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Commentary

The 'Future of Food' is Genetic Engineering!

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A recent Washington Post article, "The Future of Food," discussed the methods we use to breed food crops, but the piece suffered from "pseudo-balance": seeking out clueless commentators to contradict advocates of superior modern genetic modification techniques. We hate to break it to the author of the article (who holds a bachelor's degree in "magazine journalism, international relations and Spanish") but, in spite of what they teach you in journalism classes, not every issue has two sides and benefits from point-counterpoint.

Because most of society is between two and six generations removed from farming, that subject is largely terra incognita, literally and figuratively. This lack of knowledge makes the public very susceptible to fear-based marketing of food.

Humans have been modifying the DNA of our food for thousands of years. We call it *agriculture*. Early farmers (>10,000 years ago) used selective breeding to guide DNA changes in crops to better suit our needs. Approximately a hundred years ago plant breeders began using harsh chemicals and/or radiation to randomly change, or mutate, the DNA of crops. These mutagens caused innumerable changes to the DNA, none of which were characterized or examined for safety. Problems were rare. Today more than half of all food crops have mutagenesis breeding as part of their pedigree.

Ancestral varieties bear little resemblance to the domesticated crops we eat today. There are many striking pictorial examples here.

Approximately 30 years ago agricultural scientists and plant breeders began to use recombinant DNA technology ("gene splicing") to make far more precise and predictable changes in the DNA in our crops. This molecular genetic engineering (GE) takes a gene with a known function (e.g., toxicity to certain insect predators) and moves it into a crop to transfer the desirable trait. That enables the GE crop to protect itself from insect pests. This one trait has allowed farmers around the world to reduce broad spectrum insecticide spraying by billions of pounds. One would think environmental non-governmental organizations (eNGOs) would cheer such innovation. Sadly this is not the case; once again, no good deed goes unpunished.

Activists (many of whom are paid for their activism) have teamed up with companies that sell organic and natural food products to vilify crops crafted with molecular techniques, which have been dubbed "GMOs," genetically modified organisms, or "Frankenfoods." This anti-genetic engineering industry and their lobbyists are primarily responsible for the significant public apprehension towards this technology. They have been very successful generating fear towards Genetically Engineered (GE) crops (aka GMO's) in the public. They then use that fear to sell alternative food products to unsuspecting consumers.

Now this same industry is lobbying globally for even higher regulatory barriers for gene edited crops and animals. They have had success in Europe and are now setting their sights on North America.

USDA's 30-year-old regulatory approach to GE crops epitomizes regulation that makes no sense. It violates two fundamental rules that should dictate oversight of all products or activities: The degree of oversight should be proportional to risk, and similar things should be regulated similarly. Except for wild berries and wild mushrooms, virtually all the fruits, vegetables, and grains in our diet have been genetically improved by one technique or another, including through wide crosses, which move genes from one species or genus to another in ways that do not occur in nature. The newer molecular techniques are part of a seamless continuum, more precise and predictable extensions, or refinements, of

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earlier techniques for genetic modification, and yet, as described above, they have been singled out for hugely expensive, debilitating regulation.

The modern molecular genetic engineering techniques are neither difficult nor capital-intensive to employ, so the inflated development costs are the primary reason that more than 99% of genetically engineered crops that are cultivated today are large-scale commodity crops—corn, cotton, canola, soy, alfalfa and sugar beets. Virus-resistant Hawaiian papaya, bruise – and fungus-resistant potatoes and non-browning apples are among the few examples of genetically engineered "specialty crops" such as fruits, nuts, and vegetables.

Early concerns from the food industry about possible food contamination led to onerous USDA restrictions on the once-promising sector of "biopharming," using genetic engineering techniques to induce crops such as corn, tomatoes, and tobacco to produce high concentrations of high-value pharmaceuticals; and that entire, once-promising, potentially important sector is now moribund. Likewise, the once high hopes for genetically engineered "biorational" microbial pesticides and microorganisms to clean up toxic wastes are dead and gone.

Not surprisingly, confronted with imposing regulatory barriers and high R&D costs, few companies or other entities are willing to invest in the development of badly needed genetically improved varieties of the subsistence crops grown in the developing world. While multinational corporate crop developers can bear these high regulatory costs for high-value, high-volume commodity grains, excessive regulation disproportionately affects small enterprises and, especially, public research endeavors, such as those at land-grant universities, which lack the necessary resources to comply with burdensome and costly regulatory requirements. Therefore, land grant universities have been put at a substantial competitive disadvantage and are no longer able either to expose their students to state-of-the-art breeding programs or to deliver important new varieties to their constituencies.

The Post article quoted perennial genetic engineering skeptic Jennifer Kuzma as saying, "We need a mandatory regulatory process: not just for scientific reasons, but for consumer and public confidence." But thirty years of excessive regulation of GE crops have neither reduced public anxiety nor quieted the critics. If anything, these regulations have fanned public concerns about this safe, superior technology. As Barbara Keating-Edh, representing the consumer group Consumer Alert, testified before the U.S. National Biotechnology Policy Board in 1991:

> For obvious reasons, the consumer views the technologies that are *most* regulated to be the *least* safe ones. Heavy involvement by government, no matter how well intended, inevitably sends the wrong signals. Rather than ensuring confidence, it raises suspicion and doubt" [emphasis in original]. (Keating-Edh, B. Statement before the National Biotechnology Policy Board (20 September 1991), cited in Biotechnology Law Report, March-April 1993, 12 (2); 127–182.)

Now the anti-genetic engineering activists are calling for crops modified with gene editing, the newest and most precise techniques, to be lumped in with overregulated, nebulously defined "GMOs." Unfortunately, many regulators agree. Regulators love to expand their mandates, empires and budgets.

There is a long-standing, unequivocal consensus about the continuum of genetic engineering techniques and the safety of the newer ones. As far back as 1987, a report from the U.S. National Academy of Sciences clearly stated: "There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms." And a 1989 analysis by the U.S. National Research Council concluded:

> Recombinant DNA methodology makes it possible to introduce pieces of DNA, consisting of either single or multiple genes, that can be defined in function and even in nucleotide sequence. With classical techniques of gene transfer, a variable number of genes can be transferred, the number depending on the mechanism of transfer; but predicting the precise number or the traits that have been transferred is difficult, and we cannot always predict the phenotypic expression that will result. With organisms modified by molecular methods, we are in a better, if not perfect, position to predict the phenotypic expression.

And, it should be noted, the new gene editing techniques are an improvement over the decades-old recombinant DNA techniques in precision and predictability.

We have more than 20 years of data on commercialized GE crops. It is very clear GE crops are as safe, or in some cases safer than crops from other breeding methods. Putting it another way, there is no evidence that the use of molecular genetic engineering techniques confers unique or incremental risks. Even though European politicians are wary of GE crops (in large part, pandering to misguided public opinion), the views of scientists there are congruent with their counterparts in North America.

The European Academies Science Advisory Council said in 2013, "There is no valid evidence that GM crops have greater adverse impact on health and the environment than any other technology used in plant breeding."

Even the World Health Organization of the notoriously risk-averse United Nations agrees; WHO said in a 2014 report: "GM foods currently available on the international market have passed safety assessments and are not likely to present risks for human health. In addition, no effects on human health have been shown as a result of the consumption of such foods by the general population in the countries where they have been approved." Literally hundreds of other analyses by governmental and professional groups have echoed these findings.

Some activists have called for heightened regulations because of the fear of an "off-target edit, or an inadvertent change to a plant's DNA." This makes no sense, inasmuch as thousands of food crops routinely consumed today were created by chemical or irradiation mutagenesis, which introduces innumerable, uncharacterized, random mutations in DNA – and these varieties are not subject to government review and approval at all. Thus, to call for increased regulations on the most precise methods we have ever used to breed new crops defies logic and reason.

There are occasional glitches in genetic modification, to be sure, but here's what the author of the *Washington Post* article (and especially the comments on it) miss: The newer molecular techniques for genetic modification — from recombinant DNA technology ("gene-splicing") in the 1970's to gene-editing now — are so much more precise and predictable that they can minimize the possibility of mishaps. Consider the example of the devastating epidemic of Southern corn leaf blight in 1970-1971, as described in a 1989 National Research Council report: It is exactly the kind of inadvertent glitch in genetic modification that is far *less* likely with the modern molecular techniques. Those who would impose *sui generis* regulation on the new techniques have it exactly *backwards*.

There's method in their madness, however. The organic agriculture and food industries saw that modern genetic engineering techniques were transforming the gap between organic and conventional agriculture into a chasm, so they decided their only recourse was to find a way to distinguish and disparage the opposition.

In the mid-2000's the anti-genetic engineering forces began an aggressive campaign to get food derived from GE crops to be labelled. Consumers Union's Michael Hansen, a long-time critic of GE crops, was typically disingenuous when he said, presumably with a straight face: "I don't understand why the companies don't want to be labeled." He understands very well why. His fellow-travelers have revealed the strategy. From Ronnie Cummins, the head of the Organic Consumers Association: "How – and how quickly – can we move healthy, organic products from a 4.2% market niche, to the dominant force in American food and farming? The first step is to change our labeling laws." And from Joseph Mercola, the purveyor of various "natural" nostrums and quack cures: "Personally, I believe GM foods must be banned entirely, but labeling is the most efficient way to achieve this." And still more, from Andrew Kimbrell, of the Center for Food Safety: "We are going to force them to label this food. If we have it labeled, we can organize people not to buy it."

They have had mixed success. They have failed at achieving a patchwork of state-by-state regulation, which would have created chaos in the food industry and provided a windfall for the plaintiffs' bar to bring lawsuits for unintentional and inconsequential violations. (That prospect would have diminished the appeal of the products made with the techniques that required labeling and, therefore, discouraged the use of those techniques.)

In order to pre-empt state-by-state initiatives that threatened to create a patchwork of labeling requirements that could prove vexing and expensive for food producers, in July 2016 Congress enacted the National Bioengineered Food Disclosure Standard (NBFDS). Congress could simply have pre-empted the ability of states to create their own labeling requirements, but it went a bridge too far, by creating a federal mandate to label "bioengineered" food and delegating to USDA responsibility for fleshing out the regulation. It was published on December 21, 2018.

The statute made clear that labeling was not in any way linked to safety, which is why the rule came not from UDSA food safety regulators but from the Agricultural Marketing Service (AMS). The statute clarified (Section 293) that bioengineered food "shall not be treated as safer than, or not as safe as, a non-bioengineered counterpart of the food," thereby expressing agreement with the FDA that bioengineered foods are, in general, "substantially equivalent" to non-bioengineered foods in regard to health and safety attributes. The text of the regulation is widely considered to be incoherent gobbledygook.

It seems that consumers crave technology in every aspect of their lives except in food production. Why is that? It is because of a multi-decade, multi-national, multi-billion dollar fear-and-smear campaign against genetically engineered crops and derived foods by the anti-GMO industry.

Technology has helped to double food production in the last 50 years. We have the cheapest, safest, most abundant food supply in history, but now those who seek to increase the market for organic/natural products want to force agricultural science to an earlier, less productive time by embracing primitive, inefficient practices. Although they have been successful creating a niche for their products we cannot let them reverse the stunning scientific, economic and environmental advances that have come from genetic engineering and gene editing technology.

Article

Proposal for an Innovating Business Model for Supporting Biotechnology Companies, Ecosystem and Their Founders

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ABSTRACT

The pharmaceutical industry has been revolutionized by the new biotechnology companies during the last years. Facing patent expirations, lack of innovation and depleting product pipelines, the important structures turned to the funding of small biotechnology companies aimed at research and intellectual property securization. Alliances are primordial in the current economic climate. The market growth was questioned for years, but biotechnology companies shifted to product-driven strategies and the market performance has been verified during the last decade. Researchers still face challenges in transforming their science into businesses. They need to be fully equipped, and accompanied towards the right objectives to ensure the sustainability of the market as a whole.

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THE PARADIGM SWITCH

There are several ways of looking at a company performance; one of the most valued is the Resources-based view (RBV) theory. It argues that heterogeneous resources lead to performance. But companies depend on the environment in which they evolve to acquire resources.[1] As Wang, C. and Wu, L. (2012) identify from Lee et al. (2001)'s work, "networks influence firm ability to mobilize environmental resources, attract customers, and identify entrepreneurial opportunities."[2,3] Houghton et al. (2009)'s work on social capital theory suggests that a strong mean to get those resources from the environment is the firm network.[4] Similarly, Powell (1990) identified the need to acquire resources as an important incentive to develop the network.[5]

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From previous studies, Powell (1998) specifically states that high technology fields are more inclined towards alliances even if at the time he saw the youth of the market as a limit.[6] The current situation of the market proves him right. Big corporations are replenishing their pipelines by funding projects and diversifying their portfolio. Biotechnology companies highly rely on their capacity of producing new technologies and research has shown that their innovative capacity is positively affected by the capacity to forge new alliances.[7,8] The work on network links is of utmost importance and facilitators are now unavoidable. Gulati, R. (1999) has worked on the influence of network resources and firm capabilities to alliance formation.[9] His study proved that network resources have a very strong impact its capacity to form alliances, internal processes as well as external human resources are also strong assets for building those alliances. This network has to be built around trustworthy leadership: based on competence (science) and human relationships (management).[10] The work of Pisano (2006) has been very important towards identifying the

leadership issue in the biotechnology field. He underlines that those two skills are rarely existing in the same individual, especially when leading a biotechnology company.[11] Gurdon, M. and Samsom, K. (2010) made a 20 years' research on success and failures on such companies. They point out that "an effective combination of management team processes and access to capital was observed among the successful ventures. […] The financial-driven leaderships appear correlated with success. Those who failed experienced a more intense conflict between business and science values."[12] In their study, they state that the affiliation between scientists and the corporate world is casual, and that this superficial relationship is exposed when scientists confront real difficulties. Numerous scientists who failed in their project became blinded by science and retreated into it. Hence the support of mindful people is mandatory, and a catalyst for success. A strong quote concluding their study is very representative of the current needs of the new biotechnology companies: "For a scientist, trained to be skeptical and fact-based, it is hard to see the glass always as half full, to be risk-oriented, to embrace and believe in the sweeping vision of a commercial opportunity. The latter being a must to build a successful venture."[12]

RESOURCE ALLOCATION

In building a company, the relevance of an accompaniment towards the final goal of the project is therefore a major factor for success. In addition to that, the biotechnology field becomes an increasingly competitive environment. "In the short-term, the amount of technology transfers to SME and start-ups (2/3 of university technology transfers) will lead to a global reduction of technology transfers as they will have trouble attracting investors to provide the necessary capital for new product development."[13] Rock-solid science will have to be carried by teams and leaders fully equipped to face the business challenges to come. The paradigm switch in the scientists' work landscape is a very strong one, and seasoned people with the ability to accompany and advise on every topic of the company project are a vital asset.

The importance of the switch between an academic researcher position to an entrepreneur in biotechnology is even more important if we consider that in the stakeholder's mindset an entrepreneurial opportunity cannot be abstracted from the individual instigating it.[14] It does not imply that every party will reach the same conclusion on the feasibility of the project – hence the importance of keeping a large scope and an open view on the business industry. Indeed, McMullen and Shepherd (2006) defined that the different attitudes towards uncertainty, the many differences in knowledge and research efforts put on the specific projects will lead to different conclusions.[15] Scientists might have difficulties to keep an open mindset which highlights even more the importance of a strong management team. Van Werven, Bouwmeester and Cornelissen, (2015) have performed an extensive study on how arguments can bend the opinion of stakeholders on the legitimacy distinctiveness of their ventures and are decisive in carrying their projects onwards. Extensive research has been done on the communicating issues researchers face.[16] Fallowfield, L. et al. (2002) showed that despite time and clinical experience, senior doctors working in cancer medicine are not resolved.[17] They encourage more resources to be allocated to the training of the doctors in the communication area. This observation relates to the importance of the resource allocation and highlights even more the importance of the right accompaniment. We can state that being able to provide the right resources, allocated in the right direction and at the right time is critical.

Nikolaus Thumm, (2001) has studied the management of patents in European biotechnology companies.[18] He covers all the aspects of patenting the intellectual property, and explains the importance of assuming its core costs at the time the concept has been proved for small structures. According to his study, the patenting strategy can be aimed at economic exploitation, negative patenting (for protection purposes) and swap patenting (combination and cross-dependent therapy). Efficiently managing the strategy is another tipping point for a small biotechnology venture, and Thumm also states that "monitoring the patents of competitors is an effective way of obtaining competitive intelligence."[18] Entrepreneurs must consider the value of seasoned people who gained experience on the patenting process and in the industry in its entirety. Much research highlights the critical issues that biotechnology must address. And some advise to get support from external parties to manage them.

We can resume those findings into 4 main ideas:

- Powerful network is mandatory
- The researcher-to-entrepreneur paradigm shift must be managed
- Attracting the investors requires efficient resource allocation
- The right management is mandatory

COLLABORATION

The starting phase is crucial for biotechnology ventures. If too much time is spent on the starting phase, without

beginning the proof-of-concept through the launching of clinical trials, the structure is most likely to die. Data extracted from the US Bureau of Labor Statistics shows that the older a company gets, the most likely it is to survive. During the first five years, a structure starts from 100% chance of failure, to less than 50% (Figure 1 – Appendice).

This issue is even more important if we consider the importance of funding, securizing the intellectual property and the lack of resources of a small biotechnology company at its starting point. If a small biotechnology company cannot find the necessary competencies and funding, the project is likely to fail, and intellectual property to get lost forever if not secured properly.

