of politicians, pundits, and other competing stakeholders. It goes relatively unreported that insurance companies continue to increase their monthly premiums without really explaining why. The industry claims its costs are increasing because prescription drug costs are busting their budgets. But prescription drugs account for only a small part of monthly insurance-premium hikes. From 1998 to 2003, insurance companies increased premiums by an average of $104.62 per person. During that same period, drug costs rose by $22.48.[31]

Still, it's true that a majority of Americans with private health insurance are spending more for drugs—not only because they're taking more but also because their insurance is paying less. And it's no surprise that with rising pharmacy co-pays—the only healthcare costs that many of us actually see and feel—we tend to swallow the lie that increased healthcare costs are Big Pharma's fault.

Should we blame "Big Insurance"? Out-of-control out-of-pocket expenses cause many patients to stop using prescription drugs for controllable chronic conditions. The unfortunate result is that visits to the ER have jumped by 17 percent and hospital stays have risen 10 percent.[32] And a new Integrated Benefits Institute study shows that when employers shift too much of their healthcare costs to employees, the companies lose more than they save, through absenteeism and lost productivity.[33]

Should we blame our skewed priorities? American healthcare often works miracles when people become very ill, but it needs to do a better job with preventive care. Equally to blame is the fact that we spend a disproportionate amount of our healthcare budget for end-of-life care.

But rather than tangle up the already volatile healthcare debate in ethical arguments over whose life is worth more, it would be smarter to shift the focus to keeping people healthier longer. Earlier diagnosis and care are crucial to the future health of both Americans and American healthcare—and pharma has a starring role here.

Why? Because prevention is our first line of defense. Now is the time to promote prevention, so that we have the funds to invest in promising treatments for conditions like cancer and Parkinson's disease. We are on the cusp of a pharmacogenetic revolution that will finally make personalized medicine a reality.

We cannot afford, in terms of dollars or lives, to continue the blame game. In order to deliver on the promise of affordable and quality healthcare for all citizens, all the players in the healthcare debate must work together. At the end of the day, we should unite against our common enemy—disease.

And our most potent weapon in innovation.

30 http://www.innovation.org/index.cfm/insidedrugdiscovery

31 http://www.cms.gov/CCIIO/Programs-and-Initiatives/Health-Insurance-Market-Reforms/Review-of-Insurance-Rates.html

32 http://www.cdc.gov/nchs/data/nhsr/nhsr007.pdf

33 http://www.ibiweb.org/community-events/detail/more-evidence-that-improving-health-can-improve-productivity

From the Boardroom

Characteristics of great bioscience leaders

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ABSTRACT

Good leaders in the biosciences share multiple characteristics, starting with certain personality traits – some that are particularly unique and important to the bioscience sector. They also understand certain concepts, which are necessary for bioscience companies to be successful.

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Good leaders in the biosciences share multiple characteristics, starting with certain personality traits – some that are particularly unique and important to the bioscience sector. They also understand certain concepts, which are necessary for bioscience companies to be successful.

LIMITATIONS & PROBLEM SOLVING

The first, vital characteristic of good leaders is recognizing that their knowledge is limited by the scope of their personal experiences. No one person can know everything – even one deemed an "expert" in an area of a particular field. An individual's awareness is limited to what has already been discovered and processed, or to what they have been able to thus far ascertain. This also applies to a leader's team and the firm they represent. No one individual or group can know everything and should not expect to.

It is very important for people in leadership positions to understand that there are limits to their personal knowledge and experience; and equally, that there are limits to the information held by their team and organization. Logic dictates that, if people, teams, and institutions all have limits on their data, experiences, and knowledge, then people can not be experts all the time. A good leader understands this.

Yet, people in leadership roles often insist on portraying an image of being the expert and are afraid of these three, little words: "I don't know." Why? Possibly the fear of looking inferior or lacking in some way. Those who are comfortable with publicly identifying their limitations in a subject or area of expertise are much better leaders because they respect the unknown — perhaps, even relish it, as scientists. They will perform additional research when necessary to seek an answer; and the final solution they provide and decisions they make will be much sounder because of it.

It is always refreshing to hear people, especially those in power or leadership positions, admit they don't know an answer to a question. True leaders are problem solvers. They will always follow up with something like, "…but I will certainly find out and get back to you with an answer."

Smart leaders and also not afraid to admit a mistake; and if they do, they will make sure they correct it. When they understand and acknowledge possible limitations, they will continue the process of data gathering and problem solving long enough to collect an adequate amount of data to correctly and efficiently resolve an issue or challenge the first time. An effective leader's integrity seeks to have an answer for an unresolved question.

THE PATIENT COMES FIRST

Those who work in the biosciences indirectly but ultimately deal with end-customers who are medical patients. Bioscience companies run a business, but a business that holds customers' lives in their hands. Therefore, the best leaders build a corporate culture around a "patient first" mentality.

One leader who ran a bioscience company effectively promoted this philosophy by reminding staff to

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ask themselves a simple question every day: "Would you put this implant in your mother or father tomorrow?" If the answer was no, then he would consider an immediate, world-wide product recall.

In another company, every employee had the ability to pull this imaginary cable in a passenger car that would effectively "stop the train." The employee could run their concern to the corporate office, and a decision would be made: they would continue operations without change; make a change; and, if necessary, put a product recall into effect that very same day.

This policy also positively influenced the behavior of that firm's outside sales people in how they handled customers and their sales. By empowering their employees in this way, they also strengthened their knowledge that the firm appreciated and respected their contributions. Every individual at the company had a say in the testing and making of our products. They understood that, at this great company, their opinions mattered.

OPPORTUNITIES TO IMPROVE

A good leader knows that mistakes or problems can turn into opportunities. In one particular case, the company determined that the steam sterilization machines used at that particular hospital had been wiped down using a detergent that was not completely removed during cleaning. As the sterilizer filled with steam, some of the residual detergent landed on the company's implant, turning the white hydroxyapatite coating a bright blue. It was only a few molecules deep, and completely biocompatible, so it would not have harmed the patient; but the unexpected color created anxiety and indecision over the implant's safety. The surgeon didn't want to postpone the operation, but the company's CEO promptly ordered a halt and a thorough investigation.

What the systematic analysis of the incident taught all involved was that on-site sterilization was an uncontrolled variable and potentially problematic for future products. To address the issue, the firm began selling the product packaged and sterilized in hermetically sealed pouches and boxes, eliminating the on-site sterilization process and any opportunities for unforeseen incidents.

The surgeon, although initially a bit upset about having to make a change from a custom made device to an off-the-shelf device, was later thankful and full of praise. He commended the firm for multiple reasons: first, that the company CEO came to the operating room personally to protect the patient; that their focus was on the patient and not on the sale, making excuses, or performing a CYA drill; that the company researched and resolved the origin of the mystery quickly and at significant expense, with transparency; and lastly, that they reported back to the surgeon promptly. He was so impressed that he ordered many more custom implants over the next few years and became a vocal spokesman for the company.

From this experience, the company ended up making a safer and more robust product, with fewer opportunities for problems or future lost sales. In the end, it was a success for the company, both in terms of patient safety, employee motivation and training, and surgeon marketing. The firm additionally improved our process for delivering safe and effective implants.

Good bioscience leaders understand that the right thing is sometimes an incremental cost in the short term, but when handled correctly and with integrity, it is almost always an economic win for the company in the intermediate to long term.

THE CONSEQUENCE OF SMALL CHANGES

We have seen how a small change outside of the firm can impact product quality. Leaders must also consider internal variables. A leader who understands the limits of knowledge and experience is perhaps more critical in the bioscience, biomedical, medical, and pharmaceutical fields than in any other. The business of bioscience involves treatments, medicines, implants, instruments, tools, and therapies for human beings. Therefore, industry leaders must be especially aware and respectful of what they don't and may not know, as mistakes are costly. Many aspects of the business often literally have life or death consequences on our ultimate customers: the patients. Little and seemingly unimportant changes to the product or the manufacturing process can have a profound effect on the patient population, and these effects can be dramatically positive or negative. There are numerous cases where a small change in the design, testing, or manufacturing of a device resulted in hundreds or even thousands of revision surgeries or deaths.

One of the most widely reported and early medical device failures was with the Shiley artificial heart value, where the welded struts on the implant failed due to cumulative fatigue fractures from the small repetitive loads put on the device by the pumping heart. This could have been easily avoided using relatively simple fatigue and fracture failure mechanics and laboratory, repetitive testing.

Another famous case one still reads about in the press is the Sulzer artificial hip socket failure. Sulzer engineers made a small change in the manufacturing operations that they felt was too insignificant to warrant any additional testing before implementing the change. Shortly after the change was implemented, the artificial

hip socket implants began loosening at an alarming rate. At first, Sulzer blamed these negative, clinical outcomes on surgeon error and poor instrumentation (both of which were still the company's responsibility to address with training and instrument monitoring). It turned out that the change in the sequence of manufacturing operations resulted in microscopic amounts of manufacturing lubricant residue remaining on the implants. This lubricant residue prevented the favorable bony ingrowth from occurring, which normally provides permanent fixation of the implant to host bone.

At the time, Sulzer was a multi-billion dollar, highly respected, Swiss implant manufacturer. The lawsuits mounted and, as part of the class action settlement, the plaintiffs were awarded a significant ownership position with company stock. Shortly thereafter, the plaintiff's forced the liquidation of the company and a sale of assets to Zimmer Holdings, a competitor in Indiana.

In the case of Sulzer, a small change in the sequence of manufacturing operations effectively killed the company. Had the engineers and their superiors realized that even small changes can have unforeseen and serious consequences and that they should have researched and tested again before releasing to the public, they would still be the Fortune 500 company they once were. It's a sad outcome that could have been easily prevented with foresight and acceptance that even the tiniest change can lead to serious results.

Good leaders take into account the safety issues involved, and they carefully weigh every product detail and proposed modification. Realizing the limits of their current understanding and insisting on researching and understanding the long-term effects of changes and decisions, no matter how small, is mandatory for maintaining public trust and safety.

CREATING GREAT TEAMS

Experience shows that many so-called "self-starters" had been raised to be very independent individuals, sometimes to a fault. This becomes problematic when leaders who are capable of doing everything themselves often don't give enough credit to the people that work under them, leaving good talent to waste or creating ineffective teams.