Ann Baker (2003) published an opinion piece where she states that the resources must be oriented towards discovery, development and marketing.[19] She further identifies four areas where a biotechnology company must excel:

1. Repetitive innovation discoveries
2. Early value generation
3. Multiple products portfolio
4. Exceptional management and communication to investors

This soliloquy offered a strong emphasis on the importance of accompaniment and how a network-based model brings an edge to ensure the sustainability of a company. She is a senior member of Accenture's Health & Life Sciences industry group, which provides technical and performance oriented solutions and services. This company is one among many, who can bring solid added value to scientists up to the creation of a biotechnology structure.

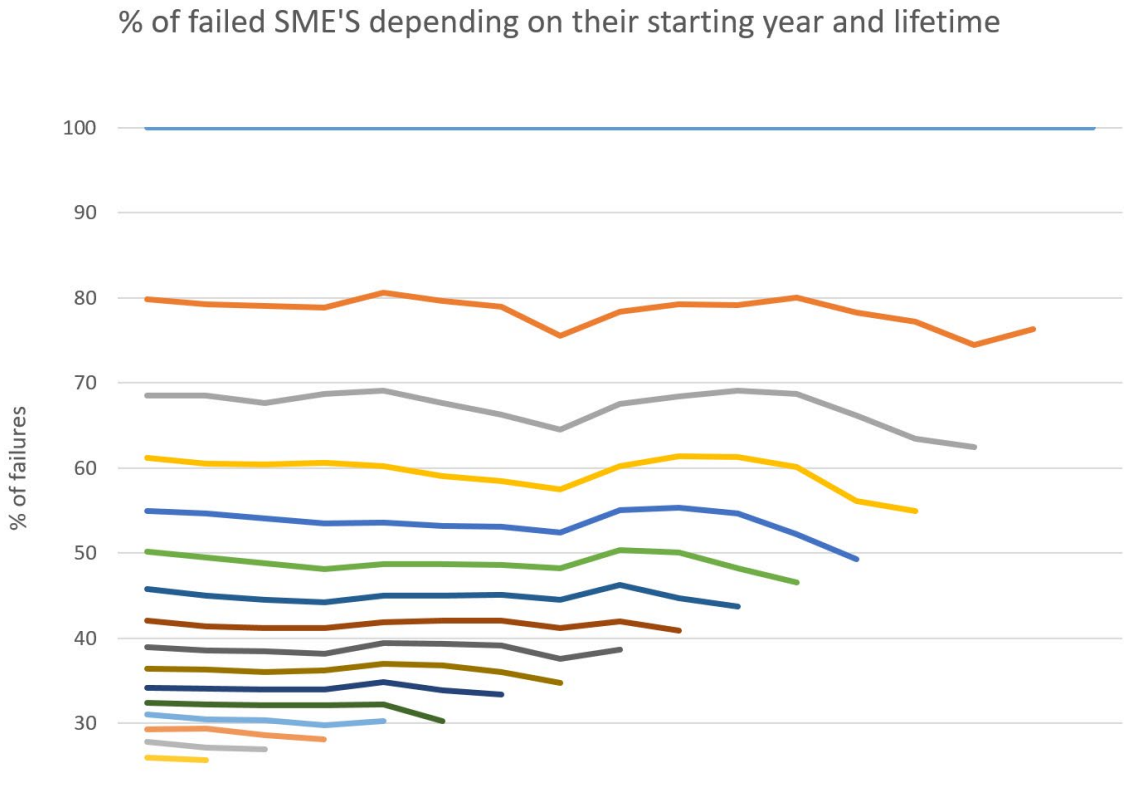
As stated in the first part of this study, network is of utmost importance. The links in the networks are oriented in two ways: affectively or economically.[20] From Lee et al. (2001), we can point out the influence of network on several topics: attractiveness to customers, opportunity identification and resource mobilization.[3] This network is managed through trust according to Powell (1990), and much research has been done on the benefits trust incurs. There are different classifications of trust, making the difference between trust based on competence or capabilities, and trust based on affect.[2] The issue with such an accompaniment is related to the 2 first main findings in the first part of this paper. Network and trust can be economically driven and contractually settled, but it also is affectively oriented. Such structures have strong performance and technical experts, but they lack the trust built through relationship among scientists. Another important issue is the cost related to the use of their services. Small structures have strong economic barriers, which oriented many conclusions in the management research in the biotechnology and high technology fields.

Terziovski, M. and Morgan, J. P. (2006) found out that collaboration is a strong trend in the industry.[21] The collaboration process and its benefits on research has been studied for a long time.[6] McCutchen, W. W. and Swamidassb, P. M. (2004) have performed an extensive study on the reasons for alliances for small biotechnology ventures. One major point they did not explore is the collaboration aspect, and its link with the affective aspect of a relationship.[22] They consider the venture as a purely functional structure, which is very different from the paradigm and human challenge that a researcher faces when changing his idea into a business.

SOME OPPORTUNITIES TO EXPLORE

The idea behind this analysis is to propose a new vision to the biotechnology field and the consulting structures evolving around it. To manage the paradigm shift, the structure that wishes to accompany researchers needs to have a clear overview of every aspect of a biotechnology venture. It requires experience, a strong management and business orientation and a powerful capacity to communicate. An overview does not only consist in having the knowledge of a company creation and management: it requires mastery of it. And one person is not very likely to have all of those, but a full network of experts – seasoned in the biotechnology industry and specialized in their field – is likely to be able to provide the necessary and right resources at the right time. The current atomized structure of the consulting field is severely impacting the costs for small biotechnology companies. It also plays an important role in the dehumanization of the services provided, with a lack of vision towards the psychological changes operating for the researchers-leaders of those small structures. An aggregated offer, combining flexibility and expertise might be able to apprehend those stakes. And last, the collaborative approach is mandatory: to be able to build a long lasting relationship, which is bound by trust and likely to increase the potential network of the different parties. The performance is positively affected by this network, and in an increasingly competitive environment, the importance of allocating the right resources, or persons, to the right objectives at the right time is key to securing the sustainability of a biotechnology venture.

APPENDICE



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2	80	79	79	79	81	80	79	76	78	79	79	80	78	77	74	76	
3	69	69	68	69	69	68	66	65	68	68	69	69	66	63	62		
4	61	61	60	61	60	59	59	58	60	61	61	60	56	55			
5	55	55	54	54	54	53	53	52	55	55	55	52	49				
6	50	50	49	48	49	49	49	48	50	50	48	47					
7	46	45	45	44	45	45	45	45	46	45	44						
8	42	41	41	41	42	42	42	41	42	41							
9	39	39	39	38	39	39	39	38	39								
10	36	36	36	36	37	37	36	35									
11	34	34	34	34	35	34	33										
12	32	32	32	32	32	30											
13	31	31	30	30	30												
14	29	29	29	28													
15	28	27	27														
16	26	26															
17	25																

Figure 1: Percentage of failed companies across all industries based upon the number of years in business and the year started. (Source: U.S. Bureau of Labor Statistics)
Adapted from Shimisaki, C. (2013) Biotechnology entrepreneurship

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Article

Financial Investment Risks in Parmaceutical Industry: Analysis on Fluctuation of Stock Price

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ABSTRACT

With the constant development of market economy, medical industry is developing rapidly, and many listed pharmaceutical companies have emerged. Stock price is an important standard for measuring the industrial development condition, and its influence factors are concerned by investors and issuing enterprises all the time. In this study, the factors affecting stock price were investigated taking the stock price of listed pharmaceutical companies in Shanghai in 2016 as the research samples and using correlation analysis and regression analysis. Variables such as earnings per share, drug price policies and quick ratio were introduced for correlation analysis. The research results suggested that the influence of earnings per share on stock price was the largest; the higher the earnings per share, the higher stock price; interest rate could also affect the fluctuation of stock price. This works aims to offer an evidence for investors who are subject to invest listed pharmaceutical companies.

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Keywords: Medicine, Stock price, Influence factor, Regression analysis, Investment

INTRODUCTION

Pharmaceutical stock market, an important part of market economy, has high research values. Reasons for the fluctuation of stock price is one of the key points in relevant studies carried out by scholars in China and abroad. Zhang et al. [1] estimated the prospective earning using a market model according to the characteristics of the event of toxic capsules and obtained the abnormal return of pharmaceutical stock. Moreover they found that the event of toxic capsules had no remarkable influence on the stock price of pharmaceutical sector in a short time through correlation analysis. Prabha [2] investigated the variables influencing the stock price of pharmaceutical industry in Indonesia using linear multivariate regression model. The results demonstrated that Jakarta Composite Index had positive influence on the stock price and the reliability of the proposed model in predicting stock price was 63%, which provides a reference for investors. Furnback et al. [3] studied the influence of patent loss on the variation of stock price based on the data related to the variation of stock price in four companies between 2011 and 2013 and found that there was no obvious influence. Using fixed and random effect models, Khan [4] investigated the correlation between dividend stock and stock price by taking the stock market data of 29 KSE-100 index listed Pakistan companies between 2001 and 2010. He found that earnings per share was in an obvious positive correlation with the market price of stock; hence dividend irrelevance theory was not applicable to the chemical and pharmaceutical industry in Pakistan.

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1. FINANCIAL INVESTMENT AND RISKS IN THE PHARMACEUTICAL INDUSTRY

In recent years, the aging of Chinese population has become worse. Medical insurance for the elderly has also become a major social problem in China, which puts forward higher

requirements for health care services. In response to this problem, China take efforts to implement the strategy of "healthy China", actively speed up the reform of public hospitals [5], promote the implementation of new medical reform, and accelerate the standardization of drug prices and the marketization of essential medicines. In the period of the new medical reform, the pharmaceutical industry has also developed rapidly and has become one of the important economic pillars of China, and the annual growth rate of output value in the pharmaceutical industry has reached 17%. The pharmaceutical industry is featured by high investment, high risk and high return. It often requires a lot of capital and resources to support the development and manufacture of medicine, which also attracts a large number of foreign capital. Investment in the pharmaceutical industry includes two parts, one is investment for the scientific research of medicine, and the other is stock investment for listed pharmaceutical companies. Securities market is an important indicator for measuring the development of an industry [6].

Stock financial investment is often accompanied by risks. The fluctuation of A share, changes of governmental policies and the operation conditions of pharmaceutical companies will all affect the stock of listed pharmaceutical companies and bring risks. Therefore before investment, investors should make an assessment on the investment value and risks of the stock of a pharmaceutical company. Stock price of a pharmaceutical company usually can reflect the investment value of the stock. Stock market as an important outlet for investment is extremely attractive. How to gain expected yield after investment in stock market is the greatest concern of every stock investor. The stock of the pharmaceutical industry fluctuates slightly and remains stably when the whole market fluctuates sharply [7]. Normal fluctuation of stock price [8] is the basis for investors gaining reasonable and lawful investment income. Therefore investigating the fluctuation properties of stock price and factors influencing stock price is of great significance to investors, listed companies and government.

2. ANALYSIS MODEL FOR PHARMACEUTICAL STOCK PRICE AND FINANCIAL INFORMATION

Focusing on the factors influencing the stock price of the pharmaceutical industry, this study made correlation and regression analysis on financial data using panel ordinary least square (OLS) model [9] and Econometrics Views 8.0 to analyze the correlation between the stock price of listed pharmaceutical companies and accounting and financial information.

2.1 Selection of Dependent Variable and Independent Variable

It was assumed that the stock price of listed pharmaceutical companies was in a causal relationship with financial information; then dependent variable and independent variable were selected.

(1) Selection of dependent variable

It was assumed that stock price could be explained by the financial information; hence stock price was selected as the dependent variable.

(2) Selection of independent variable

Earnings per share which refers to the ratio of after-tax stock profit to total capital stock can reflect the business performance of listed companies. Investors can predict the earning capacity, profit-making level and growth potential of a company and make decision of economic investment based on earnings per share. Earnings per share is one of important financial indexes.

Net assets yield rate [10] which can reflect the effect and value of net asset of listed company is an important basis for supporting stock market and ensuring stock price. It can also suggest the wealth competitiveness and ability of creating profits and defending foreign influence of a company.

Total assets growth rate refers to the ratio of the increased asset of a listed company in current year to the total asset in the beginning of the year. It can reflect the growth and expansion of asset scale of a company in current year and suggest the expansion speed of a company in a period.

Quick ratio refers to the ratio of quick assets to circulating liabilities [11], which can be used for measuring the ability of repaying debts through liquidating floating assets.

Rate of interest refers to the ratio of dividend per share to market price of stock. Stock profit includes dividend income and profit brought by increase of stock price.

2.2 Calculation and Analysis

(1) Correlation analysis

In this study, simple linear correlation analysis was made on stock price and financial information using software

to analyze the positive and negative correlation between them and the degree of correlation.

(2) Regression analysis

The following computational formula was obtained according to multi-element regression theory [12].

$$y = b_0 + b_1 x_1 + b_2 x_2 + \ldots + b_h x_h + \lambda \qquad (1)$$

Where y refers to dependent variable, x refers to independent variable, h refers to number of dependent variables, b_0 stands for regression constant, $b_1, b_2, \ldots, b_h$ stand for regression coefficients, and λ stands for error term.

Parameter was estimated using least square method [13].

$$\min \sum_{i=1}^{n} \left(y_i - y_i \wedge \right)^2 = \min \sum_{i=1}^{n} e_i^2 \qquad (2)$$

Take the partial derivative of the above formula, and let the derivative as 0. Then linear system of equations containing h+1 unknown parameters was solved. Finally the estimate of parameter could be obtained.

Hypothesis test of parameters: Hypothesis test of parameters was performed after parameter estimation to test whether the hypothesis for model parameters was correct. It included t test on significance of variables, comparison of p values of significance level and estimate of parameter and F test on the significance of the equation. If regression coefficients b_0, $b_1, b_2, \ldots, b_h$ were not significant, then it indicated that the changes of independent variable x could not explain the changes of dependent variable y. The regression coefficient corresponding to x was 0, and that dependent variable was eliminated. In this study, the level of significance used in regression analysis and correlation analysis was 0.05, i.e. independent variables had significant explanatory significance to dependent variables when the level of significance was smaller than 0.05.

3. RESULTS ANALYSIS

According to the industry classification of listed companies released by Shanghai Securities Exchange Commission, listed companies in the pharmaceutical manufacturing industry were selected as the research subjects. Considering the effects of data deficiency or abnormality conditions induced by financial condition or other factors on the research results, listed pharmaceutical manufacturing companies which had data deficiency or abnormality or special treatment (ST) stock in the research period were eliminated. Financial data of forty-five listed pharmaceutical manufacturing companies which have been authenticated by Shanghai Stock Exchange were taken as the research samples. The financial data of the 45 listed companies were acquired from WIND financial database, and the data included closing price and interest rate of stock and annual financial statement. The annual report of stock market is usually released in April of next year; therefore the closing price of stock market of the 45 listed pharmaceutical manufacturing companies in May 2017 was selected as the dependent variable. The following is the analysis results.

3.1 Descriptive statistics of variables

Table 1 shows the descriptive statistics of the mean, standard deviation, minimal value and maximal value of dependent variable and independent variables. As shown in table 1, the standard deviations of the independent variables were small, indicating low dispersion degree and uniform distribution of data; the data of the independent variables were close to the means; the minimal values and maximal values of quick ratio

Table 1 The descriptive statistics of variables

Variables	Mean	Standard deviation	Minimal value	Maximal value
Stock price y	22.02515	18.67325	3.21	107.90
Earnings per share x_1	0.57163885	0.602902150	−0.869	4.100446
Total assets growth rate x_2	0.32686934	0.453018911	−0.325019	2.232525
Quick ratio x_3	3.1258845	3.90255836	0.3201	21.8727
Rate of interest x_4	2.79781461	1.858263036	0.100909	11.365932
Net assets yield rate x_5	0.09491139	0.081116904	0.09491139	0.081116904

and rate of interest were significantly different, and the standard deviations were large, suggesting that the data fluctuated greatly. Quick ratio can reflect the short-term debt repayment ability of a listed pharmaceutical company. Rate of interest refers to the profitability ratio of stock. The data of quick ratio and rate of interest fluctuated greatly because the differences of capital strength, scientific research ability and channel development ability between different listed pharmaceutical companies were not small. The standard deviation and minimal and maximal values of stock price were large, indicating the great fluctuation of stock price. Instable stock price can partially reflect the economic strength of a company. The 45 listed companies had different levels of strength, which was why the fluctuation of stock price was large. The descriptive statistics of variables also lays a basis for the following analysis.

3.2 Correlation analysis

The correlation between dependent variables and independent variables were tested using linear correlation coefficient *r*. Effects of financial indexes of the listed pharmaceutical companies such as stock price, earnings per share and quick ratio on the decision making of investors were analyzed. Linear correlation coefficient *r* was usually between – 1 and 1. If the value of the correlation coefficient was a positive number, then it indicated positive correlation between variables; otherwise it indicated negative correlation between variables. The value of the correlation coefficient was divided into three grades according to the absolute value of the correlation coefficient. $|r|<0.35$ indicated a low linear correlation between the variables, $0.35 \le |r| < 0.7$ indicated a significant correlation between the variables, $0.7 \le |r| < 1$ indicated a high linear correlation. The calculation of correlation between the variables is shown in Table 1.