Successful leaders, on the other hand, recognize that, as Aristotle said, "The whole is greater than the sum of its parts," surrounding themselves with people who are better at their individual jobs than the leader alone would be. Great teams are composed of talented individuals. A CEO, for example, is the generalist who speaks the languages of the individual department heads and provides the grout between the tiles that make up the mosaic of the company and its culture. Good leaders are not opposed to surrounding themselves with smart people; on the contrary: they demand it. Within each department of a company, managers find and hire the best experts available. In effect, good leaders create great teams.

A good leader also understands the unique nature and impact of the industry in which they lead. Bioscience is unique in several ways, the first being the impact the industry has on individual lives. At the very least, the products and services sold in this industry improve the well-being of individual consumers and, in many situations, save lives. This is the singular fact that drives not just bioscience companies, but many of the people who work in this industry. Good leaders recognize this and how it motivates companies and individuals, and they run their organizations accordingly.

UNDERSTANDING DIFFERENT PERSONALITY TYPES

Some industries benefit from similar personalities populating most of their workforce. For example, while this is not a stereotype, smart leaders in the finance industry understand how to motivate the dominant personality type that thrives in that arena.

Bioscience is populated by a wide range of personality types, which include scientists, engineers, former government officials, and a wide range of positions and skill sets. A smart bioscience leader understands the different types of personalities dealt with on a daily basis, and can bring out the best in individuals. This leader will motivate people according to their individual drives and passions and combine varied skill sets to work together as a cohesive team. While each industry and each company is populated by individuals with different motivations, bioscience leaders seem to have the ability to take individual staff motivations and easily mesh them together to create effective and efficient teams.

THE ROLE OF GOVERNANCE & THE LAW

One, unique characteristic of bioscience is the role government plays in the industry. The Government regulates medical and pharmaceutical products and services that bioscience provides, and also takes a key role with our medical system. Smart leaders not only comprehend this, but also have an understanding of how this role in government works. As such, they are better positioned to understand the effects governance plays upon their organizations.

For example, suspending a medical procedure due to a possible defect is not only the ethical approach, it's the law. In the case of the blue implant, the firm additionally reported the event to the FDA through a Field Incident Report, as required by federal law. The accurate reporting of questionable or adverse events in clinical practice – whether ultimately posing a risk to the patient or not – is legal policy. Breaking this law is considered Public Endangerment by the National Government and a Felony punishable with prison time and very large fines. It is not an issue to be taken lightly by company leaders or their employees.

EMBRACING TECHNOLOGY

Technology plays a key role in the biosciences. As with other technical fields, technological advances drive the introduction of new products and services and companies frequently establish themselves by offering products and services that are based on new, technological advances. Effective leadership in bioscience means understanding the importance and proper place of technology in the services and products that are provided. To achieve the implementation of technology effectively, a company requires a certain comfort and enthusiasm with technology in general. Good leaders understand that technological advances drive the benefits of the industry. They know how to motivate key individuals within their company who can utilize technology to further the advancement of products and services.

That said, strategic leaders also balance enthusiasm for technology with the understanding that the ultimate goal is the benefit and well-being of patients. Therefore, technology should not interfere with this goal or be the main focus of results, but rather an enhancement to the tools used in the final care of the patient.

To summarize, great bioscience leaders possess characteristics shared with other leaders, while also having skills, experiences, and considerations unique to their field. Like many, successful leaders, a bioscience executive understand their limitations; they are not afraid to admit deficiencies in their knowledge or admit mistakes. They recognize opportunities for improvement for both company policy and products and services. They create great teams, hire the best and the smartest, while understanding what motivates their people. More common to the bioscience industry however, they must problem-solve thoroughly, providing sufficient research and data sampling, without needing to repeat efforts. They need to be aware of how the government and Law affect their business. They never forget that the patient comes first, and that even the smallest changes can create the greatest of errors. Lastly, effective bioscience leaders understand and embrace technology as a tool to create better products and services.

Case Study

Cell therapy: Early process development and optimization of the manufacturing process are critical to ensure viability of the product, quality, consistency and cost efficiency

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ABSTRACT

In recent years cell therapies have evolved and matured, moving from academia to industry. Scale up of a process is the natural path of any product evolutionary development and maturation, this process not only allows higher manufacturing capacity to meet demands but rather to increases the yields and reduces cost of goods. Cells are living things that react to the environment and conditions in which they grow, therefore process changes should be done as early as possible. The traditional 2D culturing systems can not be truly up scaled, therefore there is a need to advance to bioreactors that will influence the product. Additionally, in order to make cell therapy viable, the cost of manufacturing is critical. Cost drivers such as media, serum, footprint, human resource and infrastructure must be optimized without changing the cells critical quality attributes. The paper analyze the main cost drivers on the cost of goods and is based on the experience of cell manufacturing in both traditional 2D and three dimensional (3D) bioreactor systems produced in Pluristem therapeutics GMP site. Furthermore, the paper discussed possible process development steps to insure cost efficiency emphasizing the need and benefit of early process development investment.

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INTRODUCTION

In recent years cell therapies have evolved and matured, moving from academia to industry. In cell therapy cellular material is injected into a patient. The injected cell therapy product (CTP) usually consists of intact living cells. While research has advanced from the preclinical stage to early phase clinical trials, few phase 3 trials have been conducted. There are many reasons for the slow progress. These include the complexity of cell therapy itself, and the lack of mature regulatory environments and technologies to support product development. Also contributing are differences of opinions about the merits of the autologous versus allogeneic approach, the various tissue sources for stem cells (embryonic, adult bone marrow, umbilical cord, placenta, adipose tissue, etc.), and the types of cells to be used in development (hematopoietic, mesenchymal stromal, progenitor). Furthermore, recruitment of patients for clinical trials can be challenging because patients are unfamiliar with stem cell therapy. Finally, the challenges of scaling of manufacturing also contribute to the small number of late phase clinical trials and the lack of regulatory approvals and guidelines, such as from the US Food

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and Drug Administration (FDA), for cellular therapy products.[1,2]

At the time of writing there are 8,662 ongoing cell therapy trials worldwide[3] (http://www.clinicaltrials.gov/). There are two hundred and fifty two studies of mesenchymal stem cells, and of these, only 22 studies are in phase 3. These are equally divided between allogeneic and autologous. Nine of the twenty two are being conducted in the Europe, the United States and Canada, while 13 are in China. The surge in the number of clinical trials, even though most are in early stages, will eventually drive the entry of therapies into the market. Companies must begin evaluating not only the science and clinical data behind the therapies, but also their commercial viability.

This paper will discuss the main cost drivers of the manufacture of allogeneic mesenchymal adherent cells, and the need for early process development to ensure the commercial viability of a product taking into account quality, quantity and cost. Several papers have discussed the need for automation or calculated theoretical effects on COGs based on different algorithms.[4-8] This paper is based on knowledge gained from Pluristem's experiences manufacturing cell therapies using different technologies.

Several publications[7,12,13] reviewed the active allogeneic clinical trials and reported doses that ranged from a few million cells per patient to a few billion. In order to treat indications requiring an average or low number of cells a minimum of 100,000 doses (patients) per year should be manufactured. In order to produce this many doses, cell therapy manufacturing platforms must be scaled up.

Scale up of the manufacturing process increases manufacturing capacity to meet growing demand and also increases yields per run and reduces cost of goods. Pharmaceuticals are regulated products, therefore, there are strict guidelines and limitations for process changes that ensure the quality and safety of products produced with scaled up production methods. Any change will require a study to prove that it did not impact the critical attributes of the product.[1,2]

Living cells react to the environments in which they grow by modifying their protein expression profiles, viability, and other characteristics. Any change in culture conditions, such as media formulation, serum concentration, serum replacements, duration of processing, and shear forces generated when cells are moved from culture dishes to bioreactors, will change cell phenotypes. If critical attributes are changed there can be changes in the Mechanisms of Action (MoA), efficacy and even safety of a cell product. These changes can potentially influence cell performance in clinical trials, so consistent culture conditions are necessary to produce reliable and reproducible data about a cell product. If changes in the methods of cell production occur in later stage clinical studies or after commercialization, these would necessitate comparability studies to prove that process modifications did not affect the safety or efficacy of the product, and that earlier trial results are relevant to later studies. It would be very difficult to prove comparability without additional clinical trials. Therefore, progressing through clinical trials without first developing and maturing the manufacturing process might be cost effective initially, but could result in a significant financial burden and risk later on when a company must prove comparability between cells made with early, small-scale production methods and cells created with industrial culturing technologies such as bioreactors.

ADHERENT CELL CULTURING

Adherent cells, such as mesenchymal stem cells (MSCs), are cultured on treated plastic surfaces and must adhere to these surfaces in order to grow. Small-scale culturing in laboratories is done on culture dishes with an average surface area of 75 cm^2, and with a typical yield of 1-2 million cells per dish.[6,8] An average harvest density of MSCs is approximately 25,000 cells per cm^2. However, cell therapy doses can range from a few million to over 500 million cells. Manufacturing on this scale approaches the limit of capacity of current technologies such as larger culture tray units.[6,8] Prior studies estimating the number and type of expansion technologies required to meet a demand,[4,6] were solely based on technical inputs such as surface area, size, and density. Table 1 illustrates the surface area required to culture MSCs on plastic culture surfaces for commercial-scale manufacturing, assuming an average dose of 50 million[7,10] cells for one to 100,000 net doses per run. A therapy requiring a 50 million cell dose per patient and a treatment target of 100,000 patients (doses) per year, might be manufactured at a rate of three lots/week (~120 lots/year)[i].

Each lot size would need to consist of 1,000 doses (50 billion cells per lot) with additional cells required for quality control; the additional cells are an average of approximately 10% — 25% of each lot.

Even though, theoretically, it is possible to culture large quantities of cells in multi-trays, several publications[6,9] report a maximum capacity of 50 billion cells per lot (100 doses) using this method due to long processing time and variation between vessels, incubations and hold times during processing that cannot be shortened and can affect the cells viability and quality.

i Assuming 40 working weeks per year

Table 1. Surface area and culture trays needed for cell therapy manufacturing

Dose/Run 50 million	10	100	1,000	10,000	100,000
Net Cell number	500,000,000	5,000,000,000	50,000,000,000	500,000,000,000	5,000,000,000,000
Surface area cm^2	20,000	200,000	2,000,000	20,000,000	200,000,000
Multitray 10 per lot	3	32	316	3,165	31,646
Multitray 40 per lot	1	8	79	791	7,911

Surface area needed to culture different amounts of MSCs at a ratio of 25,000 cells per cm^2. Based on this ratio volume and footprint of culture trays. The calculation is for net cells excluding those needed for quality control, which can increase the batch size by 10%-25%.