The results of the correlation analysis suggested that earnings per share was in a positive correlation with stock price, and the correlation coefficient was 0.707564, the highest; the rate of interest and net assets yield rate were in a low correlation with stock price, and the correlation coefficients were –0.248762 and –0.197607 respectively; quick ratio and total assets growth rate were in a low correlation with stock price, and the correlation coefficients were –0.086489 and 0.056092 respectively. Thus it was concluded that earnings per share had large impact on the stock of the listed pharmaceutical companies; and rate of interest also had certain influence on stock price. The development of stock market in the pharmaceutical industry has not been mature enough, and moreover investors focus more on stock yield, which increases the investment on stock which has high earning per share and improves the price of that stock. But investors consider less about the debt repayment ability of listed pharmaceutical companies, which results in higher risks. The correlation between the stock price of the pharmaceutical industry and earnings per share was more remarkable.

3.3 Regression analysis

Firstly the model was corrected using stepwise regression method; regression was made on the dependent variable, i.e. stock price, and five independent variables. Then an estimated result was obtained. It was found that the optimization degree of regression equation was the highest when earnings per share was taken as the independent variable. A benchmark regression model was obtained.

$$y = 9.03771899871 + 18.7875787881 * x_1 \quad (3)$$

Other variables were added to the benchmark regression model for regression analysis. When rate of interest

Table 2 Results of the simple correlation analysis on different factors of the listed pharmaceutical companies

	Stock price	Earnings per share	Rate of interest	Net assets yield rate	Quick ratio	Total assets growth rate
Stock price *y*	1.000000	0.707564	–0.248762	–0.197607	–0.086489	0.056092
Earnings per share x_1	0.707564	1.000000	–0.042934	0.313892	–0.153749	0.070872
Total assets growth rate x_2	0.056092	0.070872	–0.060581	0.277660	0.100326	1.000000
Quick ratio x_3	–0.086489	–0.153749	–0.029865	0.216824	1.000000	0.100326
Rate of interest x_4	–0.248762	–0.042934	1.000000	–0.009095	–0.029865	–0.060581
Net assets yield rate x_5	–0.197607	0.313892	–0.009095	1.000000	0.216824	0.277660

Table 3 Relevant results of the OLS regression analysis

Parameters	Regression coefficient	Standard deviation	*t* value	*p* value
Regression coefficient	31.33483	4.740030	6.610624	p<0.01
x_1	18.62600	1.217791	15.29495	p<0.01
x_4	−7.590040	1.583702	−4.792594	p<0.01

F = 131.8546. Then OLS model was obtained.

x_4 was added, the goodness of fit of the equation was improved to 0.548576, and the P value was smaller than 0.05 and got closer to 0.01 compared to the benchmark equation. When x_2, x_3 and x_5 were added, the improvement of goodness of fit was not obvious, and the *P* values were larger than 0.05. Therefore x_2, x_3 and x_5 were eliminated as they were unable to optimize the equation.

Therefore the equation turned into

$$y = 31.3348389935 + 18.6260000437 * x_1 - 7.59004009701 * x_2 \quad (4)$$

The variation of stock price was predicted based on earnings per share x_1, rate of interest x_4 and OLS panel.

A model was established.

$$y = b_0 + b_1 x_1 + b_2 x_4 + \lambda \quad (5)$$

The values of estimate of parameters were obtained using OLS regression analysis.

$$y = 31.3348389935 + 18.626 + 0000437 * x_1 - 7.59004009701 * x_2 \quad (6)$$
$$(6.610624) \quad (15.29495) \quad (-4.792594) \; F = 131.8546$$

The analysis of the model suggested that earnings per share and rate of interest had strong influence on stock price, and the influence of earnings per share was larger; the regression coefficient of the model was 18.62600, and *t* value was 15.29495. Therefore earnings per share was the key factor for the variation of stock price. The marginal contribution of earnings per share was 18.626, indicating that stock price increased for 18.626 yuan if earnings per share increased for 1 yuan. Earnings per share could be taken as an important reference standard for investors evaluating the variation of stock price in the pharmaceutical industry.

With the constant deepening of marketization and continuous implementation of reforms in the pharmaceutical industry of China, demands on the pharmaceutical industry are increasing. Under the support of both market and technology, the overall scale of the pharmaceutical industry increases rapidly, and the booming pharmaceutical market also attract many investment. The aim of investment is profit; therefore investors usually focus on several indexes which are associated to stock yield such as earning per share and rate of interest, which was also proved by correlation analysis and regression analysis. The earnings per share of the selected listed pharmaceutical companies had a great contribution to stock price and could affect the variation of stock price, and investors gain profits from the reasonable fluctuation of price.

4. CONCLUSION

In this study, it was found that earnings per share was in a strong positive correlation with stock price, which was consistent with the investigation on the stock price of popular food and beverage companies in Indonesia carried out by Maskun [14]. Moreover rate of interest also had certain influence on the variation of stock price. Relevant studies concerning variation of stock price suggested that indexes such as asset-liability ratio and debt paying ability [15] also had an obvious association with the variation of stock price of listed companies besides earnings per share and rate of interest. It indicates that the fluctuation of stock price in the pharmaceutical industry is special, or the stock market of the pharmaceutical industry has not been mature enough and the stock price cannot thoroughly reflect the economic strength of listed companies. Earnings per share and rate of interest of stock can provide some reference for investors. Investors should not pursue for indexes which are associated to rate of interest blindly, but also need to take indexes such as debt ratio and debt paying ability and relevant policies of the pharmaceutical industry into account.

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Article

Supervision and Legal Control of Illegal Marketing in Medical and Health Care Enterprises

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ABSTRACT

With the development of social economy and the improvement of living standard, demand on healthcare products has increased, and the industry of medicine and health care has tended to have a good development prospect. But many illegal marketing problems exist in the current healthcare products sales. Moreover the deficiency of relevant legal provision made the situation more and more serious. Dishonest operation and commercial bribe has severely disturbed market and damaged the interests of people and even the society. Hence supervision and legal control for medical and health care enterprises has become the priority among priorities. In this paper, the status and illegal marketing phenomenon of the industry of medicine and health care in China were analyzed, and internal and external control was proposed to normalize marketing means and strengthen internal supervision and control by laws and regulations to reduce illegal marketing and stabilize the market of medicine and health care.

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1. INTRODUCTION

With the development of social economy and the improvement of living standard, more attentions have been paid to health, healthcare products which can enhance immunity and regulate body functions has been favored by more and more people, and medicine and health care has gradually become a rising sun industry. But the competition pattern in the field of medicine is constantly being upgraded because of the absence of powerful supervision and legal restraint; as a result, problems such as virtual-high price, offering or accepting bribes and smuggling gradually appear in the step of medicine circulation [1]. Therefore it is urgent to supervise and control illegal marketing in medicine and health care enterprises in the aspects of laws. Chen et al. [2] considered that illegal operation of those enterprises should be supervised in two aspects, one was to reduce the opportunity factors of fraud through external monitoring, organize illegal marketing management, and relieve the problem of agencies, and the other was to achieve short-term performance and reduce the probabilities of illegal marketing behaviors by pressuring managers. The fundamental of solving the problem was to benefit investors and strengthen the moral accomplishment of

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enterprises. Angelucci et al. [3] suggested enterprises to supervise the behaviors of enterprise staffs for the purpose of resisting illegal marketing crimes. Authority, shareholders and managers should all be monitored; moreover staffs should be monitored by the management layer. Xie SM [4] considered that the current commercial bribe related laws were insufficient to include diversified commercial bribery behaviors and clearly define some "gray" phenomena. Peng et al. [5] considered that innovating supervision and management mode and perfecting anti-commercial bribery legislation and management systems and self-discipline mechanisms inside pharmaceutical enterprises and medical organizations were effective for controlling commercial bribe. In this study, the status of medicine and healthcare industry in China was analyzed, then the current illegal marketing problems were simply described, and moreover the enhancement of internal control and improvement of laws were proposed to reduce illegal marketing in medical and healthcare enterprises and stabilize the medical and healthcare market.

2. OVERVIEW OF THE MEDICAL AND HEALTHCARE INDUSTRY IN CHINA

2.1 Overview of medical and healthcare products

The Administration of Health Food Registration [6] defined health food as foods which have specific healthcare functions or taken as vitamin or mineral supplements. That means it is suitable for a specific population with the actions to adjust body functions. It is not intended to be used to treat any diseases and it will not have any acute, sub-acute or chronic harm to human body.

Healthcare product belongs to the category of food rather than medicine. It is mainly used for regulating body functions, but is unable to prevent or treat any diseases. But there are also differences between food and healthcare products. It is suitable for a specific population, and moreover the usage and dosage have specific regulations. Many studies have suggested that the application of healthcare products is effective in supplementing nutrition and improving the health level of skeleton and muscle [7, 8]. In recent years, the use of health-care products has increased year by year in many developed and developing countries [9]. But the recognition on healthcare products is not sufficient. Motivated by the purposes of acquiring nutrition and keeping health, most consumers pay less attention to the functions and safety of healthcare products [10].

2.2 Characteristics of the industry of medicine and healthcare products

(1) Concentrated consumption population

The consumption population of healthcare products mainly includes the middle-aged and old people, women and children.

With the aggravation of population aging and the increase of life pressure, more and more elderly population tend to have chronic diseases such as hypertension, diabetes and coronary heart disease. Healthcare products which are effective in preventing diseases and improving immunity undoubtedly will be favored by middle-aged and old people. Healthcare products which can regulating blood pressure, improve sleep and delay aging has a huge market among the elderly population.

For the consideration of health and beauty, the female group is the backbone of the consumption of health care products. Healthcare products with the efficacy of weight loss, blood supplement, detoxification and eye maintenance have an extensive market among women of all age groups.

The majority of children's demand for health care products comes from their parents. Infants need to strengthen immunity, and students need to take vitamin supplements. For children's health, parents are willing to increase input on healthcare products. Healthcare products which can supplement calcium and iron and benefit brain are the main consumption target of children.

(2) Strong purchasing blindness

Differing from drugs, healthcare products are not purchased under the guidance of doctors. Understanding healthcare products via advertisement and drugstore is very limited. Middle-aged and old people, females and parents of children are easy to purchase healthcare products blindly. Under the effect of exaggerated advertisement and propaganda, consumers usually purchase healthcare products under the lead of operators rather than from their own point of view.

2.3 Related policies of medical and healthcare products

The Administration of Healthcare Food released by the Ministry of Health in 1996 [11] stipulates that all foods which are claimed having healthcare function shall be reviewed by the Ministry of Health, only qualified products can obtain approval number, i.e. Wei Shi Jian Zi (year) No. X", Wei Shi Jian Zi need to be converted to Guo Shi Jian Zi after the

establishment of China Food and Drug Administration in 2004.

The Administration of Healthcare Food Registration and Recordation [12] raises stricter requirements on healthcare food. The components, content and function of healthcare food should be labeled clearly when being registered, and content which exaggerates and misleads consumers is forbidden. Article 55 stipulates that the main content of label and instruction of healthcare food shall not involve disease prevention and treatment and must claim that the product cannot replace drugs. Those regulations make the approval system stricter and improve the access threshold. But misleading advertising is still quite serious in actual sales, and the law enforcement is also difficult.

The Regulations on Direct Selling Administration [13] makes some stipulations on the sales of healthcare products to more strictly manage direct sales companies and staffs. Clear regulations are proposed for staff training and salary component in direct sales companies. Article 14 stipulates that direct sales enterprises and its branches are forbidden to advertise the sales salary of direct sellers and take paying charges or purchasing commodities as the employment condition. Direct selling activities are also stipulated in details. Article 25 stipulates that direct selling enterprises shall establish and implement perfect systems of goods exchange and returning. Direct selling enterprises which violate regulations should bear legal liability. Article 43 stipulates that direct selling enterprises which cheat and mislead consumers shall be fined amounting to more than 30, 000 yuan and less than 100, 000 yuan by the industrial and commercial administrative department; for a severe violation, enterprises shall be fined for more than 100, 000 and less than 300, 000 yuan, and moreover the business licenses of the branches of the direct selling enterprises shall be revoked by the industrial and commercial administrative department until the direct selling license is revoked by the commercial administrative department of the State Council; direct sellers shall be fined amounting less than 50, 000 yuan by the industrial and commercial administrative department, and for a severe violation, direct selling enterprises will be ordered to revoke the qualification of the direct seller. These regulations place greater demand on the sales of healthcare products, which reduces the confusion phenomenon of healthcare product sales.

3. ILLEGAL MARKETING IN THE INDUSTRY OF MEDICINE AND HEALTHCARE

3.1 Dishonest operation

(1) Quality problem

Though many legal policies have been released to place strict requirements on the quality of healthcare products, some enterprises remain to take risks for benefits. To reduce cost, some medical and healthcare enterprises cheat in work and cut down on materials in the process of production and even claim that the product contains rare medicinal herbs. Other medical and healthcare enterprises add prohibited materials in the process of production to obtain expected effects, for example, adding hypnotic components in healthcare products which can improve quality of sleep and diuretic in healthcare products which can reduce weight. They pursue for economic benefits in regardless of the health of consumers.

Because of the strict requirements for approval of healthcare products, many medical and healthcare enterprises cannot meet the approval requirements and moreover do not have enough time and money. As a result, some enterprises operate illegally without obtaining legal approval number. The produced healthcare products are illegal and unusable, but the enterprises induce consumers to purchase through counterfeiting brands and approval number.

(2) False advertisement

Differing from drugs, healthcare products attract the attentions of consumers mainly by means of advertisement. Many advertisements of medical and healthcare enterprises are false. Many advertisements will exaggerate the effectiveness of the products and even tout them as miracle drugs. They encourage elders with weak identification ability to purchase their products. In order to win the market, many enterprises make false promises of free trial and returning if ineffective, but deny or disappear when consumers come for customer service. These exaggerated advertisements have a huge impact on consumers. They confuse the judgment of consumers, mislead consumers, and damage the stability of the market.

(3) Virtual-high price

The prices of many healthcare products are abnormally high. In many medical and healthcare companies, the imperfect budget control system results in high spending, leading to many bribery behaviors inside enterprises; the

failure of financial reimbursement control, authorization and approval system facilitates the internal staffs to gather capital to lubricate relationships. The capital used in commercial bribery is counted in the cost of products; hence the price of healthcare products is much higher than the actual cost.

In actual sales, healthcare products often attract customers by the form of promotion. The difference between the original price and promotion price was small. The sellers label the original price as the special price or set a price which is much higher than the original price but label it as the special price. Some sales agents improve the price based on the purchase price for the purpose of profit. This is why the price of healthcare products is so high. Under the current supervision system, improving sales charge and cost has been a conventional means for enterprises to earn more profits [14].

3.2 Commercial bribery

Healthcare products are mainly sold directly to consumers by salesmen or through channels such as drugstores; commercial bribery is inevitable in the sales process. In order to maximize the benefits, medical and healthcare enterprises often increase sales volume by providing concealed benefits and interests to trading objects. For example, they encourage trading objects to purchase bulk of healthcare products by providing them considerable kickback or commission or obtain the support of sales agents such as drugstores through bribe. There are several means.

(1) Kickback

Kickback is typical and common in the sales of medical and healthcare products. The medical kickback can be large after the secrete operation of the two trading parties. Medical and healthcare enterprises usually default such a behavior for the pursuit of large benefits, leading to the high price of healthcare products.

(2) Paying real objects

To improve the trading volume, sellers may provide the trading object with cash, credit card and gift in a discreet or legal way in the process of sales.

(3) Sponsorship and donation

Medical and healthcare enterprises provide the trading object with capital in the name of sponsorship, scientific research and donation. Finally all the money falls into the pocket of the trader.

3.3 Telemarketing and conference marketing

Conference marketing means carrying out marketing activities via conferences. The current conference marketing of healthcare products in China is facing credit problems. Various counterfeit and shoddy products have caused large harms to consumers [15]. Medical and healthcare enterprises vigorously agitate their products in conference and deceive consumers by inviting so-called experts and recovered patients.

Telemarketing is exactly the same. Enterprises attract the attention of consumers via phone call and then promote their products and tempt them with small gifts. Healthcare products which are marketed in such ways are mostly substandard, illegal, exaggerated and even ineffective or harmful [16].

4. COUNTERMEASURES

4.1 Strengthening internal monitoring in enterprises

(1) Cultivating excellent enterprise culture

Bribe and kickback are "chronic diseases" in the medical system. Poor sales culture will form if enterprises ignore such behaviors, which may aggravate illegal sales [17].

For enterprises, a reasonable, positive and honest enterprise culture should be cultivated at first. Then enterprises should fully understand that only taking the interests of consumers and society into account, ensuring quality of products and avoiding cheat and concealment in the process of sales can bring long-term interests for enterprises.

The training of staffs should be strengthened. Moreover reasonable salary system needs to be established to avoid consumer fraud. Law popularization is also needed to make staffs understand the importance of honest marketing.

(2) Establishing internal supervision mechanism

An internal supervision mechanism needs to be established. Enterprise construction can be strengthened through supervision between superiors and subordinates and between subordinates. Reward and punishment mechanism should be formulated. Zhao et al. [18] advised to eliminate illegal marketing phenomena such as commercial bribe in enterprises through establishing supervision mechanism.

(3) Controlling and managing pricing of healthcare products

To eliminate the phenomenon of virtual-high price, enterprises need to control and manage the pricing of healthcare products, establish perfect medical price control system, formulate written price management documents, clearly define the full responsibility of pricing and price adjustment mechanism and range, and put into practice following management system.