AVAILABLE CULTURING PLATFORMS

Adherent cells must be cultured on surfaces, so several technologies have been developed to allow better surface to volume ratios. Higher ratios can significantly reduce the required facility size footprint and allow for larger cell batches with smaller infrastructure. There are three types of available technologies known to the authors at the time of writing. One uses static cultures that have a static surface mimicking culture dishes, but grow cells in a more efficient manner; examples include hollow fiber based reactors or stacked and packed surfaces within a reactor, which maintain the same dimensions and ratios as the multi-trays to limit change and allow higher-scale production. The above methods are much more efficient and practical than simple culture dishes but are still limited in scale. Another technology allows better utilization of culture surfaces and includes the suspension-based micro-carrier solutions which change the dynamic environments of the cells; these methods can introduce shear forces that stress the cells and are also limited in the ability to perfuse media allowing optimization of the culture conditions. The most efficient technology available to date is the three-dimensional packed bed carriers which allow 70 times higher surface to volume ration, low shear forces and sufficient perfusion to allow media condition optimization.

Each of the above approaches will affect cell phenotypes differently and might affect quality and safety profiles of cell therapy products. The more the technology differs from the traditional dish culturing, the greater the probability is for change of the cells characterization and quality attributes. The earlier in the development process the modifications of the technology platform are introduced, even on a small scale, the lower the risk of needing large comparability studies and repetition of clinical trials later on. As the product moves through the stages of clinical development, the need for comparability for any change introduced will grow. Comparability studies in late-stage clinical development introduce the risk of failure, delays and increased costs.

TECHNOLOGY S-CURVE FOR CELL THERAPY MANUFACTURE

Technology S-curves illustrate the introduction, growth and maturation of innovations and have been used to analyze the evolution of technologies in several industry sectors ranging from semiconductors to renewable energy sources.[5,11,12] For cell expansion technologies, Samaria *et al*[7] had showed a conceptual illustration of a technology S-curve which was created by plotting the performance of each technology in terms of billion cells achieved per lot (when using the maximum number of units/devices per lot) against R&D effort and investment. The x-axis represents qualitatively the R&D effort required for a company currently using T-flasks to change to other cell expansion technologies.[7]

COST OF GOODS MANUFACTURED

Cost of Goods manufactured (COGs) is influenced by several elements; for this discussion the COGs is derived only from cost of material used for the manufacturing of the product per dose excluding the human resources, infrastructure and capital expenditure, which will be discussed later on in this paper. The main cost driver for cell culturing is the growth media which includes within it the serum portion (usually fetal bovine serum) of 5-20%.This component is responsible for approximately 40% of the cost of goods manufactured in a 10% serum culture. The cultured dishes are the second highest cost driver responsible for 14% of the total cost. Figure 2 represents the breakdown of cost of goods based on internal Pluristem Therapeutics data for two-dimensional culturing.

As can clearly be seen in Figure 2, the main cost driver is the serum within the culture media. In most

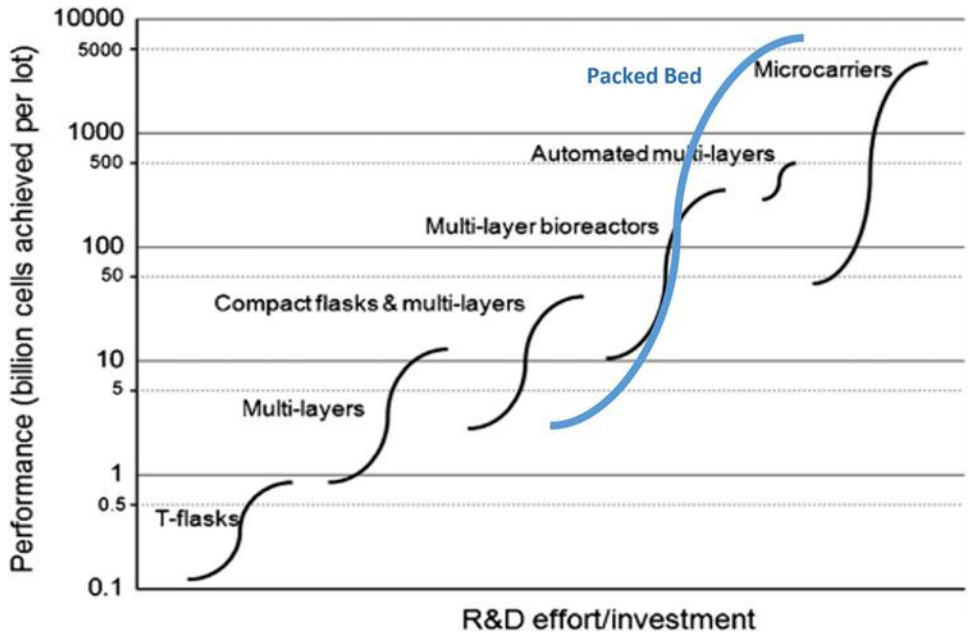

Figure 1: Technology S curve of lot size versus R&D cost. Quantity limitation per platform compared to R&D effort and investment, was taken from (Samaria *el al*)[7] with addition of the 3D packed bed carrier solutions. The data for the packed bed investment cost compared to alternative solutions came from Pluristem's experience and represents its carrier solution.

cases, these conditions are determined in early stage governed primarily by early serum concentration experiments and dish structure/volume that determines the surface to volume ratio. Serum and nutrient contents are critical elements in cell culturing of cells and can determine not only the phenotype and wellbeing of the cells but population doublings limit and speed resulting in the total cell yield and quality. As the serum is one of the most dominant cost factor (34%) its concentration and quantity can affect the total cost dramatically. Serum is a byproduct of the food industry and therefore limited in quantity and quality,[16] the higher the demand grows the higher the price will raise. Additionally, as growth factors which are part of the serum affect cell proliferation, optimizing serum concentration with experiments during early development can be very beneficial for both cost and yield. As cells proliferate and increase their concentration in the media the consumption rate of the media nutrients and serum components change and in many parts of the culturing the serum and nutrients are in access resulting in waste. On the other hand, in later stage of culturing as the cells proliferate, serum components and nutrients might be limited resulting in low cell quality, health and yields. Bioreactors such as the packed bed reactors allow media perfusion, which supports a constant and controlled media replacement, adjusted by measurement of critical nutrients such as glucose levels. This option allowing optimization of the nutrients and

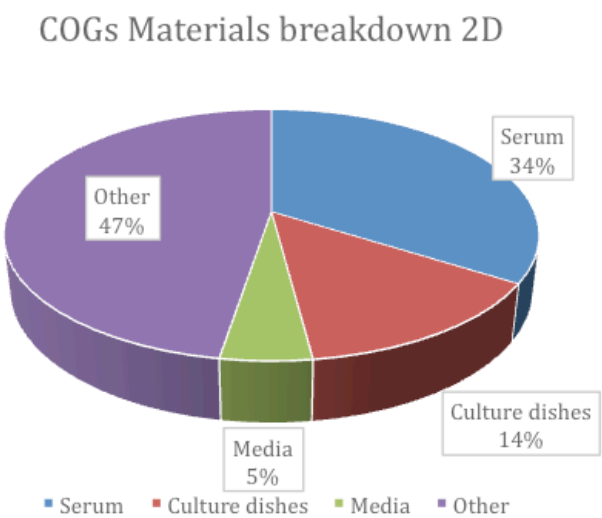

Figure 2: COGs material breakdown for 2D culturing, based on internal Pluristem therapeutics data for 2D traditional culturing. The data is calculated based on data coming from Pluristems experience of culturing a batch of 10 billion cells including material cost only.

maximal cell growth and health, resulting in healthier cells and higher yields. Table 2 shows the amount of media needed to culture cells in different quantities using 2D culturing; the estimates are based on Pluristem's 2D culturing experience. Table 3 shows results of the same

calculations done on the 3D packed bed systems that are part of Pluristem's culturing technology. It is clear that the move to controlled, packed bed bioreactors with good perfusion results in at least a 40% reduction in the media volume needed to culture the same amount of cells with a 2D technology. This data does not take into account any future media optimization which might lead to a greater cost reduction but represents the measurements to-date.

INFRASTRUCTURE NEEDS

Cell culturing for cell therapy is done in a sterile environment which consists of clean rooms, biosafety and laminar flow cabinets, incubators (or incubation rooms), preparation of clean rooms, media storage and preparation areas. Table 3 below shows the computed infrastructure size needed for culturing cells in 2D to meet market needs (120 lot/year of 1000 doses); the calculations are based on the small-scale 2D culturing that has been done at Pluristem, taking into account use of automation for larger scale manufacturing which might not be possible.

Table 2 shows the footprint of the clean rooms and media volumes needed for culturing of different lot sizes of adherent cell therapy in 3D bioreactors. The data is based on the manufacturing of 10 billion cells per batch in the Pluristem cell therapy manufacturing site.

Table 3 shows the footprint of the clean rooms and media volumes needed for culturing of different lot sizes of adherent cell therapy in 3D bioreactors. The data is based on the manufacturing of 10 billion cells per batch in the Pluristem cell therapy manufacturing site.

HUMAN RESOURCES AND AUTOMATION

Culturing cells in a clean room using 2D technology requires many highly trained personnel if done manually. Automation can drastically reduce the number of people required, thereby reducing costs and substantially cutting down on product variation and environmental microbiology exposures in the clean room. The use of automation can reduce human error and the cost of training and re-qualifying of staff. Hence, automation should be integrated into manufacturing processes as they are scaled out. Automating 2D cultures is feasible and some robots are already commercially available and used in the manufacturing of some vaccines.

Table 2. Infastructure size and media volume needed for culturing of cells in 2D culturing systems

Dose/Run 50 million	10	100	1,000	10,000	100,000
Cell number	500,000,000	5,000,000,000	50,000,000,000	500,000,000,000	5,000,000,000,000
Surface cm^2	20,000	200,000	2,000,000	20,000,000	200,000,000
Incubator foot print per lot in m^2	1	4	40	396	3,956
Incubator footprint for 3 lots	3	12	119	1,187	11,867
Net clean Room size m^2	40	220	2,200	22,000	220,000
Media volume per/run/ week	19	190	1,899	18,987	189,873

Table 3. Infrastructure size and media volume needed for culturing of cells in 3D culturing systems

Dose/Run	10	100	1,000	10,000	100,000
Cell number	500,000,000	5,000,000,000	50,000,000,000	500,000,000,000	5,000,000,000,000
Surface fibracell cm^2	20,000	200,000	2,000,000	20,000,000	200,000,000
Gram fibracel	17	167	1,667	16,667	166,667
Bioreactor volume (L)	2.5	5	50	500	2,000
Media Volume	10	100	1,000	10,000	100,000
clean Room size m^2	40	80	150	300	500

Nevertheless, benefits of automation of 2D are limited because automation does not affect the process duration and yield efficiency, since 2D cultures can only be scaled out (more dishes are required to grow more cells). The 2D scale out model, even when automated, will have a high cost of capital exposure and maintenance. Looking at the evolution of the biological therapies such as vaccines or antibodies, the efficiency and cost effectiveness of such 2D culturing is limited and companies are transitioning to bioreactor based technologies to reduce costs and improve yield. Bioreactors make possible a completely different culturing process. The process can be scaled up (to a limit), require similar human resource and control systems to operate throughout the scales resulting in additional savings. That means that the same control system with similar number of operators can run a bioreactor of 5L and 500L. Furthermore, the scale up model of reactors generate an advantage in cost on CAPEX and infrastructure as its footprint increases slightly with scale as opposed to the linear increase of footprint and labor associated with 2D culturing. Figure 3 shows the number of personnel needed as quantities increase taking into account automation were possible.

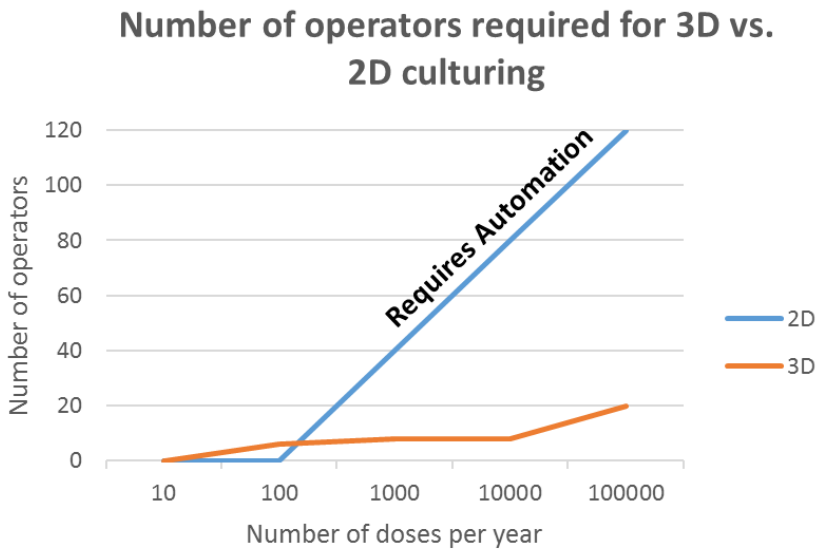

Figure 3 Number of operators required for culturing of cells in different dose ranges 2D vs. 3D, based on available technologies and data of manufacturing at Pluristem Therapeutics cGMP cell manufacturing facility.

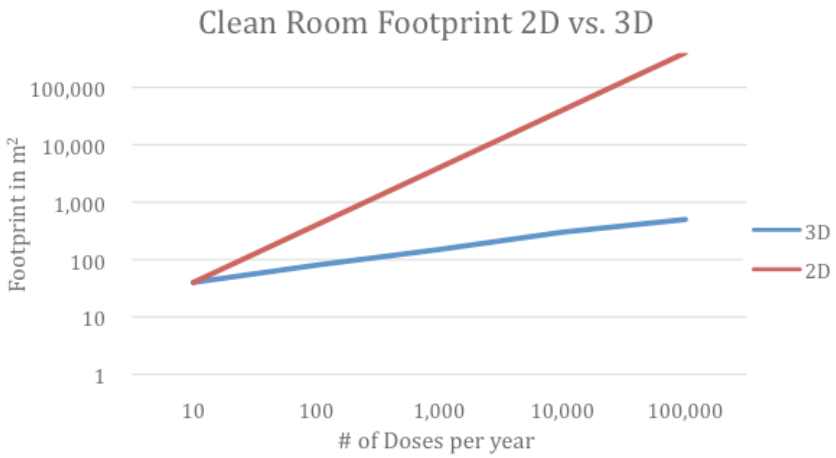

Figure 4: Growth in the clean room foot print for culturing adherent cells in 2D vs 3D systems based on the culturing experience of Pluristem Therapeutics GMP cell manufacturing facility shown in relation of the number of doses manufactured per year in both platforms.

ACCUMULATION OF COST

Generally, up scaling of any manufactured product results in reduction of its cost which is driven by reduced material cost due to volume, improved efficiency, automation and operational excellence. Cell therapy is different due to the nature of the product being a living thing which are sensitive to the environment and highly regulated. Driving down cost and up scaling of such a product must focus on the main cost driver which is the media/serum component. This can be achieved by improving the surface to volume ratio which in turn, not only will it reduce the footprint of the culturing area but allow optimization of culture conditions which will result in efficient utilization of the media and serum. Additionally, improvement of yields and quality of the cells harvested per run by reducing the population doubling time using optimal culture conditions and nutrients consumption can further improve the cost per cell. Such improvements in yield and quality could only be achieved by tightly controlling the critical culture parameters such as nutrient concentration. Tightly controlling the above will allow optimization resulting in minimal changes to the cells with higher efficiency and yield. Figure 5 shows the accumulated effect on COGs of investing early in process development which will allow up scaling to bioreactors and optimization of the high cost drivers. The data presented does not take into account further media optimization above the 40% decrease which is part of the manufacturing process in Pluristem. The authors believe that further optimization of media could easily be achieved cutting the cost in the bioreactor even more.

Figure 5 shows the accumulated cost reduction of culturing cells in traditional 2D systems compared to 3D bioreactors. The data based on the culturing of cells in Pluristem Therapeutics GMP cell manufacturing facility.

SUMMARY

In recent years as cell therapies mature from the bench top to the clinic and the scientific data base and clinical efficacy is accumulating, it is clear that many of the 20th century diseases are complex and multifactorial. Therefore, only a multifactorial approach for treatment such as cell therapy could be a solution. Several publications had concluded that traditional 2D culturing systems is not capable for large scale manufacturing of cell therapies. This conclusion is based on quality and cost parameters using theoretical modeling.[7] The data analyzed in this paper further supports the theoretical findings showing clearly that the 2D path is not viable and could not lead to a commercial product, not even for small indications. The most efficient way for up scaling will be to improve the surface to volume ratios by using dynamic 3D based bioreactors which allow control and perfusion for media optimization. As opposed to traditional drugs or even biological, cells are living things that react to their environment, any change to the process could affect the cells phenotype and critical quality attributes, resulting in a different product. This in turn will change the product and require, to the minimal, a large and expensive comparability study but more reasonable, it will require a new clinical trial.

Now, as the industry evolves companies should invest time, money and effort on process development in early stages. The strait forward notion of waiting for clinical significance (Phase 2-3 study) and only then investing in process development will basically result in a much higher investment in time and money and probably will require redoing the clinical trials and product development. In today's economic arena, a company that has to redo its clinical trials to have a viable product will not survive, and the product will never reach the market.

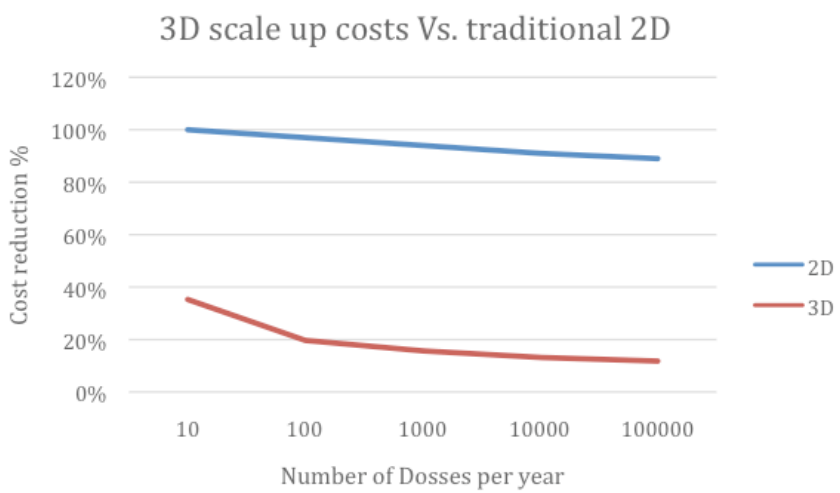

Figure 5: Accumulated effect on COGs without infrastructure and CAPEX 3D vs. 2D

Therefore, investment in translation of the culturing to controlled bioreactor based systems in early stage will not only result in higher quality cells but is a cost effective and required step as early as possible.

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From the Classroom

Using biotechnology, CSI, and zombies to promote science education in one of America's most challenging regions

Dave Menshew
is the co-creator of a nationally recognized forensic biotechnology program at James Enochs High School in Modesto, California. He became a teacher after a successful career in business. Acting on a challenge from a guard at a local juvenile justice center to help change the lives of the incarcerated students, Mr. Menshew returned to school and obtained his teaching credential and ultimately his M.A.Ed. and certification by the National Board for Professional Teaching Standards. Mr. Menshew has garnered many honors including being selected as the 2009 BIO Teacher of the Year, 21st Learning Centers Teacher of the Year, and California Foundation for Lifelong Learning Teacher of the Year, and Amgen Excellence in Education Award. Mr. Menshew's passion for education has led him to create learning opportunities for his students that have resulted in superior standardized testing schools, multiple scholarships as well as college and university admissions leading to STEM degrees.

ABSTRACT

This paper examines the creation of a forensic biotechnology program that engages students, promotes science learning beyond the classroom and makes available novel STEM opportunities to an area which previously had little biotechnology educational offerings. Findings indicate improved student performance in comparisons with non-program students in the same school site as well as district and state. Students connect with core science concepts through the use of their existing interest in popular media topics such as Crime Scene Investigation and zombies. Highly motivated learners then have shared their engagement in STEM learning through numerous public science outreach efforts and vertical articulation from grades K to university promoting science education.

Numerous graduates have reported real-world academic value to their participation in the program. Scholarship and college/university applications are enhanced by program participation.