(4) Budget management

Budget management is an indispensable means to supervise illegal marketing in pharmaceutical enterprises. The effectiveness of budget management will directly affect the achievement of internal control plan of pharmaceutical enterprises [19]. Many pharmaceutical enterprises adopt trans-regional distribution, and the existence of different sales branches causes many conflicts between operation decentralization and management centralization; hence management of distribution budget should be strengthened. In this paper, a distribution budget management framework for pharmaceutical enterprises was proposed to prevent the illegal marketing of pharmaceutical enterprises.

Distribution budget management in pharmaceutical enterprises requires enterprises to design budget management based on sales income and profits, subdivide budget according to the categories and organization structure of medical products, and fulfill budget preparation, execution, control, warning and evaluation. There are several key points in the target budget management implementation. The first point is to keep the consistency between budget target and enterprise strategic plan and find out the balance point between sales volume of medical products and profits. The second point is to establish budget control platform which is suitable for multi-level distribution structure of pharmaceutical enterprises and stipulate decentralization ranges of different levels through optimization and overall planning. The third point is to subdivide sales expenses according to the cost of products and constantly adjust and optimize price. The last point is to strengthen supervision and evaluation in the process of budget enforcement and analyze and manage executive report.

4.2 Perfecting related legal system

The government has released some policies to restrain illegal marketing. But the current definitions for illegal marketing behaviors are not detailed enough, and the protection of consumers' rights and interests is also not sufficient; further definition and specification are needed. Moreover the fight against illegal marketing is also not enough. Criminal punishment for illegal marketing should be strict and loose at the same time. The related system of criminal procedural laws needs to be perfected, and the importance of criminal prevention and the roles of other management measures should be paid attention to [20].

There are relevant laws and regulations for supervising the market of healthcare products around the world. Food Drug Administration in USA manages the market of dietary supplement, i.e., healthcare products, by Dietary Supplement Health and Education Act [21]; unqualified products must be removed from the market, and there are also definite specifications for the labels of dietary supplement. Therapeutic Goods Administration in Australia records information of medical products and manages different categories of medical products with a database and moreover checks production enterprises irregularly. More detailed legislation and law enforcement are needed for control the market of healthcare products in an entire reasonable way. A volunteer once complained to a supervision department, but failed to get expected result. EU directive 2005/29/EC is basically ineffective in preventing misleading health claims of products [22]. In conclusion, the supervision and legal control of healthcare product market need more farsighted construction.

The examination and approval system for healthcare products in China is strict in China, but the supervision is not sufficient. Many small and medium medical and healthcare enterprises produce products without examination and approval and have various illegal marketing behaviors. The government should strengthen supervision and punish with due severity.

Article 7 in the Anti-unfair Competition Law passed in the 3rd Session of the Executive Committee of the 8th National People's Congress [23] in September 2nd, 1993 stipulates that operators shall not seek trading opportunities or competition advantages by bribing staffs from the trading party, organizations or individuals who are entrusted to handle related affairs by the trading party and organizations or individuals who may affect trading with authority or influence. Article 8 stipulates that operators shall not do false or misleading commercial promotion in the aspects of the performance, functions, quality and sales condition of commodities, user evaluation and previous honors. Article 19 stipulates that operators who bribe other as described in article 7 will be given punishment of confiscation of illegal gains and fine of more than 100, 000 yuan and less than 3, 000, 000 yuan; for severe cases, business license will be revoked. Article 20 stipulates that operators who make false or misleading commercial promotion as described in article 8 or help other operators to do false or misleading commercial

promotion via fictitious trading will be ordered to stop illegal behaviors by supervision department and fined amounting to more than 200,000 yuan and less than 1,000, 000 yuan; for severe cases, enterprises will be given punishment of fine of more than 1, 000,000 yuan and less than 2,000,000 yuan and revoking business license.

Decision on Punishment over Crimes against the Company Law [24] passed at the 12th Session of The standing Committee of The 8thNational People's Congress and promulgated on February 28, 1995 stipulates that a company's director, supervisor or staff member who exploits his office to extort and accept bribery, if to a fairly large amount, shall be sentenced to no more than 5 years' imprisonment or criminal detention, and, if to a huge amount, to no less than 5 years' imprisonment, and his property may, together, be forfeited to the state.

Article 390 in Criminal Law [25] stipulates that anyone who commits crime of offering bribes shall be sentenced to no more than 5 years' imprisonment or criminal detention, and be fined; anyone who seek unfair benefits by offering bribes, thus resulting in a grave effect or seriously infringing upon the interests of the state, shall be sentenced to imprisonment for more than 5 years but less than 10 years, and fined; if the circumstances are especially serious or cause extraordinary huge losses to state interests, the person(s) shall be sentenced to more than 10 years' imprisonment or life imprisonment, and his property may, together, be forfeited to the state.

The government shall refine legal provisions to restrain illegal marketing in healthcare product enterprises. The current diversified illegal marketing means should be punished. In the aspect of law enforcement, strict punishment should be carried out according to the Advertisement Law, Trademark Law, Anti-unfair Competition Law and Criminal Law. Both the staffs that violate laws and his superior administrative unit should be punished. Moreover the government should encourage the public to report illegal marketing behaviors and prefect informer protection mechanism, i.e., encouraging the public to be involved in the supervision of healthcare enterprises in forms of reward and opening reporting channels.

4.3 Improving legal consciousness of consumers

Many consumers are cheated by sales staffs because of insufficient understanding on healthcare products and the examination and approval procedures. Therefore the government is obliged to popularize knowledge about healthcare products, differences between healthcare products and drugs and the marking of healthcare products to improve the identification ability of consumers on counterfeit and shoddy products and help them understand the functions of healthcare products more scientifically and comprehensively.

Moreover the government should improve the consciousness of rights safeguarding of consumers while perfecting related laws. Consumers should positively ask the government for help and complain and report when being deceived to alert the market of healthcare products.

5. CONCLUSIONS

With the improvement of social economic level and living standard, the industry of healthcare products has tended to have a more extensive market. But due to the lack of effective and standardized management, illegal marketing phenomenon becomes more and more frequent in healthcare products companies, which is not conducive to the stability of healthcare product market and also brings huge damages to consumers and society. Compared with other researches, this paper made a simple analysis on the current illegal marketing phenomenon in medical and healthcare enterprises and put forward countermeasures such as internal budget control and establishment of internal supervision mechanism, further improvement of related laws and regulations and strengthening the fight against illegal marketing behaviors.

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Article

Barriers of Knowledge in Biopharmaceutical Research and Development in Japan

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ABSTRACT

The purpose of this research was to explore major barriers and issues in knowledge for biopharmaceutical research and development (R&D) in Japan and discuss why Japan had lagged behind Western nations in the field of biopharmaceutical R&D. Cases of three therapeutic antibodies and one therapeutic protein originating and released in Japan were studied and the Web of Science Core Collection was used to analyze biopharmaceutical drugs of Japan and the US with various indexes. Analysis results suggested that establishment of a high-level clinical research network connected with global networks would lead to development of blockbusters. Many of Japanese pharmaceutical companies failed to establish such clinical research network and this is presumably one reason of the gap between Japan and Western nations. On the other hand, acquisition and exchange of knowledge within and between organizations were also explored. The few successful Japanese companies acquired not only formal knowledge but also implicit knowledge for various R&D phases from basic researches to applied researches from top pharmaceutical companies of Western nations, whereas most Japanese companies have not successfully acquired such knowledge. It was assumed that this has also contributed to the gap from Western counterparts.

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INTRODUCTION

Currently, the global biopharmaceutical industry primarily led by the Western players plays the central role in development of cutting-edge technologies in the 21st century. Among all, therapeutic antibodies have drawn significant attentions as one of the core elements of today's biopharmaceutical industry. Therapeutic antibodies are one type of biopharmaceuticals that directly recognizes molecules associated with diseases by antibodies. Size of the therapeutic antibody market accounts for 80 billion USD globally as of 2016[1] and 720 billion JPY domestically as of 2015.[2] In 2016, there were 43 so-called blockbusters, which sell over one billion USD annually, among biologicals (total=114) and many of them were therapeutic antibodies.[3] Of the 43 blockbusters, only two were developed primarily by Japanese pharmaceutical companies – soluble interleukin-6 receptor antibody "Tocilizumab" (Chugai Pharmaceutical) and PD-1 antibody "Nivolumab" (Ono Pharmaceutical and Bristol-Myers Squibb) – and this suggest Japan's significant lagging behind Western R&D.[3]

For the purpose of this study, biopharmaceuticals are narrowly defined as recombinant DNA derived drugs (therapeutic proteins and therapeutic antibodies) and cell culture derived drugs.

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THREE TURNING POINTS IN BIOPHARMACEUTICAL R&D IN JAPAN

First of all, three important turning points were extracted from the history of biopharmaceutical R&D in Japan. The initial turning point was the "initial entry" of over 40 companies in different industries in the 1980's. The second turning point was the "sustainment & continuance" phase in the 1990's where many of the Japanese companies failed to continue the R&D activities and were forced to withdraw. The last turning point was the "course selection & considering" in the 2000's, at which Japanese companies had to choose the path toward development of unique and new drugs or the path toward development of biosimilars after the emergence of therapeutic antibodies.

Several cases that support the three turning points are described below.

Following the establishment of gene recombination technologies by the Nobel Prize-winning scientists Cohen, S.H. and Boyer, H.W.,[4] so-called new biotechnologies based upon gene recombination emerged in the US in the 1970's and spread into Europe and Japan. In the 1980's, a number of businesses in the US entered into the R&D in this field, followed by those in Europe and Japan. Especially in Japan, over 40 companies in not only the pharmaceutical industry but also different industries including food, chemical and textile industries commenced the R&D activities on new technologies such as interferons.[5,6,7] As for the landscape in Japan as of 1980, Japan's microbial fermentation and enzyme-related technologies were sophisticated and, in relation to fermentation product separation and purification processes, the antibiotics production volume of Japan were the world highest;[7,8,9] there was no reason to think that the quantity and quality of researchers and engineers in the field were inferior to the Western nations. In fact, some recognized Japan's R&D capabilities [8,9] and basic researches of Japanese companies in some interferons and tumor necrosis factors (TNF) were comparable with those of the Western nations[6,7] while lagging behind in insulin and human-growth hormone;[5] Chugai Pharmaceutical and Kirin Brewery having strengths in fermentation technologies could even enter into patent litigation with US bio-venture companies Genentech and Amgen in discovery of a hematopoietic factor erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF).[10,11]

A particular example of "initial entry" from different industries in the 1980's is a major textile manufacturer Toray, which commenced R&D of interferon-β in 1971.[6] Toray attempted to produce interferon-β by cell cultivation and successfully released it to the market in 1985.[12] In 1985, Asahi Kasei Industry (now Asahi Kasei Pharma), which was also a major textile manufacturer, commenced the research on interferon-γ based on its own fermentation technologies.[6] The company led the field as it entered into the clinical testing phase of recombinant TNF in 1985 for the first time in the world.[13]

There were not a great number of biopharmaceutical products that were placed on the market by 1995, including human-growth hormone, insulin, interferon-α, interferon-β, EPO, thrombolytic agent TPA, blood coagulation factor VIII, G-CSF and interleukin-2.[12]

However, as Toyobo lost patent litigation against Genentech regarding TPA,[14] Japanese companies became falling behind their Western counterparts in R&D of next-generation technologies, i.e. antibodies without side effects, and many of them withdrew from the R&D fields in the 1990's. Naturally, less reporting is available regarding companies that withdrew from biopharmaceutical R&D,[15,16] but the reduction of companies engaged in clinical development over time suggests that a large number of companies withdrew. One of the few records reports that three major pharmaceutical and food companies abandoned development of TNF and a leading chemical company and a middle-ranking pharmaceutical company stopped development of interferon-γ.[17]

Specific cases in the "sustainment & continuance" phase include Suntory, which was one of the major food manufacturer and the largest whiskey producer in Japan. After entering into the field in 1979, the company actively engaged in R&D activities on then-promising future drugs, such as interferons, interleukin-2, TNF, and human atrial natriuretic peptide (ANP),[6] but the only fruit of its R&D efforts was the release of ANP in 1995.[12] In 2002, the company co-founded a new company with Daiichi Pharmaceutical, which marked its withdrawal from the pharmaceutical business in a practical sense. Further, a major textile manufacturer Toyobo established the Toyobo Biotechnology Foundation and entered into the biopharmaceutical industry at full scale in 1982. The company engaged in highly-competitive TPA and EPO R&D activities and built its own manufacturing facilities.[6] However, it eventually lost a dispute with Genentech in the US over TPA, and was forced to completely withdraw from the industry in the 1990's.[5,14]

For the last turning point "course selection & considering," a venture company CHIOME Bioscience founded in 2005 has set out to develop new biopharmaceuticals utilizing its technologies to quickly produce high value-added complete human antibodies as an advantage. The company became enlisted on the TSE Mothers market in 2011.[18] Also, Daiichi-Sankyo, one of the largest pharmaceutical companies in Japan, resolved its decision to work on biosimilars as part of its engagement in biopharmaceuticals. The company proceeded

with biosimilar R&D activities through collaboration with Coherus BioSciences and Amgen in the US.[19] Fujifilm is a late new entrant from the film manufacturing industry. Entering into the biopharmaceutical business in 2006, the company established a joint-venture with Kyowa Hakko Kirin in 2012 and has focused its resources on a joint research with the Center for iPS Cell Research and Application, Kyoto University for development of biosimilars, and contracted manufacturing of biopharmaceuticals.[5,20,21]

The three turning points in biopharmaceutical R&D in Japan were set based on the above representative cases.

FRAMEWORK OF RESEARCH

As mentioned in the Introduction section, today's biopharmaceutical industry of Japan basically lags behind the Western counterparts.

Thus, the research question of this article was: Why had Japan lagged behind Western nations in the field of biopharmaceutical R&D? In other words, what were barriers facing Japan's biopharmaceutical industry?

Also, the purpose of this research was to discuss why Japan had lagged behind Western nations in the field of biopharmaceutical R&D with focus placed on major barriers and issues in knowledge for biopharmaceutical R&D. There were several possible reasons of Japan's lagging in biopharmaceutical R&D behind the Western countries, but those unrelated to the above research purpose were left to future studies.

Previous studies that were related to the research question were extracted.

In a magazine titled *Iryo to Shakai* (Healthcare and Society), Tanaka of Chugai Pharmaceutical reported three reasons of the lagged Japanese biopharmaceutical R&D activities in the "sustainment & continuance" phase as an opinion of the Biopharmaceutical Committee of Japan Pharmaceutical Manufacturers Association (JPMA).[22] First, biopharmaceutical R&D activities in the 1980's, which were comparable with those of the Western nations at that time, resulted in limited distribution of products in the domestic market due to issues in patents, etc. Second, as in the Western nations, major domestic players in the field concentrated resources on development of drugs for lifestyle-related diseases. Third, domestic pharmaceutical companies failed to keep pace with major Western players in enhancement of biopharmaceutical pipelines through M&A.

Miyata of Nikkei BP also pointed out three reasons:[23] (1) excessive focus on manufacturing technologies; (2) neglect of patents; and (3) R&D initiatives relying on the government. As for the reason (2), patent application processes were neglected due to lack of the concept of substance patents in Japan during the period following WWII in which R&D on antibiotics started, according to Miyata. As for the reason (3), it was mentioned that businesses did not assign their best resources to national R&D projects but used such projects as opportunities of human resource development, which resulted in waste of investments. Importantly, it was also pointed out that businesses could have only chance to acquire non-exclusive licenses through national R&D projects. Thus, it was a contradictory situation where businesses relied greatly on government R&D initiatives but they could not expect much from such initiatives.

However, no previous studies focused on major barriers and issues in knowledge for biopharmaceutical R&D were found.

BARRIERS OF KNOWLEDGE

As mentioned above, this research aimed to explore major barriers and issues in knowledge for biopharmaceutical R&D. For the purpose of this research, such major barriers and issues are referred to as "barriers of knowledge," which lead R&D activities lacking knowledge and know-how required to create new biopharmaceuticals to failure.

CASE OF THREE THERAPEUTIC ANTIBODIES AND ONE THERAPEUTIC PROTEIN ORIGINATING AND RELEASED IN JAPAN

This section describes cases of three therapeutic antibodies and one therapeutic protein originating and released in Japan. Specifically, cases of two blockbuster therapeutic antibodies thought to be the most successful biopharmaceuticals in Japan, one other therapeutic antibody that did not become a blockbuster, and one therapeutic protein developed and released primarily through Japanese pharmaceutical company's R&D activities were reviewed as follows.

The first antibody drug case is the Chugai Pharmaceutical's soluble interleukin-6 receptor antibody (Tocilizumab).

As mentioned earlier, this is one of the blockbuster biopharmaceuticals in the world, and was primarily created through Japanese pharmaceutical company's R&D activities. As it is recognized as a blockbuster across the world, it is safe to assume that the R&D activities of the drug were successful.

Chugai Pharmaceutical is regarded as one of the few successful biopharmaceutical companies in Japan as

it commercialized EPO (1990) and G-CSF (1991) in the "sustainment & continuance" phase.[12]

R&D of the soluble interleukin-6 receptor antibody originated in an article on interleukin-6 gene cloning, published in 1986 by Kishimoto et al. of Osaka University.[24] Later, Kishimoto et al. published articles on interleukin-6 receptor and on gp130 gene cloning that attached to interleukin-6 receptor in 1988 and 1989, respectively.[24] In 1989, Kishimoto et al. also reported that Castleman's disease (an autoimmune disease) is caused by abnormality in production of interleukin-6.[24] Thus, Kishimoto Laboratory, Osaka University implemented extensive basic researches on interleukin-6 and interleukin-6 receptor.