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Keywords: STEM; NGSS; Enochs High; Forensics; LLNL; ETEC

INTRODUCTION

California's Central Valley is home to 19 counties and is one of the world's most productive agricultural regions. It holds 1% of the nation's agricultural land but produces crops comprising approximately 8% of the nation's agricultural dollar value.[1]

The city of Modesto is located in the heart of the Valley's agricultural region. This city has attracted national attention for a number of negative reasons. A former mayor of Modesto as quoted in *The Economist*, cites the "badly educated workforce" as a major reason for Modesto's woes. The article went on to describe the Central Valley as the nation's "Appalachia of the West."[2] In 2013, Modesto was ranked as #5 in Forbes list of "the most miserable cities in the US" with an unemployment rate of near 15% and a foreclosure rate of 3.8% — third in the nation.[3] In 2006, the city was ranked as having the nation's highest car theft rate by the *Insurance Journal*, as it was the previous two years.[4] In 2014, according to SF Gate, the web publishing arm of *The San Francisco Chronicle* newspaper, Modesto ranked #1 among with "worst places in the nation to start a career."[5] *Health* website ranked Modesto #10 in the nation in terms of air pollution.[6]

Within this challenging environment an innovative, nationally recognized forensic biotechnology program

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has developed which has served to promote biotechnology and STEM learning far beyond the classroom.

RIGHT TIME FOR THE RIGHT SCIENCE

During the 1999-2000 academic year Modesto City Schools' educators became aware of the "Science on Saturday" public outreaches offered by the Lawrence Livermore National Laboratories (LLNL). The Edward Teller Education Center (ETEC), located at LLNL, began offering professional development workshops for K-14 teachers in a variety of STEM disciplines, including biotechnology. Through these presentations and (workshops at ETEC,) the LLNL Edward Teller Education Center (ETEC), Enochs staff became highly interested in biotechnology.

Dr. Doug Kain, a biotechnology professor at the ETEC, noticed that MCS staff had attended numerous workshops and were appearing at surplus biotechnology lab equipment give-a-ways being held in the San Francisco Bay Area. Dr. Kain was also the lead teacher in a community college biotechnology program at Merced College, 40 miles south of Modesto and was working on building more STEM opportunities in the region. Dr. Kain suggested to the MCS staff that they develop a biotechnology elective for the District. At the same time, he challenged the staff to complete the Associate in Biotechnology degree at Merced College. One accepted and was chosen Biotechnology Student of the Year upon graduation in 2006.

In 2004, staff took the idea of a biotechnology elective to the district Director of Secondary Education, Dave Cooper, who himself was a former science teacher and had a son-in-law who worked in the biotechnology industry. Mr. Cooper had been looking for ways to enhance the district's science offerings. He determined that if the new course was developed, it would be offered at Modesto's newest institution, James C. Enochs High School then being built. He formed a program development team led by himself, the interim principal of James C. Enochs High School, mathematics teacher Philip Jaramillo and life science teacher Dave Menshew. At the same time, a steering committee was formed consisting of the study team, as well as industry and higher education representatives. This group included Dr. Kain, Dr. Elaine Johnson Director of Bio-Link, a National Science Foundation funded organization that promotes U.S. biotechnology education, Dr. Tom Pugh Director of Enology Research at Gallo Wines, and Kirk Brown, teacher at Tracy High school, site of a biotechnology elective program. Also selected was Michael Coats, principal of Enochs High, along with science educator Dan Iverson, the Science Department chairperson.

SUPPORT FROM THE BEGINNING

Over the following months, several meetings were held by the program development team and steering committee, with several visitations to other biotechnology efforts within the Bay Area and beyond. Substantial support was provided in terms of curriculum direction by Ellyn Daugherty of San Mateo High School, who had been selected as a Biotechnology Industry Organization's Teacher of the Year in 2004. Dr. Johnson of Bio-Link helped to form numerous industry and college/university connections which would prove vital to the program in succeeding years. She also provided opportunities for program staff to attend a variety of learning experiences in the Bay Area including Bio-Link Summer Fellows. This immersive week-long residential experience held at University of California/Berkeley gave staff the opportunities to work with the authors of the adopted texts as well as broaden their understanding of biotechnology topics. She included teachers from Enochs High School in the development of the Bio-Link Depot, a resource where biotechnology companies in the San Francisco Bay area could donate surplus materials for use by local science teachers.

Dr. Katy Korsmeyer of the Bay Area Biotechnology Educational Partnership (BABEC) networked with the Enochs team, becoming a key steering committee member who arranged numerous learning opportunities and material donations as well. Biotech Firms such as Amgen, Bayer, Genentech, Life Technologies, Novartis, VWR and others have supplied the Enochs program with donations of materials estimated at more than $450,000 during the past 8 years through Bio-Link and BABEC.

Support from other organizations began to expand the network and depth of the program. Early members were the Santa Clara County Biotechnology Educational Partnership (SCCBEP), followed by the East Bay Biotechnology Educational Partnership (EBBEP), the California State University Program for Research in Biotechnology (CSUPERB) and BayBio, a biotechnology industry organization. Each offered Forensic Biotech program staff the chance to attend workshops, consortia meetings and network with Bay Area industry and educational leaders. This worked to deepen the nature of the program's offerings.

LLNL became a key player in staff training and curriculum develop with one of Enochs High teachers completing all four levels of the ETEC STEP program culminating with a summer internship as an ETEC

research associate working on cancer research in the LLNL Biosciences directorate.

Other organizations joined to support the program; for example, Stanislaus County Partners in Education (SPIE) provided an internship at Gallo Wines and later with the Stanislaus County Coroner's Office. This introduced new dimensions in lesson design in depth by rooting them in industry applied learning opportunities in both biotechnology and forensics. At Gallo, teachers participated in yeast crossings and cell mortality studies, enology protocols, and real time PCR. At the Coroner's Office, teachers have assisted in numerous autopsies and learned fundamentals of law enforcement investigations. As a result of this partnership, the program has added an optional senior experience where graduates have the opportunity to observe and in some cases assist in an actual autopsy.

SCANNING ELECTRON MICROSCOPE PARTNERSHIP BROADENS PROGRAM

During the 2011 academic year, staff attended Hitachi scanning electron microscope training at one of the program's partners, Ohlone College in Fremont, CA. Arrangements were made to bring a TM3000 desktop device with a magnification of 35,000x to the campus for a summer training and curriculum development day. Two experts in SEM from Hitachi, Dr. Robert Gordon and Dr. Nancy Weaver, along with Dr. Johnathan Krupp from nearby Delta College worked with a team of eight program students. These highly motivated teens gave up a summer's day to develop the crime scene scenario that was used in class to train their peers. The Hitachi SEM was used to provide images of evidence samples that were then compared with others from crime scene and suspects. The device returned the following January for a week wherein all classes in the program interacted with it, as well as numerous other teachers and visiting dignitaries including school board members and the county superintendent of schools. It returned again in 2013 for a three week period and was used to gauge parasite infestation in a salmon raising project with the California Dept. of Fish and Wildlife that produced 177 Chinook salmon fry from 180 eggs delivered. These were released to a local river.

The use of the Hitachi TM3000 attracted the attention of the International Society of Optics and Photonics, with the invitation to submit a paper which was accepted for publication in 2014. It will be presented in September in Monterey, CA at the Scanning Microscopes 2014 meeting.

U.S. DEPARTMENT OF LABOR TAKES NOTICE

The establishment of the Enochs High Biotechnology Program triggered other events. Soon after classes began in 2007, the local workforce development agency Alliance Worknet approached staff to participate in an application to the U.S. Department of Labor for a $220,000 Regional Innovation utilizing National Emergency Grant funding. Enochs High staff were contributors on the grant and served on the resulting life science and educational committees for the next three years. The firm of Frost and Sullivan was retained to study the viability of bringing more life science firms to the region. Called the Regional Biotech Diversification Plan, the focus of the study was to examine a region of the Central Valley which included Merced, Stanislaus, and San Joaquin counties. The findings, released in 2008 showed that the region faced both constraints and offered possibilities. Constraints include the minimal number of firms identified as having biotechnology as their principle focus and educational institutions to support them as is seen in the San Francisco Bay Area. At the same time, the tri-county region offers excellent transportation hub possibilities, much lower land and construction costs. In addition the overall cost of living would contribute to a less expensive workforce. It was the recommendation of the study that the region representatives lever their affordability and available development space to attract biotech manufacturing operations while encouraging the same kind of STEM promotion and education already in development in the Enochs High School Forensic Biotech Program.[7]

At the time of this paper, the region is still trying to induce biotechnology firms to consider relocating to the tri-county area. Since 2006, Kohl's and Long's Drugs/CVS, then Grainger Industrial Supply and Affinia Auto Parts in 2011, followed by Amazon in 2013 have all located major distribution centers in the area, utilizing 3.7 million square feet of warehouse space. To date, no biotechnology firms have followed.[8]

ADDITION OF FORENSICS TO THE PROGRAM

As the program was being developed, the decision was made by Mr. Cooper to add a forensic emphasis to engage the students. This required an additional skill set by the teachers who would be teaching the courses as their training was principally in life sciences. In support of this new emphasis, SPIE arranged for teacher internships with the Stanislaus County Coroner's Office as discussed above. To further reinforce student achievement,

the decision was made by Mr. Cooper to use a spiral curricular model aligned to the California State Standards for Integrated Science years 1-3 to satisfy state testing requirements.

First researched by Jerome Bruner in 1960, the basis of the spiral curriculum is that even the most complex concepts can be taught to learners if it is revisited each year over their learning career.[9] In practice at Enochs High School these meant students would be taught biology, chemistry, Earth science and physics each year.

At the same time, teachers were expected to develop forensic biotechnology units and lessons designed to be highly engaging, building on existing student interest in popular media stories of crime and investigation. The staff were well qualified to do this. Among the teachers was one with National Board for Professional Teaching Standards certification, two holding Master's Degrees in Education with an emphasis on curriculum and Instruction. Course approval for the sequence grades 9-11 was submitted to the district and accepted. California State University and University of California approvals were also sought and granted.

Funding was sought from the California Department of Education under Specialized Secondary Program (SSP) funding. The initial grant was awarded in 2006 in the amount of $75,000 with additional funding to be supplied through 2008 for a total of $125,000. Additional funding was given increasing the amount to $250,000. This was subsequently used to equip the lab classroom, send teachers to training and other curriculum development expenses. All reports were accepted as satisfactory and all obligations met.