Meanwhile, Chugai Pharmaceutical's key researcher Osugi deepened his knowledge through a pathogenesis research using mice with autoimmune disease in the US and in 1984 Osugi et al. commenced an exploratory research on B-cell inhibitor.[25] This was because manufacturing and marketing of Carfenil (antirheumatic and immunoregulator) was approved in the same year and with the new drug they had experiences in a mechanism to activate the suppressor T cells.[25] Osugi et al. of Chugai Pharmaceutical had proposed a hypothesis that a drug for treatment of autoimmune diseases such as rheumatism required an agent to control B-cells. Osugi et al. explored B-cell inhibitors according to the hypothesis, and this was when Kishimoto et al. discovered the interleukin-6. Coincidentally, Osugi and Kishimoto had been friends since their childhood. This helped them enter into a collaborative research instantly.[25] Fortunately, in the Institute for Molecular and Cellular Biology of Osaka University there were a number of former members of the Third Department of Medicine of Osaka University including Kishimoto; in other words, Kishimoto et al. had immediate access to clinicians familiar with their basic immunity researches and patients with autoimmunity diseases such as rheumatism and Castleman's disease.[25]

Thus, Chugai Pharmaceutical commenced the collaborative research with Osaka University. For production (application and commercialization researches), as mentioned above, Chugai Pharmaceutical had experiences in successful commercialization of animal cell-based biopharmaceuticals EPO and G-CSF in the 1990's, which was an advantage of the collaborative research.

In 1991, Chugai Pharmaceutical started preclinical testing on multiple myeloma.[24] In therapeutic antibodies there are antigenic side effects and it is necessary to humanize mouse antibodies as close as possible to reduce side effects.[26] To this end, Chugai Pharmaceutical started collaboration with the Medical Research Council (MRC, UK) in 1990 and eventually succeeded in production of humanized antibodies.[24]

In response to introduction of TNF antibody (infliximab) in Japan by its competitor Tanabe Seiyaku in 1996, Chugai Pharmaceutical changed the target disease from rheumatic arthritis to Castleman's disease and acquired approval from the domestic authority in 2005.[24] Then, the company acquired approvals for rheumatic arthritis successively in Japan in 2008, in Europe in 2009, and in the US in 2010.[24] Meanwhile, Chugai Pharmaceutical became a subsidiary of Roche, one of the world's leading pharmaceutical companies in 2002.[24]

The second antibody drug case is Ono Pharmaceutical's PD-1 antibody (Nivolumab).

PD-1 (Programmed Cell Death-1, CD279) was a gene product whose expression was enhanced by induction of T-cell death, discovered by Honjo et al. of Kyoto University in 1992.[24] The discovery of PD-1 was not intended but was incidental.[27] The function was suggested by its structure to some extent, but PD-1 gene knockout mice was created to identify the whole picture of PD-1. It was in 1996 when the research efforts started to bear fruit, finding of advanced immune response.[27]

As it had been already known that PD-1 was a cell surface receptor structure, they looked for ligand to be bound with the receptor.[27] They could not effectively search for the ligand and entered into a joint research with a US venture Genetics Institute. When Genetics Institute referenced resources owned by its collaborative research partner Harvard University, ligand that bound with PD-1 was discovered and then published in 2000.[27]

The research group investigated cells in which the ligand was expressed and found a possibility that PD-1 took negative control of immune response. Thus, experiments were conducted in consideration of tumor control as an application of PD-1.[27] First, tumor was transplanted to the aforementioned PD-1 knockout mice to see cancer cell proliferation and as a result slower proliferation was observed. Then, an experimentation scheme using an antibody inhibiting PD-1 signal was developed and resulted in successful preparation of PD-1 ligand (PD-L1) antibody, exhibiting tumor proliferation inhibition effect. Discovery of the antibody was published in 2002.[24,27] Assuming that PD-1 ligand on cancer cells inhibited activation of lymphocyte system and thereby resulted in cancer cell proliferation, the research group investigated the PD-L1 antibody effect on cancer cells expressing the ligand. Consequently, inhibition of cancer cell proliferation was observed.[27]

In view of PD-1 antibody's possibility as an anti-cancer drug, the company hereupon patented it jointly with Ono Pharmaceutical,[24,27] which had had a relation with the Honjo Laboratory. Ono Pharmaceutical had long closely worked with Honjo's laboratory on prostaglandin "Onon" since the age of his predecessor Professor Hayaishi.[24] Honjo proposed Ono Pharmaceutical a

development project of PD-1 antibody as an anti-cancer drug, but the company was reluctant to proceed with the high-risk R&D because at that time it had no experiences in biopharmaceutical production and also clinical development of anti-cancer drugs.[27] In response, the company invited over 10 major domestic pharmaceutical companies as well as Japanese branches of some US companies in 2002 to diversify the risk, but the invitation was declined.[27] The author remembers seeing Ono Pharmaceutical's representatives called for collaborative research partners in a conference.

After twists and turns, Ono Pharmaceutical partnered with a US-based venture company Medarex, which owned antibody humanizing technologies, and Ono Pharmaceutical, Kyoto University and Medarex commenced the joint R&D of the PD-1 antibody.[24,27] Later Medarex prepared fully humanized PD-1 antibody and application for patent was filed in 2005.[27]

In 2006, their application for Investigation New Drug for the PD-1 antibody was approved by FDA and the phase I study on solid tumors was commenced in the US.[27] In Japan, on the other hand, the phase I study on solid tumors was started in 2008.[27]

Then in 2009, Honjo et al. faced with an unexpected event; Medarex was acquired by Bristol-Myers Squibb (BMS).[24] Through the acquisition, BMS obtained the right of development and commercialization of PD-1 antibody in North America.[24] At that time, BMS had already had experiences of R&D of CTLA4 antibody, which was similar to PD-1. Looking back, Honjo expressed the BMS's entry into PD-1 R&D as a fortunate event and said their clinical development was much accelerated thereafter.[27] In fact, BMS invested considerable resources in overseas clinical development. Ono Pharmaceutical obtained manufacturing and marketing approval for PD-1 antibody on malignant melanoma in Japan and the US in 2014, and then in Europe in 2015.[24]

The third therapeutic antibody case is Kyowa Hakko Kirin's CCR4 antibody (Mogamulizumab).

Kyowa Hakko Kirin commenced a joint research in 1996 with Matsushima of the University of Tokyo, which led to successful acquisition of the murine monoclonal antibody against the human C-C chemokine receptor type 4 (CCR4).[28,29] After converting the antibody converted into human IgG1, the company started a collaborative research on adult T-cell leukemia lymphoma (ATL) with Ueda et al. of Nagoya City University.[28] ATL is a malignant blood tumor associated with human T-cell leukemia virus type I (HTLV-1). The rate of patients infected with HTLV-1 is higher in southwestern part of Japan, Caribbean Sea coastline, and Central Africa. The situation is similar regarding ATL; the rate of ATL patients in lymphoma patients was said to be over 20% in Japan.[29]

Initially, Kyowa Hakko Kirin set development of an anti-allergic drug as a goal of its R&D of CCR4 antibody since CCR4 was associated with exacerbation of allergy symptoms, but the company was concerned about risks associated with antigenic side effects specific to therapeutic antibodies. Therefore, the company decided to work with Ueda et al. on ATL.[29] Although profitability of the drug was questioned because ATL was a rare disease with incidence as low as only 1,000 cases annually in Japan, the R&D project was carried on by on the initiative of Kyowa Hakko Kirin's then President Matsuda.[30]

Kyowa Hakko Kirin had already completed R&D of a technology to dramatically enhance the antibody-dependent cellular cytotoxicity (ADCC) exhibiting killing of cancer cells (i.e. POTELLIGENT technology) and filed an application for patent in 2000.[30] This technology modifies antibody structure to exclude only fucose from antibody's sugar chain binding. Accordingly, the company decided to apply the POTELLIGENT technology to the CCR4 antibody.

In 2006, a domestic clinical test of the CCR4 antibody was started. In the phase I study, the CCR4 antibody was administered to 16 subjects. In the phase II study, eight out of 26 subjects achieved complete remission (CR) and five achieved partial remission (PR) and thus the objective response rate was 50%. After it was designated as a drug for rare disease for positive recognition acquired through the phase I study, application for manufacturing and marketing approval was filed in Japan in 2011 and approved for ATL in 2012.[28,30] It has not been approved in other countries.

The last case reviewed in this research was a therapeutic protein, Asahi Kasei Pharma's Thrombomodulin (alfa).

Asahi Kasei Pharma was one of the active players in the "initial entry" phase of Japan's biopharmaceutical R&D and competed to be the first rider in R&D of TPA besides aforementioned TNF. The company's R&D activities did not reach to commercialization for both TPA and TNF, but Asahi Kasei Pharma gained in-house genetic engineering technologies from TNF R&D and mass cell culture technologies from TPA R&D.[31]

The R&D target of the company following those biopharmaceuticals was the anticoagulant Thrombomodulin.[31] The first successful preparation of Thrombomodulin was done by Esmon et al. of the University of Oklahoma in 1982 by purifying from leporine lung. In 1984, Maruyama et al. of Kagoshima University succeeded in purification of Thrombomodulin while studying in the University of Washington. In Japan, Suzuki et al. of Mie University reported purification of bovine Thrombomodulin in 1984.[31] Given reporting of the above, Asahi Kasei Pharma commenced a

collaborative research with Kagoshima University and Mie University in 1985.[31]

Through a keen competition in R&D of human Thrombomodulin across the world, Suzuki et al. finally prepared Thrombomodulin from human lung and determined the its amino acid sequence in 1985, and succeeded in gene cloning and obtained patent in 1987.[31]

Since drugs solely composed of Human Thrombomodulin molecules were poorly water-soluble, a structure composed of three domains only with sulfate sugar chain unbound (Recomodulin) was employed for practical application and commercialization of the drug. Since Recomodulin was a complex glycoprotein structure containing sugar chains, it had to be cultured with animal cells. Therefore, the experiences in TPA R&D were utilized in establishment of the Recomodulin manufacturing process.[31,32]

The clinical test was started in 1992. The target was disseminated intravascular coagulation (DIC). Conventional DIC clinical testing collectively evaluated patients of respective underlying diseases. For Asahi Kasei Pharma's clinical testing of Recomodulin, underlying diseases were narrowed down to representative hematopoietic malignancies and infectious diseases for valid evaluation of its efficacy and safety.[31] After a long period of R&D, the company applied for the manufacturing and marketing approval in Japan in 2006, which was then granted in 2008.[31,32]

ANALYSIS OF BIOPHARMACEUTICALS WITH WEB OF SCIENCE CORE COLLECTION (1)

The four bio-pharmaceuticals described above are representative cases of successful bio-pharmaceutical R&D primarily led by Japanese pharmaceutical companies after 2000. This section describes results of analysis of the four cases based on several indexes.

Basically, the Web of Science Core Collection (Clarivate Analytics) which was one of the world's largest professional literature database, was used for the analysis. Various evaluation indexes based on academic article information were analyzed, including: article count, citation count, average citations per item, h-index, g-index, Hg-index, A-index, R-index, individual h-index, individual h-index (hl), and the average number of authors in h-score.

The h-index is a qualitative and quantitative index of academic publications, quantified by comparing the number of articles and citation count.[33,33] For example, h-index of a given author is deemed *h* if h articles out of all publications of the author receive at least h citations. The g-index is a complementary index of the h-index, defined as the largest number of the top g most cited articles whose citations are at least g^2 in total.[33,34] It amplifies information of highly-cited articles of a given author. The Hg-index is a complementary index of the h – and g-indexes, defined as the square root of the product of the h- and g-indexes.[34,35] The A-index is the average citations of highly-cited articles of a given author, calculated by dividing total citations of the top *h* most cited articles (h-score) based on the h-index by the h-index.[34,36] The R-index is a complementary index of the h- and A-indexes, defined as the square root of the product of the h- and A-indexes.[34,36] The individual h-index is a variant of the h-index calculated in consideration of the number of co-authors (citations / number of authors).[34] The average number of authors in h-score is the average number of authors in the top *h* most cited articles calculated for the h-index.[34] The individual h-index (hl) is an index considering the number of co-authors (h-index / (average number of authors in h-score)).[34]

The timespan was set to 1967-2016 and database search was conducted on February 4, 2017 by using SCI-EXPANDED and CPCI-S.

The specific search formula and results were indicated in Table 1. The results showed that article count, as well as citation count, were notably lower with the CCR4 antibody in comparison with the three other therapeutic antibodies. The average citation per item was higher with the PD-1 antibody and Thrombomodulin.

For each index, Thrombomodulin ranked the first in the h-index, followed by the soluble interleukin-6 receptor antibody. In the g-index, Thrombomodulin ranked the first, followed by the PD-1 antibody. In the Hg-index, Thrombomodulin ranked the first, followed by the soluble interleukin-6 receptor antibody. In the A-index, the PD-1 antibody ranked the first, followed by Thrombomodulin. In the R-index, Thrombomodulin ranked the first, followed by the PD-1 antibody. In the individual h-index and individual h-index (hl), Thrombomodulin ranked the first, followed by the soluble interleukin-6 receptor antibody. All the above indexes of the CCR4 antibody were the lowest. In the average number of authors in h-score, the PD-1 antibody ranked the first, followed by the CCR4 antibody.

Among the three therapeutic antibodies, R&D of the soluble interleukin-6 receptor antibody and PD-1 antibody was carried out jointly with Western major pharmaceutical companies, whereas the CCR4 antibody was basically developed by Japanese parties due to its intended applications. The former drugs were associated with higher figures in most indexes including the article count and citation count than the latter.

The next focus here is Chugai Pharmaceutical that commercialized the soluble interleukin-6 receptor

Table 1: Biopharmaceutical examples which were primarily researched and developed in Japan

No.	Drug name	Generic name	Company	Marketed in Japan	Article count	Citation count	Average Citations per item	h-index	g-index	Hg-index	A-index	R-index	individual h-index	individual h-index(hl)	Average number of authors in h-score
1	Soluble IL6 receptor antibody	Tocilizumab	Chugai	2005	1,687	16,903	10.02	55	107	76.71	166.89	95.81	22	6.38	8.62
2	PD-1 antibody	Nivolumab	Ono	2014	719	15,072	20.69	39	121	68.70	344.85	120.35	17	2.44	17.23
3	CCR4 antibody	Mogamulizu-mab	Kyowa-hako-kirin	2012	105	1,175	11.19	16	33	22.98	63.69	31.92	6	1.31	12.19
4	Thrombo-modulin	Thrombo-modulin alpha	Asahi-kasei	2008	2,400	44,661	18.61	94	152	119.53	196.43	135.88	36	16.07	5.85

Searched by the Web of Science Core Collection on February 4. Timespan: 1967-2016. SCI-EXPANDED, CPCI-S.

1. Search formula: title: (((((IL6 OR IL-6 OR interleukin6 OR interleukin-6 OR BSF-2 OR BCDF) AND receptor)) AND (antibody OR antibodies))) OR title: ((Tocilizumab OR actemura OR Atlizumab OR R-1569 OR RG-1569 OR RO-4877533)) R title: (((CD126) AND (antibody OR antibodies)))

2. Search formula: title: (((PD1 OR PD-1 OR CD279 OR "programmed cell death 1" OR "programmed cell death-1" OR "programmed cell death1") AND (antibody OR antibodies))) NOT title: ((Lambrolizumab OR Pembrolizumab OR Keytruda OR MK-3475 OR SCH-900475 OR h409A11)) OR title: ((nivolumab OR optivo OR MDX-1106 OR ONO-4538 OR BMS-936558))

3. Search formula: title: ((CCR4 OR CCR-4 OR (chemokine AND receptor-4) OR (chemokine AND receptor4)) AND (antibody OR antibodies)) OR title: (Poteligeo OR Mogamulizumab OR KW-0761 OR KM-8761 OR AMG-761)

4. Search formula: title: ((Recomodulin OR Thrombomodulin OR ART123 OR TMD123 OR rhs-TM OR AT-908 OR CD141 OR BDCA-3))

antibody. The author regards the company as one of the few Japanese companies that overcame the barriers of knowledge and acquired valued knowledge, because the company successfully released EPO and G-CSF even in the "sustainment & continuance" phase before the release of the soluble interleukin-6 receptor antibody in 2005. Moreover, the company still continues its efforts in the field of biopharmaceuticals with support of Roche starting in 2002. Chugai Pharmaceutical appears to have knowledge and know-how in varied phases from basic researches to industrial and clinical researches of biopharmaceuticals.[26] Further, the company's choice of becoming a subsidy of the world's leading pharmaceutical company Roche in 2002 gave the company access to vast knowledge of biopharmaceutical recipes and clinical development owned by Genentech (US), which was the world's largest biopharmaceutical company also under the wing of Roche. Thus, Roche, Genentech, and Chugai Pharmaceutical formed a triple alliance of Japan, the US, and Europe.

As mentioned earlier, a previous study pointed out that the strong connection between Chugai Pharmaceutical and Kishimoto Laboratory of Osaka University played a critical role in the company's R&D project of the soluble interleukin-6 receptor antibody.[24,25] The author agrees with the importance of the strong connection during the basic research phase, but proposes here a hypothesis that the triple alliance the company formed with Roche was critical in establishment of the global clinical testing network in and after the application phase. To exemplify the hypothesis, an analysis was conducted by using the Web of Science Core Collection as follows.

First, the articles in publications on the four biopharmaceuticals primarily developed by Japanese companies (i.e. soluble interleukin-6 receptor antibody, PD-1 antibody, CCR4 antibody, and Thrombomodulin) were counted by chief countries (Table 2). The results certainly indicated that Japan ranked the first with 555 articles in the list regarding the soluble interleukin-6 receptor antibody, followed by the US and the UK. However, the number of articles of the other countries was over 1,500 including the US's 380 and apparently Japan, where the R&D activities of Chugai Pharmaceutical took place, did not account for a dominant part of the list. For the PD-1 antibody, Japan's Ono Pharmaceutical was rather overshadowed. The first and second places were occupied by the US with 442 articles and Germany with 119 articles, and Japan ranked the fourth with 81 articles. For the CCR4 antibody, Kyowa Hakko Kirin was more influential as Japan leaded the list with 78 articles, followed by the US with 20 articles, and the UK with eight articles. For Thrombomodulin, Japan represented by Asahi Kasei Pharma and the US were dominant with 697 and 747 articles, respectively.

Then, article count data for the soluble interleukin-6 receptor antibody were analyzed by "Extended Organization" (Table 3). Among the top 10 organizations in "Extended Organization," there were two Japanese universities which appeared to be collaborative research partners of Chugai Pharmaceutical: Osaka University in the second place with 156 articles and Keio University in the eighth place with 46 articles. The parent company Roche Holding and its Swiss branch Roche Holding Switzerland rank the first and third with 397 and 87 articles, respectively. The other organizations in the list include institutions of the European academia. The article count of the PD-1 antibody was also analyzed by "Extended Organization" (Table 4). As a result, no institutions that participated in the collaborative research with Ono Pharmaceutical were not included in the top 10 organizations, which were all US-based institutions.

These findings suggested that the soluble interleukin-6 receptor antibody was developed by the fullest use of clinical development networks of not only Chugai Pharmaceutical but also Roche, which eliminated the significant gap in clinical development experiences between the company and Western major pharmaceutical companies and eventually made it a blockbuster of the world. The scheme of basic medical researches and clinical researches based on the industry-academia collaboration of Chugai Pharmaceutical and institutions including Osaka University is illustrated in Figure 1. The networks have allowed the company to deliver superior outcomes and publish high-level articles through collaborative researches (clinical researches) with optimal and influential institutions from across the world. True knowledge was obtained as a product of the triple alliance of Roche, Genentech, and Chugai Pharmaceutical.

Figure 2 shows the scheme of basic medical researches and clinical researches based on the industry-academia collaboration of Ono Pharmaceutical and institutions including Kyoto University. The networks have also allowed the company to deliver superior outcomes and publish high-level articles through collaborative researches (clinical researches) with optimal and influential institutions from across the world. However, the degree of dependence on allied BMS appears to be much higher than Chugai Pharmaceutical's case, because influential publications related to the PD-1 antibody were of institutions relating to BMS, not Ono Pharmaceutical as indicated in Table 2 and Table 4. Schemes in Figure 1 and Figure 2 are similar in appearance but qualitatively differ.

As supplementary information, the most proximate academia institutions in Figure 1 and Figure 2 are thought to roughly satisfy the following conditions, based on previous studies.[24]

- Jointly conducting a basic research with the business (joint application for patent)

Table 2: The number of articles in publications by country on the biopharmaceuticals which were primarily researched and developed in Japan.

No.	Drug Name	Generic name	Company	Marketed in Japan	Article	
					Country	Article count
1	Soluble IL6 receptor antibody	Tocilizumab	Chugai	2005	Total	1,687
					Japan	555
					US	380
					UK	275
					Germany	188
					France	185
					Spain	125
					Switzerland	119
					Italy	114
					Canada	91
					Sweden	60
2	PD-1 antibody	Nivolumab	Ono	2014	Total	737
					US	442
					Germany	119
					France	95
					Japan	81
					Italy	71
3	CCR4 antibody	Mogamulizumab	Kyowa-hako-kirin	2012	Total	105
					Japan	78
					US	20
					UK	8
					France	6
					Scotland	2
4	Thrombo-modulin	Thrombo-modulin alpha	Asahi-kasei	2008	Total	2,400
					US	747
					Japan	697
					France	188
					Germany	141
					Taiwan	111

Searched by the Web of Science Core Collection in February. Timespan: 1967–2016. SCI-EXPANDED, CPCI-S. Integrated article counts are incompatible with total article counts because of the overlap.

- Not engaging in any collaborative research with other private businesses for the same research theme
- Having a win-win relationship with the business
- Engaging in active human exchange with the business
- Being recognized by third parties as a close partner of the business

As mentioned above, the soluble interleukin-6 receptor antibody and PD-1 antibody became blockbusters. Thrombomodulin and CCR4 are inferior to the blockbusters in terms of sales performance. However, the results of analysis using the Web of Science Core Collection in Table 1 suggested that a number of high-level articles have been published regarding Thrombomodulin. Although

Table 3: The number of articles in publications and the extended organizations on the soluble interkeukin-6 receptor antibody which was primarily researched and developed in Japan.

No.	Article count	Extended Oraganization (Country)
1	397	ROCHE HOLDING (US)
2	156	OSAKA UNIVERSITY (Japan)
3	87	ROCHE HOLDING SWITZERLAND (Switzerland)
4	62	HUMBOLDT UNIVERSITY OF BERLIN (Germany)
5	62	FREE UNIVERSITY OF BERLIN (Germany)
6	58	CHARITE MEDICAL UNIVERSITY OF BERLIN (Germany)
7	56	ASSISTANCE PUBLIQUE HOPITAUX PARIS APHP (France)
8	46	KEIO UNIVERSITY (Japan)
9	46	KAROLINSKA INSTITUTET (Sweden)
10	41	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM (France)

Searched by the Web of Science Core Collection in February. Timespan: 1967–2016. SCI-EXPANDED, CPCI-S.

Table 4: The number of articles in publications and the extended organizations on the PD-1 antibody which was primarily researched and developed in Japan.

No.	Article count	Extended Oraganization (Country)
1	160	MEMORIAL SLOAN KETTERING CANCER CENTER (US)
2	152	HARVARD UNIVERSITY (US)
3	143	JOHNS HOPKINS UNIVERSITY (US)
4	138	VA BOSTON HEALTHCARE SYSTEM (US)
5	134	BRISTOL MYERS SQUIBB (US)
6	128	DANA FARBER CANCER INSTITUTE (US)
7	125	JOHNS HOPKINS ONCOLOGY CENTER (US)
8	112	YALE UNIVERSITY (US)
9	108	BRISTOL MYERS SQUIBB CO (US)
10	99	H LEE MOFFITT CANCER CENTER RESEARCH INSTITUTE (US)

Searched by the Web of Science Core Collection in February. Timespan: 1967–2016. SCI-EXPANDED, CPCI-S.

Thrombomodulin is currently distributed in Japan only, the finding as well as the data in Table 2 indicated a possibility that Thrombomodulin can become a blockbuster if distributed to the world for broader applications as it has gained attentions from the US and Europe. Meanwhile, the CCR4 antibody can hardly expect significant change in its current status unless being applied to other diseases. This is because the drug is for a rare disease ATL, for which there are few patients in industrialized nations other than Japan, and has not received much attention in the global academia as indicated in Table 2.

ANALYSIS OF BIOPHARMACEUTICALS WITH WEB OF SCIENCE CORE COLLECTION (2)

This section describes results of the analysis on US biopharmaceuticals with focus placed on therapeutic antibodies conducted using the Web of Science Core Collection as in the analysis (1) above (see Table 5). The seven therapeutic

Figure 1: Chugai Parmaceutical's collaborative research with Roche and academia.

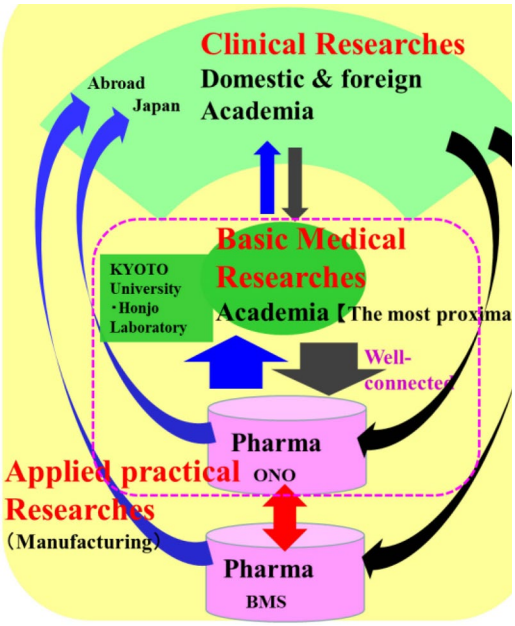

Figure 2: Ono Pharmaceutical's collaborative research with BMS and academia

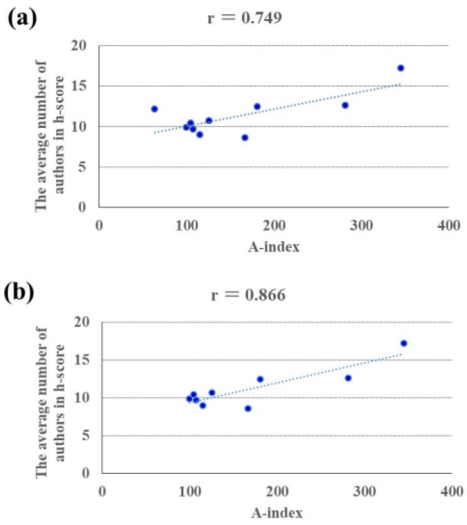

Figure 3: The correlation between the A-index and the average number of authors in h-score. (a) Values of the A-index and the average number of authors in h-score of the soluble interlukin-6 receptor antibody, PD-1 antibody, and CCR4 antibody in Table 1, and the C5 antibody, Aβ47 integrin antibody, RANKL antibody, and CD30 antibody in Table 5 were plotted. (b) The same values of the A-index and the average number of authors in h-score except the CCR4 antibody were plotted.

antibodies analyzed are human (humanized) antibodies released for popular diseases, not orphan diseases, in the US between 2007 and 2014.[37] They are not improved variants of existing therapeutic antibodies targeting on the same antigen, but rather unique drugs.

Using various evaluation indexes of academic articles obtained through the Web of Science Core Collection, the analysis in the previous section revealed that there were differences between trends of Japan and the US, and between Japanese therapeutic antibodies developed through US-Japan joint R&D and those developed independently by Japanese companies' R&D. The purpose of the analysis described in this section was to find any similarity between Japan's therapeutic antibodies based on US-Japan joint R&D and those originating in the US by investigating the trends in differences between therapeutic antibodies of Japan and the US through comparing the Table 1 and Table 5. As a result, however, no specific similarity was detected. Particular trends were hardly found in several indexes due to individual differences of the seven therapeutic antibodies of the US. It should also be noted differences in market release years result in relatively smaller number of articles and citations in newer drugs.

However, when comparing therapeutic antibodies independently developed in Japan with other drugs, it was found that the indexes other than the average citations count per item and the average number of authors in h-score (i.e. the A-index, Hg-index, and R-index, etc.) were the smaller with the CCR4 antibody.

Further, in-depth correlation analysis of various combinations of indexes identified a significant correlation between the A-index and the average number of authors in h-score.

Figure 3 shows the correlation between the A-index and the average number of authors in h-score. In Figure 3 (a), values of the A-index and the average number of authors in h-score of the soluble interleukin-6 receptor antibody, PD-1 antibody, and CCR4 antibody in Table 1, and the C5 antibody, A4β7 integrin antibody, RANKL antibody, CTLA4 antibody, Blys antibody, VEGFR2 antibody, and CD30 antibody in Table 5 were plotted. In Figure 3 (b), the same values of the A-index and the average number of authors in h-score except the CCR4 antibody were plotted.

The difference between Figure 3 (a) and Figure 3 (b) represents the impact of CCR4 antibody: The A-index of 63.69 and the average number of authors in h-score of 12.19 are apparently distinguished from other nine; as suggested by the difference between the correlation coefficient r in Figure 3 (b), 0.866, and that in Figure 3 (a), 0.749, inclusion of the CCR4 antibody lowered the indexes substantially. This is presumably because of CCR4 antibody's features distinct from the other nine

Table 5: Biopharmaceutical examples which were primarily researched and developed in the US

No.	Drug name	Generic name	Company	Marketed in the US	Article count	Citation count	Average Citations per item	h-index	g-index	Hg-index	A-index	R-index	individual h-index	individual h-index(hl)	Average number of authors in h-score
1	C5 antibody	Eculizumab	Alexion Pharma ceuticals	2007	870	7,210	8.29	43	74	56.41	104.79	67.13	13	4.11	10.47
2	A4β7 integrin antibody	Vedolizumab	Millennium Pharma ceuticals	2014	272	2,162	14.85	16	45	26.83	115.44	42.98	8	1.78	9.00
3	RANKL antibody	Denosumab	Amgen	2010	1,276	13,651	10.70	50	104	72.11	180.82	95.08	16	4.01	12.48
4	CTLA4 antibody	Ipilimumab	Bristol-Myers Squibb	2011	1,334	24,649	18.48	64	146	96.66	281.28	134.17	21	5.08	12.61
5	Blys antibody	Belimumab	GlaxoSmithKline	2011	345	4,320	12.52	32	61	44.18	100.09	56.60	12	3.22	9.94
6	VEGFR2 antibody	Ramucirumab	Med Immune	2014	295	4,755	16.12	31	67	45.57	125.39	62.35	13	2.89	10.74
7	CD30 antibody	Brentuximab vedotin	Millennium Pharma ceuticals	2011	563	6,301	11.19	40	71	53.29	107.60	65.60	15	4.11	9.73

Searched by the Web of Science Core Collection on February 4. Timespan: 1967-2016. SCI-EXPANDED, CPCI-S.

1. Search formula: title: (Eculizumab OR Soliris OR h5G1.1) OR title: ((complement AND C5 AND alpha) AND (antibody OR antibodies))

2. Search formula: title: ((Vedolizumab OR Entyvio OR (Anti-beta7 AND Mab) OR MLN-0002 OR MLN-02 OR LDP-02)) OR title: (((alpha AND 4 AND beta AND 7 AND integrin) AND (antibody OR antibodies))) OR title: ((("lymphocyte Peyer's patch adhesion molecule 1" OR LPAM-1) AND (antibody OR antibodies)))

3. Search formula: title: (Denosumab OR Pralia OR Prolia OR Ranmark OR Xgeva OR AMG-162 OR NSC-744010) OR title: ((RANKL OR (receptor AND activator AND NF-kappaB AND ligand)) AND (antibody OR antibodies))

4. Search formula: title: (Ipilimumab OR Yervoy OR 10D1 OR Anti-CTLA-4 MAb OR BMS-734016 OR (MAb AND 10D14) OR MDX-010 OR MDX-CTLA4 OR MDX-101) OR title: ((CTLA-4 OR CD152 OR (cytotoxic AND T-lymphocyte-associated AND protein AND 4)) AND (antibody OR antibodies))

5. Search formula: title: (Belimumab OR Benlysta OR LymphoStat-B OR Anti-BLys OR GSK-1550188 OR HGS-1006) OR title: ((BAFF OR (B-cell AND activating AND factor)) AND (antibody OR antibodies))

6. Search formula: title: (Ramucirumab OR Cyramza OR IMC-1121 OR LY-3009806) OR title: (((VEGFR2 OR VEGFR-2 OR "vascular endothelial growth factor receptor 2" OR "vascular endothelial growth factor receptor2" OR "vascular endothelial growth factor receptor-2" OR KDR OR FLK1 OR CD309 OR "kinase insert domain receptor") AND (antibody OR antibodies)))

7. Search formula: title: (elotuzumab OR Empliciti OR BMS-901608 OR HuLuc-63 OR PDL-063) OR title: ((SLAMF7 OR CS1 OR CRACC OR 19A24 OR CD319 OR (SLAM AND Family AND member AND 7) OR (CD2 AND subset AND 1)) AND (antibody OR antibodies))

antibodies, including its lower A-index value of 63.69. When Thrombomodulin's values of the A-index and the average number of authors in h-score are plotted to Figure 3 (b), the correlation coefficient is also substantially lowered down to 0.655.

Although R&D of the soluble interleukin-6 receptor antibody and PD-1 antibody was primarily led by Japanese pharmaceutical companies, the R&D projects were in fact joint projects with the world's leading pharmaceutical companies, Roche for the former and BMS for the latter. In the previous chapter, the author has pointed out that not only industry-academia collaboration in Japan but also global networks of such global giants in the pharmaceutical industry were important in the success of the R&D as illustrated in Figure 1 and Figure 2. The author's assumption regarding the finding of higher correlation in the A-index and the average number of authors in h-score of the antibodies other than CCR4 antibody (i.e. soluble interleukin-6 receptor antibody, PD-1 antibody, and the seven antibodies originating in the US), which was independently developed in Japan, is as follows.

As mentioned earlier, the A-index is obtained by dividing the total citations of top *h* most cited articles (h-score) by the h-index, and therefore the high correlation between the index and the average number of authors in h-score means that citations of highly-cited articles and the average number of authors should have a high correlation coefficient. The subjects of the analysis were articles related to antibody drugs released in the US between 2007 and 2014 after initial stage of therapeutic antibody R&D and full-fledged clinical development. Many of the articles were on clinical testing, suggesting that during the period clinical researchers and developers had been used to the therapeutic antibodies after the period of initial evaluation, and thus the research institutions started to be fixed while distributed across the world. The analysis results indicate that the higher the number of researchers involved in a given clinical testing report, the higher the citation count of highly-cited articles; and that research publications that drew more attentions were often written by a larger number of authors, which could be a factor of forming a global network of clinical researchers centered around the Western nations. Thus, the author believes that biopharmaceuticals independently developed in Japan without development of such clinical research networks have been facing with the barriers of knowledge.