START OF INSTRUCTION

Classes began in 2006 with 156 students and two teachers. The classes were all freshmen, with the design that the teachers would move up with their students in what is called a "looping" format. This multi-year teaching approach has shown benefits of teacher-student relationship continuity.[10] This model also promotes the small learning community (SLC) which has been shown to enhance learning. Specifically "a large body of work in the affective and social realms overwhelmingly affirms the superiority of small schools."[9] Students learn better in smaller schools. Today's high schools, which are designed to maximize the numbers of students who are taught on a given site, can contain well over two thousand individuals. SLC creation is seen as one way to address this issue. Enochs High School was designed to educate over 2400. The student program population in 2014 is approximately 380.

INITIAL METRICS WERE ENCOURAGING, STAFFING A PROBLEM

At the end of the first year, 86% of those who began the program moved up to the second year. Students in the program had grade point averages 0.48 higher than other students at the school. This trend continued in years two and three.[11]

However, the demanding nature of teaching integrated science was difficult for the teaching staff and proved to be an important factor in program continuation. For example of the two teachers that taught the first year of the program, only one returned to continue, choosing instead to teach no program classes at the site. This pattern was repeated the next two years with three staff members only teaching one year and then leaving. Finally, in the fourth year of the program a second teacher was recruited and stayed for two years leaving after the second.

NEW DIRECTION FOR THE PROGRAM

The turnover in teaching staff became a determining factor in the direction of the program. Since credentialing in California and most states determines who can teach which courses, if a suitable candidate cannot be found, a course cannot be offered. During the 2011-2012 academic year there was only one teacher in the science department who was willing to teach the course as an integrated model and the number of students, now over 300, would make this impossible. It is worth noting that the new Next Generation Science Standards have a similar approach to science teaching. Going outside of the department was problematic due to the collective bargaining agreement.

The compromise was to depart from the integrated science model for years 1-3 of the now four year program. Teachers would now teach previously approved core science already aligned to state standards and tests and accepted by the district. This solution solved many problems simultaneously. Teachers who had attempted to teach the integrated science model and left signed onto the new model. The year three course (Forensic Biotechnology 3) would be resubmitted for CSU/UC approval. A year four seniors' course that had been previously introduced became the Forensic Biotechnology 4.

As mentioned above, initial funding was from California Dept. of Education SSP monies. Ultimately the decision was made to seek California Partnership Academy funds to continue the program past the SSP limitations. This provided approximately $82,000 in

operating capital. The application was successful but this funding has been declining $52,000 for the 2014-2015 academic year and isn't certain due to budget changes in the CDE.

LESSON DESIGN AND APPROACH

The approach used by staff to teach the students is to integrate the use of forensic activities to engage the learners. For example, under the integrated science model previously used, a simple magnesium oxide formation lab common to many high school and college chemistry labs becomes a mystery to be solved when a Russian cosmonaut arrives home dead but covered in the substance. In another case, the students are testing samples taken from wells in a community reporting health issues possibly linked to groundwater contamination. In addition to staff created lessons, a forensic consultant has been employed to broaden the scope of the program's lab activities, ultimately creating complete sets of lessons for earth science and biology. Through a series of tests and discussions, students offer solutions to a real world problem. While forensics is used as the engagement tool, the students learn university level biotechnology skills and best lab practices. Students perform experiments directed at solving a crime or exposing an issue rather than simply doing a protocol with expected results. As will be discussed below, this approach will go hand in hand with the Next Generation Science Standards.

DATA SHOWS RESULTS

To judge the effectiveness of the program, a three year study for years 2010-2011, 2011-2012, and 2012-2013 was done by Derek Pendley, Associate Principal of Enochs High. The measures chosen for this study were to compare the academic performance as measured by the California State Testing and Reporting CST examinations between the students in the Enochs High against those on the same campus not in the program, and those in the district and the state. The findings are worth discussion.

As seen in Figure 1, the California Standardized Testing and Reporting (STAR) average of students who participated in the Forensic Biotechnology program achieving proficient or advanced scores on the California Standards Tests (CSTs) was 78%. This compares with non-forensic biotech students who achieved 59.7%. The non-program students in the district achieved a 46% with the state average being 47%. The STAR is the state's measure of academic performance of students annually. The stated goal of the school district is to raise student scores, hoping to have all students in the advanced and proficient categories.

As a California Partnership Academy, participating students are enrolled as a group in at least three subjects. They move throughout their day in an SLC. A comparison was done between the scores of the students in the program vs. site and district is shown below in Figure 2.

The percentage of forensic biotechnology students achieving advanced scores on the CST Science scores in 2012-2013 is 42%. This compares with 25% for non-program same site students, and 16% for non-program district wide students. Similar positive results were achieved in 2010-2011 and 2011-2012.

The English language arts scores for program students compared with site non-program and district also bear examination (Figure 3).

Here, the ELA scores showed substantial differences between program same site nonprogram and district students. For example, very few of the students in the program were below basic and far below basic in their scores. This is significant in that for all three of the years shown, one of the state requirements is that 51% of the

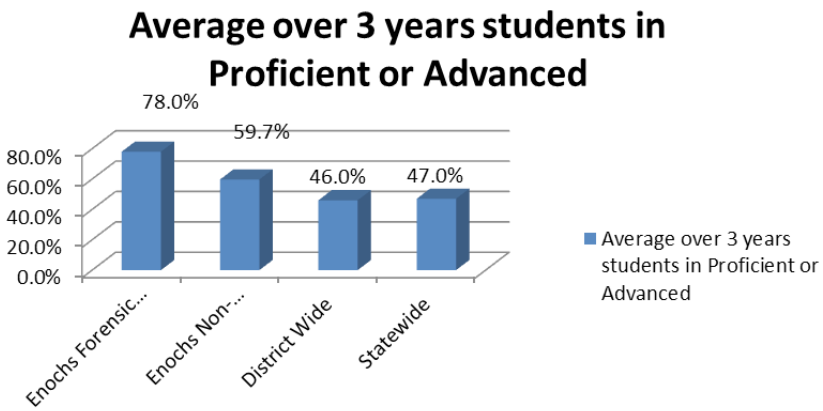

Figure 1: Averages for years 2010-2011 to 2012-2013 (Pendley 2014)

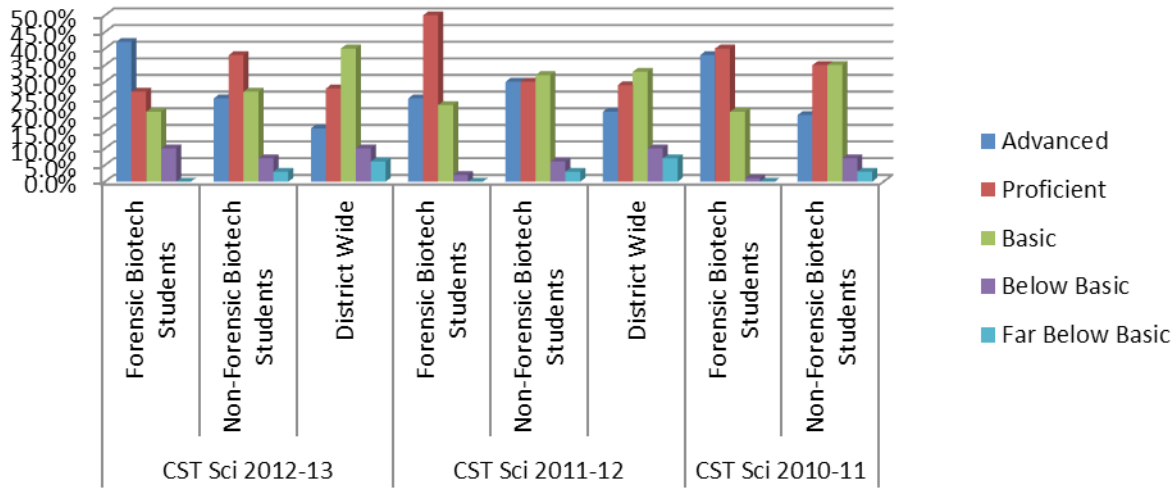

Figure 2: CST Science (Pendley 2014)

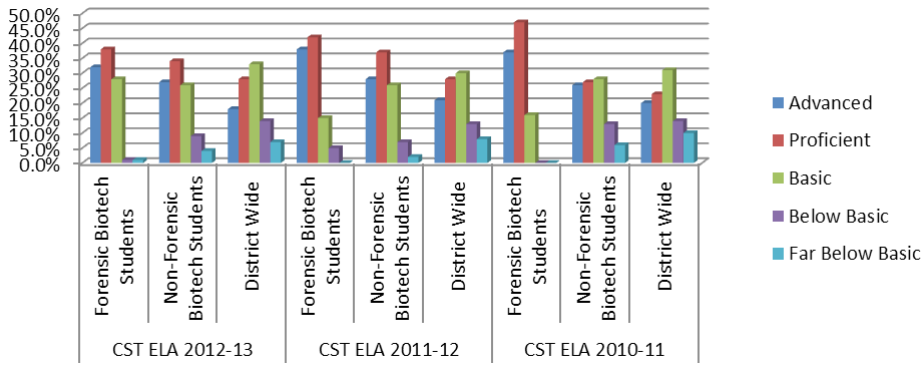

Figure 3: CST English Language Arts (Pendley 2014)

students in the program are to be considered "at risk" by falling in one or more of several categories.

Social Studies (history) scores show a similar pattern. In this case, data was only available for the 12-13 year.

In Figure 4 the total advanced and proficient scores far outperform the non-program site students. You also see much smaller below basic and far below basic of students in the program vs. other site students.

DISCUSSION OF DATA

In terms of the standardized testing, the program has shown significant results. Students in the program outperform their peers at site, district and state. They contribute to a school that has had the highest academic performance index in the region from Sacramento to Fresno for the past three years. Approximately 69% of the juniors at Enochs High School take science classes in a state that requires none of them to do so. The school was awarded a Silver ranking in 2014 by *U.S. News and World Report* among America's schools. When polled both formally and informally, students report high degrees of satisfaction with their time in the program, the ability to do investigations far beyond the scope of the textbook, and the support they received from staff.

EXCEPTIONAL POINTS OF LIGHT

Since its inception, the Forensic Biotechnology Program at Enochs High School has both attracted outstanding students as well as been an incubator for others to rise to their potential. By providing numerous innovative learning experiences both in and out of the classroom, this program has led to some interesting experiences and student performance.

For example, in 2010, two of the program's graduates were accepted to UC Davis. Both were asked to join and

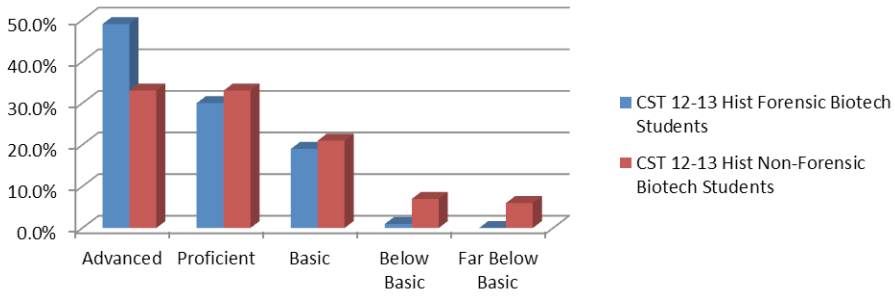

Figure 4: CST Social Studies (Pendley 2014)

work with graduate research teams in their freshman year, one in her first quarter, the second in his third. The first, Alexa Adams went on to become a Google Glass beta tester and was selected as one of *Forbes' Magazine's* 2.0 young Women to Watch for 2013.[12] She plans to do her PhD at UC Davis and will pursue a designated emphasis in biotechnology. Another student, Chris Fiscus has forgone the traditional summer job pathway of fast food and instead works for a local agriculture biotechnology company.

In 2014, two students graduated the program who had successfully completed a record eight years of science coursework. This is significant in that only two years are required for graduation in California. Of these, one was a four year competitive athlete; the other earned his Eagle Scout while still in high school.

In that same graduating class, there were 12 students completing seven years of science, 19 completing six years.[13] 100% of the students who began year four graduated.

PROGRAM RECOGNITION

Recognition that the Forensic Biotechnology Program at Enochs High was meeting the needs of a community with a limited number of advanced high school learning opportunities came in several forms. Program and staff has been recognized with the following:

2007: Amgen Award for Excellence in Education
2009: National Biotechnology Industry Organization (BIO) Teacher of the Year
Association of Mexican American Award for Educational Excellence
Omega Phi Psi Man of the Year
Certificates of Recognition by the California State Legislature and California State Assembly
Modesto City Schools Distinguished Educator Award
2010: Outstanding Educational Program of the Year by the Modesto Chamber of Commerce
2010: California League of High Schools Nominee
2014: Enochs High School Lighthouse Award for Exemplar Service

PROMOTING STEM EDUCATION OFF-CAMPUS

Since the beginning of the program, there has been an interest by staff in promoting science education through vertical partnerships. This led to the creation of the "Fun with Science Nights" public science outreach program. In the fall of 2006, students and staff of the program held Enochs High School's first event. Estimated attendance was 90 parents with 24 program students presenting core science concepts for their younger peers. The following spring semester's event resulted in a queue down the hallway of the science building, down the stair case and out the door waiting to get into the 18 learning stations. Administration estimated the attendance at more than 225 parents and children. The massive influx of attendees resulted in a shutdown of the air conditioning system and required fans be brought in. The following year an annual model was adopted and moved to the school's multipurpose room. The outreach has continued each year in the spring through 2014 with attendees numbering approximately 400+ according to site administrators.

During the 2009-2010 academic year the program was asked to bring its students and science demonstrations to a local elementary school and engage the students during their Science Night. This was reprised the next year, with invitations coming from other area schools. The 2013-2014 year resulted in the highest number of students being engaged with presentations from kindergarten to university. On multiple occasions, program students took the lead in presenting core science concepts. These included supporting a backpack give a way to disadvantaged and underserved youth during the

weeks before classes began, to four multiple learning station presentations at several area elementary schools, to hosting three rooms of interactive science demonstrations at a local state university.

ZOMBIES AND BIOTECHNOLOGY

America's obsession with zombies has provided yet another pathway to student engagement. During discussion with students during the summer of 2013, the decision was made by staff and students to pursue ways to include zombies in the lessons. For example, when approached by California State University Stanislaus to present core science concepts to the public during a Saturday science outreach, the students eagerly accepted the challenge. Students and staff designed learning stations with the apocalyptic theme by dressing the rooms to look like those in such shows as *Walking Dead*. In addition, two professional makeup artists donated their time and expertise to make the zombie presenters look authentic. Science concepts including virus structure, disease transmission were taught to a highly engaged and enthusiastic audience numbering in the hundreds during the eight hour day. Forensic concepts taught included analysis of blood spatter. Physiology concepts included perception and the sense of sight. This theme was continued beyond the public science outreaches to our senior class, asking them to bring together the different core science concepts being addressed in this engagement piece and synthesizing presentations to give them experience in higher level thinking skills and inform future instruction. Public response was highly favorable, though some younger students were a bit timid.

ROOM FOR IMPROVEMENT

While the program has been well accepted by all stakeholders, there are a number of areas for improvement and these realizations are providing the direction for the coming years.

While there have been periodic surveys of stakeholders, this has been an area that has not been consistently addressed in the proceedings of the program. While student input is sought throughout the year by way of the classroom discussions, and encouragement is made for all stakeholders to raise concerns, there needs to be a more formalized, data driven mechanism each year. This needs to be an agenda item for the following year's program operation.

The program has benefitted from considerable student input over the course of each year. For example, during the 2013-2014 academic year, former students contacted the lead instructor 23 times, through a variety of means. Most of these interactions were principally updates on their progress in school, and to express gratitude for the skills they learned in the program. the value of the program in their continuing education. Two students returned to spend substantial time with the instructor to give first-hand accounts. One spent the day giving presentations to current year three and year four students through a PowerPoint he had prepared. Another has provided numerous experiences from her time in the military, connecting to her experiences in the program. It is readily apparent from the demonstrated fact that former students seek out our leadership team and send emails and other communiqués and stay connected. What needs to be done is establishing a more formalized quantitative process, perhaps a professional social media such as *LinkedIn* could be used to initiate the connection while they are still in our program, which may lead to more input overall in years to come.

CONCLUSION

It is anticipated that the adoption of the Next Generation Science Standards will result in new interest in the spiral curriculum model which was a feature of this program when it was first developed. Using this model will reinforce the real world applications and problem solving approach that has been a hallmark of this student learning for the past eight years. Staff have engaged well with the program's demands, but continue to be stressed by the ever increasing nature of today's educational model. For example, the yearly changes in learning management systems, coupled with rigorous testing expectations has drained even the best and most dedicated teachers. At the same time, it is also expected that funding will limit the options to continue teacher training and public outreach. While we believe the model is well proven, its continuance is by no way assured.

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Legal & Regulatory Update

EU Legal & Regulatory Update – December 2014

ABSTRACT

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

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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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PROPOSED REVISIONS TO THE GUIDELINE ON THE ASSESSMENT OF IMMUNOGENICITY FOR BIOTECHNOLOGY DERIVED PROTEINS AND ITS RELEVANCE TO BIOSIMILARS

Hanneke Later-Nijland, the Netherlands

Over recent years, the landscape of blockbuster medicines in Europe has been changing, moving from small molecule drugs to biologicals. Biologicals, mainly biotechnology-derived proteins, now dominate the top 10 list of best-selling medicinal products in Europe: currently, eight of the top 10 best-selling medicinal products are biologicals. As the patents for all of these blockbuster biologicals have either already expired or will expire by 2022 at the latest, these blockbuster biologicals are targets for biosimilars developers.[1] To date, 20 biosimilars have been granted a marketing authorisation by the European Medicines Agency ("EMA").[2]

However, a major problem with protein-based therapeutics is their immunogenicity, in other words, their tendency to trigger an unwanted immune response against themselves. Immunogenicity can be influenced by various factors, such as patient or disease-related factors and also product-related factors. The consequences of an immune reaction to a therapeutic protein range from a transient appearance of antibodies without any clinical significance to severe life-threatening conditions.

As a consequence, the current guideline on immunogenicity assessment of biotechnology-derived

1 http://gabionline.net/Reports/Biologicals-dominate-Europe-s-best-sellers/(highlight)/biologicals

2 Go to www.ema.europa.eu, click on 'Find medicine', select Human medicines, then: 'browse by type' and select 'biosimilars'.

therapeutic proteins (the "Guideline")[3] states that immunogenicity assessment should be part of the clinical trial process. In addition, they state that immunogenicity should always be addressed in the Risk Management Plan — which should be included within the scope of the marketing authorisation application.

However, the Guideline will shortly be revised. This revision will be of particular interest for manufacturers and applicants of marketing authorisations for biotechnology-derived proteins, as it is expected to provide valuable guidance on the marketing authorisation application process.

The concept paper on the proposed revision of the Guideline was published for public consultation in February of this year.[4] It is anticipated that the draft revised Guideline will be released for consultation in the fourth quarter of 2014.

The proposed revisions to the Guideline

Biologicals

Currently a high number of biological products — mainly biotechnology-derived proteins — are being developed. Therefore, the knowledge on the assays required to be performed in order to obtain a marketing authorisation, the risk factors associated with biologicals and, the occurrence of potential unwanted immune responses has increased. As a result, improved assays, which detect the level of antibodies raised against a specific biological, have been developed so that the extent of immunogenicity can be more specifically determined.

The concept paper on the proposed revised Guideline highlights that the Committee for Medicinal Products for Human Use ("CHMP") has regularly raised questions related to the assays used by marketing authorisation applicants and the data generated on the clinical correlation of the induced antibodies. Such questions pertained to the sensitivity of such assays and the use of ligand-binding and cell-based assays to demonstrate the presence of neutralizing antibodies. Since many risk factors relating to immunogenicity are currently known, it may be possible to estimate the risk level of a given biological product. Such analysis can be used to justify the selected immunogenicity strategy, *i.e.* the development of a suitable set of assays and the detection and clarification of the clinical significance of the observed anti-drug-antibodies both pre- and post-marketing.

The concept paper notes that most marketing authorisation applications lack a clear strategy when considering the approach to immunogenicity. Such a strategy should be based on a comprehensive analysis of all data that may be related to the immunogenicity. Therefore, the requirements of the immunogenicity assays may need to be defined more clearly. Quality issues, such as impurities, aggregates, xenogeneic structures need to be assessed. The dose, frequency, duration and route of administration, the underlying disease as well as concomitant medication may also modify the risk of immunogenicity arising.

Biosimilars

With respect to biosimilars, the concept paper highlights that when carrying out comparisons of the immunogenicity of two forms of a product or two independent products (for instance a biosimilar and its reference product), certain specific features must be considered.

The concept paper mentions that the knowledge regarding the immunogenicity of the reference product may help to estimate the level of tolerance towards a particular protein. However, this needs care as the immunogenicity of the proposed biosimilar product may not be similar to the reference product. This has to be demonstrated as part of the comparability assessment.