The findings related to the CCR4 antibody is probably associated with the fact that the drug was created through Japan's independent R&D activities. The same can be said regarding Thrombomodulin although it is not an antibody drug. Comparison of the CCR4 antibody and Thrombomodulin with the other nine therapeutic antibodies showed a low correlation coefficient, but the factor of this is the average number of authors in h-score, which is high for the CCR4 antibody and low for Thrombomodulin. For the CCR4 antibody, the result showed that the citation count of the highly-cited articles was not high despite the high average number of authors in h-score, which suggests the failure of establishing clinical researches based on an authentic global network. For Thrombomodulin, on the other hand, the citation count was high despite the low average number of authors in h-score, which suggests a possibility that unlike the other medication fields including anti-cancer drugs and immunity, a substantial impact can be produced without involving a number of clinical researchers in the field of coagulation medication.

For data in Figure 3 (b), robustness of the high correlation coefficient (0.866) was examined. In other words, the correlation with the A-index was investigated with varied average number of authors in h-score. Specifically, the average number of authors in h-score was divided by "h-score x 1," "h-score x 1.5," "h-score x 2," "h-score x 1/2," "h-score x 1/3," "h-score x 1/4," and "h-score x 1/10," and correlation of each variant with A-index was plotted (Figure 4). Resultant correlation coefficients are 0.866, 0.841, 0.844, 0.890, 0.912, 0.867, and 0.835; the correlation coefficient was the largest with the average number of authors divided by "h-score x 1/3," which was 0.912. The correlation coefficients were constantly above 0.8 with varied h-score values, suggesting the high robustness of the correlation between the average number of authors and the A-index.

In this chapter, the new finding of the significant correlation between the A-index and the average number of authors in h-score and specific cases associated with the correlation were described. In consideration of the importance placed on articles drawing attentions, the indexes based on average citation count of highly-cited articles such as the A-index should play an important role in finding promising biopharmaceuticals. For the correlation discussed above, a higher A-index value of therapeutic antibodies can be obtained with a higher average number of authors in h-score. To obtain a higher average number of authors in h-score, more co-researchers are required per article. Especially for clinical researches, an increase of co-researchers means conducting a collaborative research with more strongly-connected institutions. Although forming a joint research partnership is generally difficult between institutions in the same region or the same level, possibility of a collaborative clinical research is higher with institutions in countries with genetically and ethnically different background can be higher. Therefore, establishment of high-level clinical researches based on global networks helps increasing the number of co-researchers, and the number of high-level

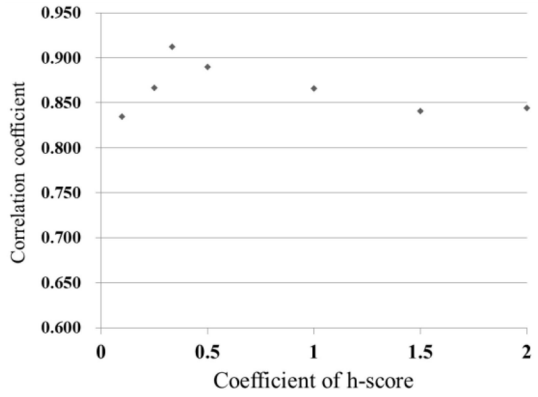

Figure 4: The correlation with the A-index investigated with varied average number of authors in h-score. The average number of authors in h-score was divided by "h-score x 1," "h-score x 1.5," "h-score x 2," "h-score x 1/2," "h-score x 1/3," "h-score x 1/4," and "h-score x 1/10," and correlation of each variant with A-index was plotted.

articles with higher A-index values. Then, articles with higher A-index values will lead to promising biopharmaceuticals with potential to be a blockbuster. In fact, the two therapeutic antibodies with high A-index values in Figure 3 - PD-1 antibody and CTLA4 antibody - became blockbusters in 2016.[3]

INTER-ORGANIZATIONAL LEARNING OF KNOWLEDGE

Cases of three therapeutic antibodies and one therapeutic protein originating and released in Japan have been reviewed in previous chapters to discuss the barriers of knowledge. Among the cases, this section focuses on Chugai Pharmaceutical that commercialized the soluble interleukin-6 receptor antibody for reasons stated in the previous chapter.

Chugai Pharmaceutical appears to have knowledge and know-how in varied phases from basic researches to industrial and clinical researches of biopharmaceuticals, as well as information obtained from the Roche Group (i.e. Roche and the world's leading biotech company Genentech).

The term "knowledge" in the context of "barriers of knowledge" refers to new knowledge and know-how for creation of biopharmaceuticals. For clarity of the term definition, several cases will be reviewed below.

Looking back the history of biopharmaceutical R&D in Japan, pharmaceutical players in Japan concentrated on manufacturing and there were no businesses that had in-depth knowledge in biopharmaceutical development even in the world during the "initial entry" phase in the 1980's. The full-scale entry into the biotech R&D by Chugai Pharmaceutical, one of the companies the led Japan's biopharmaceutical R&D around 1990, was in 1981, which was relatively later in comparison with other domestic major pharmaceutical and chemical companies.[25] Yet, the author assumes that its capital investment in the US-based bio-venture Genetics Institute[25,38] gave the company opportunities to thoroughly learn how to create EPO and new biopharmaceutics, i.e. drugs that were totally different from conventional low-molecular drugs. This is one form of inter-organizational learning.

Also, Chugai Pharmaceutical had experiences of a conventional low-molecular drug (antineoplastic drug "Picibanil") produced by using microbes.[38] Like Chugai Pharmaceutical, most of the domestic new entrants into the field had experiences in microbial fermentation; they could apply their superior microbial fermentation technologies to then-new microbial culture technologies based on recombinant DNA techniques, which allowed them to develop efficient manufacturing processes. This certainly represents the spill-over effect in economics.

Chugai Pharmaceutical had begun R&D of G-CSF prior to EPO in the "initial entry" phase[38] and synergistic effects could be expected from the two R&D projects.

In the case of Chugai Pharmaceutical's inter-organizational learning, the company deviated from the single loop of the conventional pharmaceutical R&D pattern proposed by Argyris & Schon.[39] In other words, the company dismissed the conventional pharmaceutical R&D pattern and established a new biopharmaceutical R&D pattern based on a totally-new concept. The author believes this was the double-loop learning.

In the "sustainment & continuance" phase, most of domestic businesses were engaged in clinical testing of biopharmaceuticals. They also deviated from the single loop of the conventional pharmaceutical R&D pattern and established a new biopharmaceutical R&D pattern based on a totally-new concept. We can see the double-loop learning cases here, too. However, learning in the phase was primarily in the form of intra-organizational learning, and there were no opportunities of inter-organizational learning with other organizations that were well experienced in clinical development of biopharmaceuticals such as Genentech in the US. Thus, learning in the period can be regarded as inefficient and voluntary learning. While successful in commercialization of EPO and G-CSF, Chugai Pharmaceutical was unable to distribute them overseas due to patent dispute and settlement with overseas companies,[22] and thus kept away from opportunities of learning and experiencing international clinical testing practices.

However, Chugai Pharmaceutical became a subsidy of Roche in 2002. By using the triple alliance with Roche

and Genentech as a driving force, the company thereafter acquired approval of the soluble interleukin-6 receptor antibody in Japan for Castleman's disease in 2005, and for rheumatic arthritis in 2008, and in Europe and the US for rheumatic arthritis in 2009 and 2010, respectively. The author believes that one of the major factor of this success was the inter-organizational learning of essential knowledge in biopharmaceutical R&D.

On the contrary, the majority of the other Japanese businesses could only acquire biopharmaceutical R&D knowledge through intra-organizational learning, but had no access to appropriate knowledge for biopharmaceutical preparation and clinical development through inter-organizational learning. The author believes that this is one of the barriers of knowledge that have made Japan lagging behind Western nations in biopharmaceutical R&D.

Matsuyuki et al. defined inter-organizational learning as a series of processes in which: learning organizations exchange their information and knowledge bi-directionally; and an organization receiving such information and knowledge forms and creates new knowledge through independent intra-organizational learning.[40] They also noted that integration of heterogeneous knowledge promoted creation of knowledge.[41]

According to Matsuyuki et al., knowledge is company's proprietary knowledge, management technologies, various know-how, customer trust, distribution channels, and information resources (part of management resources, e.g. corporate culture).[40] Badaracco, in 1991, defined two types of knowledge that form a chain of knowledge between businesses: "migratory knowledge" and "embedded knowledge."[42] Migratory knowledge is knowledge packaged in formulas, design diagrams and manuals and embodied in products, whereas embedded knowledge exists in individuals, groups, specific social environments, and specific techniques or professions.[42] Polanyi's "implicit knowledge" should fall under the embedded knowledge.[43] "Knowledge" discussed in the context of "barriers of knowledge" is assumed to be implicit knowledge. Matsuyuki et al. stated that it required more time and efforts to transfer implicit knowledge to an organization than migratory knowledge, but, once successfully transferred, implicit knowledge could create new knowledge and could strongly drive corporate reformation.[40]

What is deemed important in learning by corporate organizations - intra-organizational learning and inter-organizational learning - is how to acquire and learn external knowledge, how to embed such information as internal knowledge, and how to integrate internal and external knowledge, from the learning perspective in the theory of inter-organizational relationship.[44]

Here, specific examples of the knowledge discussed and defined above as implicit knowledge should be discussed. We can see some examples in therapeutic antibodies that currently receive attentions the most of biopharmaceuticals, and their R&D processes. In the R&D processes, a development target (i.e. a potential drug) is selected at first. In case of an antibody, the step can be search and selection of a target antigen. This step is assumed to be a particularly important step in therapeutic antibody R&D in order to pursue a blockbuster. Also, this is a step where research institutions can accumulate know-how and implicit knowledge effectively. Additionally, the author assumes evaluation system and screening step is an important step in the basic research phase of optimal therapeutic antibody development. Looking into patent applications filed by pharmaceutical companies seeking therapeutic antibody patent, the step was hardly stated in applications filed over 20 years ago but in those files in recent years and this is an indication of the importance placed on the step in recent R&D activities. Companies engaged in more R&D projects of therapeutic antibodies with Western major pharmaceutical companies, such as Chugai Pharmaceutical, often state an evaluation system in patent application documents and are thought to perform the evaluation system and screening step systematically in order to produce optimal therapeutic antibodies. They must also have implicit knowledge that is not disclosed in such documents.

In R&D, the step following the basic research phase is the industrial research phase, where substantial know-how and implicit knowledge are thought to be exercised in various aspects including formulation. In the phase of preclinical animal testing and clinical human testing, the author believes that there are not only know-how and implicit knowledge of research institutions in performance of specific tests, but also know-how and implicit knowledge of pharmaceutical companies in selecting and building special relationship with potential partner institutions with appropriate expertise for target biopharmaceuticals.

CONCLUSION

For the purpose of this research, major barriers and issues in knowledge for biopharmaceutical R&D in Japan, challenges called "barriers of knowledge," and reasons why Japan had lagged behind Western nations in the field of biopharmaceutical R&D were explored and discussed.

First, cases of three therapeutic antibodies and one therapeutic protein originating and released in Japan were reviewed in depth and the Web of Science Core Collection was used to analyze biopharmaceuticals with various indexes. As a result, differences between

Japanese therapeutic antibodies developed through US-Japan joint R&D and those developed independently by Japanese companies' R&D were identified: the former drugs were associated with higher figures in most indexes including the article count and citation count than the latter.

Then, the scheme of the relationship between pharmaceutical companies producing blockbuster therapeutic antibodies and academia, i.e. universities, was revealed as illustrated in Figure 1 (Chugai Pharmaceutical's collaborative research with Roche and academia) and Figure 2 (Ono Pharmaceutical's collaborative research with BMS and academia). It was then discussed that Chugai Pharmaceutical and Ono Pharmaceutical realized the blockbusters through the fullest use of clinical development networks made accessible by their strong partnership with a world's leading pharmaceutical company (Roche and BMS, respectively).

Further, therapeutic antibodies released in the US between 2007 and 2014 were analyzed in depth by using Web of Science Core Collection, and a significant correlation between the A-index and the average number of authors in h-score was identified. The correlation suggested that a higher A-index value of therapeutic antibodies can be obtained with a higher average number of authors in h-score. To obtain a higher average number of authors in h-score, more co-researchers are required per article. As mentioned earlier, establishment of high-level clinical researches based on global networks helps increasing the number of co-researchers, and the number of high-level articles with higher A-index values. Then, articles with higher A-index values will lead to promising biopharmaceuticals with potential to be blockbusters. The clinical development networks made accessible by strong partnership with a world's leading pharmaceutical company (Roche for Chugai Pharmaceutical and BMS for Ono Pharmaceutical), which are illustrated in Figure 1 and Figure 2, are typical global networks for clinical researches.

Given the above findings, the author discusses the primary reason why Japan has lagged behind Western nations in the field of biopharmaceutical R&D is failure of many Japanese pharmaceutical companies to establish such clinical research network.

Also, acquisition and exchange of knowledge within and between organizations were also explored through examples of Chugai Pharmaceutical, which was regarded as a successful Japanese pharmaceutical company that overcame the barriers of knowledge. The term "knowledge" in this context falls under implicit knowledge or embedded knowledge, which specifically lies in various R&D phases from basic researches to applied researches. Chugai Pharmaceutical acquired such knowledge by becoming a subsidiary of Roche, but most Japanese businesses have not yet had access to such knowledge. This is also the reason of the gap from Western counterparts.

Below is the complementary discussion to the two answers to the research question of this article.

There are two types of the barriers of knowledge: barriers to commercialization of biopharmaceuticals (phase I); and barriers to production of a blockbuster (phase II), where a given biopharmaceutical can be commercialized but generate minor sales volume. Naturally, knowledge required to overcome barriers differ depending on the types. The global clinical development networks described in the discussion of the correlation between the A-index and the average number of authors in h-score are related to the phase II. The intra- and inter-organizational learning of knowledge is related to both the phase I and phase II. For instance, knowledge that Chugai Pharmaceutical acquired through inter-organizational learning in the Roche Group is thought to be the knowledge for the phase II. This is accounted for by Chugai Pharmaceutical's voluntary learning and inter-organizational learning with a US-based bio-venture for commercialization of EPO and G-CSF in the "sustainment & continuance" phase, i.e. acquisition of knowledge for the phase I.

In this article, reasons why Japan has lagged behind Western nations in the field of biopharmaceutical R&D have been discussed from a standpoint of barriers of knowledge. For the future, the author will consider and report research questions from the learning perspective of the theory of inter-organizational relationship referenced above as well as other perspectives of the theory.

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Article

Biotechnology-driven Business Model Archetypes: Sustainability, Innovation and Commercial Viability

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ABSTRACT

Purpose: In spite of enthusiasm for biotechnologies to enable sustainability and the development of innovative sustainable business models, limited research, tools and resources exist. Therefore, this research questions how the business model of sustainable biotechnology-driven firms differs from other businesses.

Methodology: This article applies a structured content analysis method to enumerate sustainable business model archetypes in biotechnology firms focuses utilising secondary data from 64 existing. The triple-layer business model canvas is used as the categorisation matrix.

Findings: Five sustainable business model archetypes were identified for biotechnology firms. Findings highlight that sustainable biotechnology-driven businesses can reach a sustainable business model through either operating as an environmentally-led or economically-led domain.

Research limitations/implications: This article recognises that transitioning to a sustainable business model requires significant change to many facets of the business, therefore this study provides a template for future organisations, supporting the realisation of future, sustainable, biotechnology innovations.

Originality/value: Unlike previous studies this article focuses exclusively on biotechnology firms, as well as utilising the Triple Layer Business Model Canvas as the categorisation matrix, the first article to do so. This article provides a template for large-scale industrial businesses to build, or transition to, more sustainable business models utilising biotechnology.

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Keywords: Sustainable business model; Biotechnology; Triple layer business model canvas; Business model archetypes

1. INTRODUCTION

Role of biotechnology in sustainable innovation

Biotechnologies, as both a field of enquiry and an industry, are applications that exploit biology for industrial, scientific, medical or other purposes. The variety of life on earth provides enormous diversity that may be prospected and applied to future industrial applications. Due, in part, to this diversity, biotechnologies have long been promised as a sustainable alternative to existing industries including heavy fuel and chemical[1,2]. The nature of discussion of biotechnology in existing literature is focused on the technological capability, frequently as a substitute to an existing industrial process, rather than questioning what is the ideal operating logic needed to bring these technologies to market[3,4,5]. Across many industrial sectors novel business models have been shown to enhance technological adoption[6,7]. In the case of biotechnology this offers an opportunity to accelerate the adoption of more sustainable alternatives to both incumbent industrial processes as well as businesses.

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The emerge of new molecular biology tools, including CRISPR-Cas9, combined with the rapid improvements in synthetic biology and genetic technologies sets the stage for new generations of biotechnology breakthroughs. However, this leads to the question of how will these scientific breakthroughs are brought to market? Can we learn from past biotechnology business models to develop new, more innovative mechanism to rapidly scale these technologies, realising the sustainable advantages offered by the underlying breakthroughs?