Moreover, the concept paper states rather ominously that the regulatory consequences of a different degree of immunogenicity (both increased and decreased) need to be considered. This element in the concept paper raises questions about the degree of difference in immunogenicity which justifies such a "regulatory consequence".

At this stage, it cannot be estimated yet whether the aforementioned is a prelude to the introduction of new regulatory hurdles for applicants of marketing authorisations for biosimilars. In any case, it demonstrates the need for clear directions on the assessment and presentation of data regarding the absence or presence of differences in immunogenicity. Considering that normally only a restricted number of patients are available for studies in the pre-authorisation phase, post-authorisation studies may become more important.

Within this perspective, the question of whether the regulatory concept of conditional approval[5] could possibly play a role here, may be a legitimate one.[6] Conditional approval entails the granting of a conditional marketing

3 Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. EMEA/CHMP/BWMP/14327/2006.

4 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/03/WC500163623.pdf

5 Article 14(8) of Regulation (EC) No. 726/2004, as amended.

6 Given that the applicant is able to demonstrate being unable to provide comprehensive data under normal conditions of use which is based on one of the grounds as set out in Annex 1 of Directive 2001/83/EC (as amended), page 153 and 154. For instance:

authorisation even though comprehensive clinical data referring to the safety and efficacy of the medicinal products have not been supplied. Obviously such marketing authorisations will only be granted if specific requirements are met, for example, the availability of the medicinal product should fulfil an unmet medical need.[7]

Finally, the EMA clarifies that the aim of the revision to the Guideline is not to increase the number of studies on immunogenicity, but rather to increase the quality of studies and their clarity to the assessors.

Conclusion

Unwanted immunogenicity remains an important concern for all biotherapeutics. It therefore is and will remain an important and much discussed topic in relation to biologicals and biosimilars.

As the knowledge on immunogenicity continues to evolve, the revision and updating of the Guideline is recommended. In particular, more specific guidance with respect to the presentation of immunogenicity data, requirements of data on antibody assays and a risk-based approach to immunogenicity and clinical data is needed. Furthermore, the comparative immunogenicity studies and post-authorisation immunological studies require attention.

As the EMA states that most marketing authorisation applicants lack a clear strategy to approach immunogenicity, applicants and other interested parties should carefully monitor the developments with respect to the revision of this Guideline. It is anticipated that the draft revised Guideline will be released for consultation in the fourth quarter of 2014.

Furthermore, it is unclear at this stage whether the revised Guideline will provide clear directions on the assessment and presentation of data substantiating the absence or presence of a difference in immunogenicity and which regulatory consequences may come into play. Within this context, post authorisation studies and conditional approval may gain more interest in the near future.

— the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
— in the present state of scientific knowledge, comprehensive information cannot be provided, or
— it would be contrary to generally accepted principles of medical ethics to collect such information, marketing authorisation may be granted subject to certain specific obligations.

CJEU holds that synthetic cannabinoids do not qualify as a medicinal product

Maria-Paz Martens and Nicolas Carbonnelle, Brussels

The Court of Justice of the European Union («CJEU») found in a judgment of 10 July 2014 (joined cases C-358/13 and C-181/14) that according to EU law, mixtures of herbs containing synthetic cannabinoids cannot be regarded as medicinal products under the definition of Article 1 (2) b of Directive 2001/83, that defines medicinal products as

> *any substance or combination of substances which may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making diagnosis.*

The reasoning of the Court states that synthetic cannabinoids merely have the effect of modifying physiological functions but are not such as to have any beneficial effects, either immediately or in the long term, on human health and are consumed solely to induce a state of intoxication and are, as such, harmful to human health.

Background of the case

The CJEU's decision is rendered in response to questions raised by the German Supreme Court in the framework of a national case based on the following facts.

Between 2010 and 2012 two individuals, Mr. D and Mr. G, sold in Germany herbs mixed with synthetic cannabinoids. Synthetic cannabinoids are "new psychoactive substances", which are generally similar to those of the substance they copy without being exactly the same, which enables them in certain cases — at least in the short term — to circumvent narcotics legislation.

The German authorities brought criminal charges against Mr. D and Mr. G, based on a breach of the German Medicines Act given that, at the material time, the German Act on narcotic drugs did not cover synthetic cannabinoids. Both vendors were sentenced before the lower courts.

On appeal however, the German Supreme Court held that the vendors' criminal liability under the German Medicines Act essentially depended on

whether synthetic cannabinoids can be regarded as "medicinal products" covered by Article 1 (2) (b) of the Directive 2001/83. The sale of mixtures containing synthetic cannabinoids used as a marijuana substitute could give rise to criminal law proceedings on the ground of unlawful sale of unsafe medicinal products, unless said substance does not qualify as a medicinal product –in which case no criminal sanctions could be applied under German law. The question was subsequently referred to the CJEU.

Opinion of advocate-general Bot

In his opinion on the case, Advocate-General Bot held that based on the wording and objectives pursued by Directive 2001/83 as well as the existing EU case-law, substances and mixtures such as synthetic cannabinoids should be excluded from the legal definition of a "medicinal product" based on Article 1 (2) b of Directive 2001/83 in the absence of any therapeutic benefit.

More specifically, he considered that subparagraphs (a) and (b) of Article 1 (2) of Directive 2001/83 must be read in conjunction, and that hence the criterion related to the capacity to restore and correct human physiological functions referred to in Article 1 (2) b of Directive 2001/83 cannot be interpreted independently of its context and the medical application for which the substance is intended. The Advocate-General stated that it is not sufficient for the substances to be capable of modifying physiological functions, even more so where those substances are consumed purely for recreational purposes and may be particularly harmful to human health.

In addition, while acknowledging that Member States may be confronted with a legal vacuum in their fight against psychoactive substances, the AG considered that the rules governing medicines do not provide the appropriate tools in that respect. The AG noted that

> *Only repressive measures based on the control of narcotic drugs will enable, through the objectives of public safety, public policy and public health pursued by such measures, a response to be given with the requisite speed to the appearance on the market of substances whose effects are similar to those of narcotic drugs on account of, inter alia, their derived chemical composition and acute toxicity,*

thus rejecting any attempt at "twisting" the definition of medicinal product in order to achieve that goal.

The Judgment of the Court

The CJEU followed the Advocate-General's opinion ruling that the term "medicinal product" does not include products, such as mixtures of herbs containing synthetic cannabinoids, which have the effect of modifying physiological functions, but do not have any immediate or long-term beneficial effects on human health and are, contrarily, solely consumed to induce a state of intoxication and are as such harmful to human health.

This conclusion is based on a combined interpretation of Article 1 (2) a and Article 1 (2) b of Directive 2001/83, which require the existence of a "beneficial effect" for human health in order for a product to qualify as a medicinal product. That interpretation relies *inter alia* on the fact that the definition refers to a "medical diagnosis", of which the purpose is to identify a disease or illness so that it may be treated in good time.

The word "modify" must therefore, according to the Court, be interpreted as encompassing substances which are capable of having a beneficial effect on the functioning of the human organism and as a consequence on human health. Therefore, the term medicinal product in Article 1(2) b of Directive 2001/83 must be interpreted as not covering substances whose effects consist in a mere modification of physiological functions and which are not such as to entail immediate or long-term beneficial effects for human health.

IN A-G'S OPINION PARTHENOTES DO NOT FALL WITHIN THE TERM 'HUMAN EMBRYO'

Rachel Fetches and Toby Sears, London

On 17 July 2014, Advocate General Cruz Villalón delivered his Opinion concluding that unfertilised human ova whose division and further development have been stimulated by parthenogenesis should be excluded from the term "human embryos" in Article 6(2)(c) of Directive 98/44/EC on the Legal Protection of Biotechnological Inventions (the "Directive"), as long as those parthenotes are not capable of developing into a human being and have not been genetically manipulated to acquire such a capacity (*Case C-364/13*).

Background

In April 2013, the English High Court referred a question to the CJEU on the interpretation of Article 6(2)(c) of the

Directive (reported in the May edition of the Life Sciences Newsletter). The question asked whether a parthenote, which only contained pluripotent and not totipotent cells and was therefore incapable of developing into a human being, was included in the term "human embryo" under Article 6(2)(c) of the Directive. This arose from the application by International Stem Cell Corporation ("ISC") for a patent claiming methods of producing pluripotent human stem cells from parthenogenetically-activated oocytes and stem cell lines produced according to the methods and another patent claiming methods of producing synthetic corneal or corneal tissue from such pluripotent stem cells. ISC argued that the parthenotes were unable to develop into a human embryo because of genomic imprinting, although ISC acknowledged that this might be possible through extensive genetic manipulation and had amended the claims to exclude such a possibility.

Opinion

As noted by A-G Cruz Villalón, the question referred was almost identical to one answered by the CJEU in *Brüstle* (Case C-34/10). Cruz Villalón analysed *Brüstle* and in his view, in defining a "human embryo", the CJEU established a functional equivalence between fertilised ova, non-fertilised ova subjected to somatic-cell nuclear transfer and parthenotes. This meant the Court treated all three as being capable of commencing the process of development of a human being. Crucially the CJEU had not been provided with any technical information to the contrary evidencing the fact that, in fact, parthenotes cannot develop into human beings.

The decisive criterion in A-G Cruz Villalón's Opinion was whether the unfertilized ovum had the inherent capacity of developing into a human being. Parthenotes do not have such a capacity and the AG proposed that the CJEU exclude them from the definition of human embryos. However, in light of successful genetic manipulations conducted on non-human mammalian parthenotes (namely mice), this should only apply to those parthenotes that have not been genetically manipulated to become capable of developing into a human being.

In addition, in the A-G's Opinion, Article 5(1) of the Directive did not apply because a parthenote was neither a human body at a stage of its formation and development, nor one of its elements. This was based on the fact that parthenotes were produced by means of a technical process.

AG Cruz Villalón also analysed the *ordre public* and morality provisions of the Directive. In his Opinion, while these provisions established a core "no-go" zone in terms of what was unpatentable, the Directive did not prevent a Member State from excluding parthenotes from patentability on the grounds of ethical and moral considerations under Article 6(1) (see paragraphs 37 to 49). This would therefore provide for Member States to extend the prohibition of patentability from the perspective of *ordre public* or morality based on social and cultural context.

It will be interesting to see if the CJEU adopts the Opinion of A-G Cruz Villalón based on new technical information, in what has historically been a controversial topic.

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