Against a backdrop of increasingly globalised markets, organisations need to address both technological and administrative innovation in order to achieve a sustainable advantage. These organisations must then configure and protect technologies and knowledge assets in order to maintain this position[8,9]. This confluence of technological, competitive and administrative innovation includes a balance of output-related measures (product/ service), process-related measures and enterprise-related measures[10]. Further, it is recognised that transitioning to a sustainable business model requires significant change to many facets of the business, from production process to modes of operation, and in many cases organisations are mostly equipped to manage incremental change and innovation[11].

Reflecting these challenges is the emergence of business models, increasingly recognised as critical in creating sustainable organisations reflecting the several necessary facets described previously[12,13,14]. Within this category of biotechnology-driven firms is heavy industry, a subset of which are chemical and petrochemical industries; major emissions contributor as well as key consumers of energy and fuel resources in major markets[15]. Whilst these industries have the potential to exploit biotechnologies to increase their sustainability credentials, at this stage, research connecting biotechnology innovations and new business models is limited.

Existing literature on biotechnology business models have been detailed from the perspective of the firm's role in a value chain of other organisations[16] and the importance of intellectual property protection and management to securing a biotechnology business[17]**.** Other studies on this topic address the technologies themselves rather than the business logic required to bring these technologies to market. The aim of this article is to understand how sustainable biotechnology-driven business models differ from other sustainable business models, through a qualitative content analysis of 64 international biotechnology companies. Specifically, this study questions how biotechnologies relate to a company system (people, culture, human development, change management, and innovation), environmental system and social system in order to create a sustainable organisation. The results of this study provide exemplars for practitioners and scholars for how biotechnologies can be brought to market in order to address global sustainability challenges.

This article proceeds as follows: first the role of biotechnology in sustainable innovation is discussed, then business model and sustainable business model literature is briefly discussed, following this method and results are presented, the article concludes by discussing implications and presents a new model for how these archetypes relate to the established industry value chain.

Contextualising business model innovation

A variety of definitions exist for key terms including business model design and business model innovation (BMI)[18,19], for this article we define a business model as a summary of the underlying operating logic and organisational architecture of a firm. This includes the organisation's value proposition and mechanism of capturing value[20,21,22]. It is well known that this underlying logic and operating structure inevitably evolves as both the external and internal operating environments change for and within the organisation[23,24,25]. This business model evolution raises both economic and cognitive challenges, for a business model to function it requires a range of interrelated actors, including customers, partners and the focal firm to function as a single activity system. The economic performance of a firm has previously been related to how these actors function within this activity system[26].

Whilst evolution of a business model within the context of an organisation is typically responsive, emerging as the external or internal operating environment changes, there is increasing recognition that deliberate focus on BMI can support business/ economic/ strategic competitiveness[6]. A recent review of BMI literature by Foss and Saebi[18] enumerated four main areas of research on BMI: 1; conceptualising or classifying business models, 2; BMI as a process, 3; BMI as an outcome and 4; the implications of BMI on organisational performance, highlighting the limited consensus on what constitutes BMI. In this article, we align with Casadesus-Masanell and Zhu's[27] definition "At root, business model innovation refers to the search for new logics of the firm and new ways to create and capture value for its stakeholders; it focuses primarily on finding new ways to generate revenues and define value propositions for customers, suppliers, and partners."

The influence of a well suited and innovative business model on organisational success been shown in the literature to provide a significant performance benefit for businesses[5,28,29,30]. Within this field there are a number of

schools of thought on the purpose and process of BMI. Spieth et al.[31] describe three motivations for engaging in BMI at an organisation level: i) explaining the business, ii) running the business and iii) developing the business. Alternative viewpoints include BMI as an internal and continuous process[32,33,34]. Within the research surrounding BMI as a process are a number of tools to conceptualise a firm's underlying operating logic, including the Business Model Canvas (BMC). The BMC has seen wide adoption across the three fields described above: understanding the business, operating the business and developing the business[35]. Previous studies have indicated the novelty of a business model combined with product-market fit, are positive indicators of successful business performance[7,28,29,30]. Simultaneously, the deliberate action to reinvent or improve the business models of established organisations have been reported as a driver of organisational competitiveness[34,36].

Sustainable business models

The above section describes the concepts of business models and business model innovation generally; implicitly these fields focus on the economics of business models. Sustainable business models (SBM) represent a related field of research where the underlying logic enables the organisation to operate in a sustainable manner. This is typically measured using the 'triple bottom line' of economic, environmental and social sustainability[37,38]. Previously specific needs for SBM have been enumerated[39] with recent discussion surrounding tools to support the development of these[13,40] (França et al., 2016; Joyce and Paquin, 2016). Bocken, Short, Rana and Evans[41] discribe eight SBM archetypes across the grouping of organisations led by technology, social-focus or organisational-focus (Figure 1). This prior study describes the value proposition, means of value creation and delivery and value capture mechanism of these sustainable organisations.

Successful introduction of innovation enables firms to adapt to a changing environment[12], however, clarifying how existing firms have achieved sustainability is less known. These patterns can be replicated or adapted by established firms or considered in the establishment of new ventures in order to direct innovation efforts toward a sustainable outcome. In the case of biotechnology firms, the combination of technology, products, services offered, value proposition and value capture mechanism forms the organisations SBM. Sustainable BMI specifically has been shown to improve the potential marketability and ultimate impact of sustainable innovations[12]. However, the development of innovative SBM themselves is an emerging topic, presently there are few tools and resources available to assist companies in sustainable business modelling[42]. Exploration from other fields, including design and innovation, have considered the role of tools and processes in developing and innovating business models within organisations, drawing on fields as diverse as design thinking, mathematical modelling and innovation processes[29,33,43].

Biotechnology business models

To date biotechnology business models have been studied in limited geographies[16] as well as considering success factors of small to medium biotechnology enterprise[44]. Additional prior literature has considered the business model evolution in medical biotechnology sectors, observing the emergence of increased prevalence of hybrid business models in biotechnology firms from platform or tool business models[45]. More recent research has identified how disruptive business models emerge in pharmaceutical companies, identifying that new entrants typically replicate the business models of an incumbent firm before adopting a disruptive business model as their technology matures[46]. Outside of biotechnology specifically previous studies have also explored how BMI supports the marketability of sustainable innovations[39]. The application of high-level archetypes of business models derived from analysis of predominantly academic literature has also been explicated[41], however not in the context of biotechnology business models specifically.

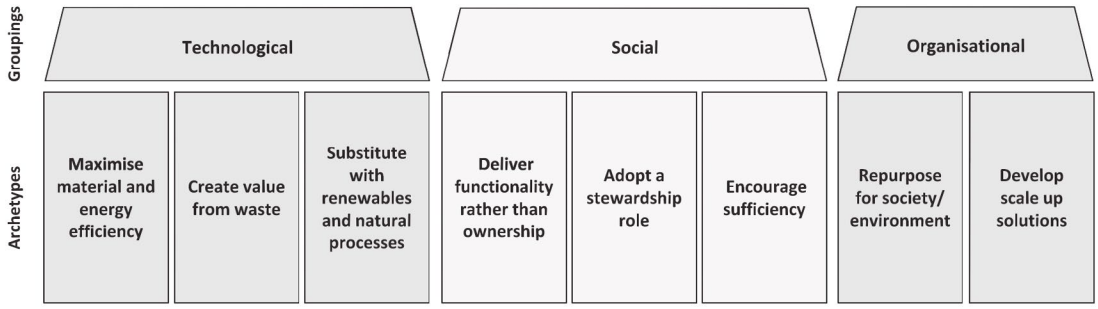

Figure 1: Sustainable business model archetypes described by *Bocken et al.*[41]

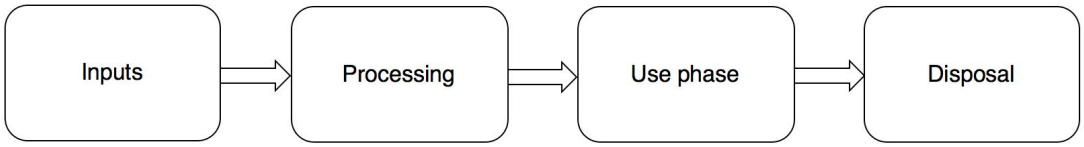

Figure 2: Overview of the biotechnology value chain adapted from *Braungart, et al.*[50]

The interaction between businesses in the biotechnology sector is complex and has been considered from several perspectives, including lifecycle analysis[47], knowledge transfer and inter-organisational relationships[48] and alliances[49]. These authors acknowledge the complexity of the interactions between actors in the biotechnology industry, some view the value chain as a more linear set of relationships between firms from input sources through to final products, which then returns as an input[50]. An adapted version of this value chain (figure 2) includes the key stages of inputs, processing, use and disposal to represent the relationship between firms.

Historically organisations are led by capitalist values, with social and environmental outcomes considered secondary[39]. In this study, the focus is not on the biotechnologies themselves, nor on the products or services enabled by these technologies, rather, the focus is the underlying business logic and the relationship to biotechnology innovations. This topic was selected to understand if initiatives addressing different elements of a company system (including people, culture, human development, change management, and innovation) impact and or contribute to sustainability dimensions (economic, environmental and social). Whilst there are a multitude of sectors and subsectors that fall into the broad category of biotechnology, this article focuses on three industry sub-segments: Industrial Biotechnologies, Environment Biotechnologies and agricultural biotechnologies, to explore our core research question: *How do sustainable biotechnology-driven business models differ from previously established sustainable business model archetypes?*

2. METHOD

This study implements a structured qualitative content analysis of 64 sustainable biotechnology-driven firms. For an organisation to be included in this study three criteria were used to select organisations:

(1) Biotechnology must be core to the organisation,
(2) The organisation must have been identified as sustainable and,
(3) The application of biotechnology is for industrial purposes rather than applied to human health.

Companies included were selected from sustainability rankings, websites of organisations involved in sustainability (e.g. UNEP, GreenPages), membership directories of biotechnology companies (e.g. BIO [USA], Ausbiotech [APAC]) and case studies on sustainable business models[51]. From this initial list, organisations that did not utilise biotechnology for industrial purposes as the basis of their offering were eliminated. As this selection process sought organisations listed in sustainability rankings, this selection process is focused on industrial biotechnology companies rather than medical biotechnologies. Organisations identified through both sustainability listing and biotechnology member organisations and listings were then pooled. From this pooled list, medical biotechnology companies and service providers were eliminated. Table 1 outlines the 64 companies in this study following this selection process, the region, location of headquarters, industry sector(s), number of employees and 2016 revenue.

Three modes of secondary data were collected, Source I included information directly from the organisation including website, promotional material and media releases. Source II included organisational information found in stock market disclosures, financial disclosures and annual reports. Source III included public media releases by third parties. Data sources and purposes are summarised in table 2. Company information which did not fall into the predetermined categories were discarded[52]. A content focused coding guide was developed so that data could be more precisely sorted into the categorisation matrix[54].

Analysis protocol

Relevant data from secondary sources was analysed using a predetermined categorisation matrix[52]. This approach draws on prior studies where the Business Model Canvas was implemented as a categorisation matrix in a content analysis study[54] and expands on this through the use of the Triple Layer Business Model Canvas (TLBMC)[13]. The TLBMC was selected as the categorisation matrix

Table 1: List of organisations included in this study

Organisation Name	Region	HQ	Industry sector(s)	# employees	2016 revenue
Abengoa Bioenergy	Global	Spanish	Energy	34	€7.150 billion (2014)
Addax Bioenergy	Global	Switzerland	Industrial	50-200	–
Advanced microbial services	USA	USA	Remediation	<50	–
Affordable biofeedstock	USA	USA	Industrial	50-200	–
Agrimetis	USA	USA	Agriculture	<50	–
Agrivida	USA	USA	Agriculture	<50	$0
Agua Inc	Global	USA	Water	50-200	$500k
AltAir fuels	Global	USA	Industrial	<50	–
Amyris	USA	USA	Industrial, lifescience	200+	$67m
Anatara Life Sciences	APAC	Australia	Agriculture	<50	$3.15m
Anellotech	USA	USA	Industrial	<50	$0
Aqua Bounty Technologies	USA	USA	Agriculture	<50	$50k
Aquabio	Global	USA	Remediation and environmental monitoring	<50	–
Arzeda	USA	USA	Industrial	<50	–
Avantium	EU	Netherlands	Process development and control	50-200	€ 10.5 million
Bayer	Global	Germany	Pharmaceutical, lifesciences, agriculture, industrial	200+	€46.769 billion
Benson Hill Biosystems	USA	USA	Agriculture	50-200	$5m (estimated)
Bgene	EU	France	Industrial	<50	–
Bio-on	EU	Italy	Material production	<50	$4.2m
Bioactive Laboratories	Australia	Australia	Agriculture, lifesciences, human health	-	–
BioAmber	North America	Canada	Industrial	50-200	$15m
BlackGold Biofuels	USA	USA	Industrial	<50	–
Blue Marble Biomaterials	USA	USA	Industrial	<50	-
Bolt Threads	Global	USA	Agriculture	50-200	$0
Calysta	Global	USA	Agriculture	<50	–
Carbios	EU	France	Waste management	<50	–
Codexis	Global	USA	Industrial	50-200	$35m
Environmental Bio-Detection Products Inc.	North America	Canada	Remediation and environmental monitoring	<50	–
Gen3 bio	USA	USA	Industrial	<50	–
Green Biologics	Global	UK	Industrial	50-200	$30m
Heliae	USA	USA	Industrial	50-200	$15.8M
Imperium Renewables	USA	USA	Industrial	<50	$0
Inventure Renewables	USA	USA	Industrial	<50	–
KAM Biotechnology	North America	Canada	Environmental cleantech	<10	–
Karma3	Australia	Australia	Waste management	<50	<$1m
Matrix Genetics	USA	USA	Industrial	<50	–
MBP Group	Global	Switzerland	Industrial	50-200	€ 75 million
Meridian Bioenergy	USA	USA	Industrial	<50	$3.9m

MetGen	EU	Finland	Industrial	<50	–
Microgen Biotech	EU (China)	Ireland	Environmental cleantech	<50	€80m
Microsynbiotix	Global	USA	Agriculture	<50	$0
Neste	North America	Canada/USA	Industrial	200+	€11.689 billion
Novozyme	Global	Denmark	Industrial	200+	12.46 billion DKK
Nuleaf Tech	USA	USA	Water	<10	–
NXT Fuels	APAC	NZ	Industrial	-	–
Parabel	USA	USA	Agriculture	<50	$650k
Perfect day	Global	USA	Agriculture	<50	$0
Phycohealth	Australia	Australia	Agriculture, human health	<50	$500k
PILI	EU	France	Industrial	<50	$0
Pond Biofuels	North America	Canada	Industrial	<50	$0
Primordial Genetics	Global	USA	Industrial and Agriculture	<50	–
Probiosphere	North America	Canada	Remediation	<50	–
Proterro	USA	USA	Industrial	<50	–
Provectus Environmental Products	USA	USA	Environmental cleantech	<50	–
Red Rock Biofuels	USA	USA	Industrial	<50	<$1m
Sensatec	EU	Germany	Environmental cleantech	<50	–
SkyNRG	Global	Netherlands	Industrial and Aviation	<50	–
Specialty Enzymes and Biotechnologies	Global	USA	Waste management, Industrial, Food	<50	–
Thermo Fisher Scientific	Global	USA	Pharmaceutical, lifesciences, agriculture, industrial	200+	$18.27 billion
Tyton BioSciences	USA	USA	Industrial	<50	$3m
Universal Biomining	USA	USA	Environmental cleantech	<50	–
Unnamed agricultural startup	USA	USA	Agriculture	50-200	–
Wood Waste to Rural Heat	North America	Canada	Energy	<50	–
Zymergen	Global	USA	Industrial	200+	–

Table 2: Types of data sources collected during this study

Type	Source I – company information	Source II – organisation disclosures	Source III – market insights
Sources	Digital platforms (website, social media etc.) Company brochures Media releases	Annual reports Financial reports Stock market filings	Media coverage Market reports Research reports
Purpose	Direct insight into the organisations perception and public actions	Insight into financial information, company strategy and marketing strategy	Commentary from third parties on individual firms as well as external perspective on self-reported sustainability.

for this study as it includes both the principles of triple bottom line (Elkington, 1999) as well as the principles of business modelling[6,35]. This research approach was used to understand systematically how organisations create and capture value and ensure sustainability.

The TLBMC is an extension of the Business Model Canvas (BMC) developed by Osterwalder and Pigneur[35].

The first of the three canvases in the TLBMC is directly adopted from this original BMC. As described by Joyce and Paquin[6] the TLBMC has 'vertical coherence', with each of the three canvases adopting the same layout, and are arranged as such the corresponding fields in each of the three layers relate directly to the corresponding field in the other layers. For instance, the value proposition in the economic layer is directly related to the functional value in the environmental layer and social value in the social layer. Definitions for the economic layer are taken from Osterwalder and Pigneur[35] and definitions for environmental and social layers are taken from Joyce and Paquin[6]. A brief summary of these definitions is included in table 3.

Once a TLBMC had been developed for each organisation each TLBMC was then clustered in order to develop categories based on similar value proposition, value creation and value delivery[55]. These clusters were iterated based on the previously established coding frameworks until a consistent clustering of business models occurred. These clusters were then generalised, and described as a single archetype. Meta-archetypes were then generated by clustering the archetypes based on the similarities in value proposition and value delivery, whether the organisation is driven by economic

Table 3: Summary of the 27 fields of the TLBMC used as the categorisation matrix in this study

Economic layer	Environmental layer	Social Layer
Value proposition The collection of products or services offered to meet the needs of a customer segment	**Functional value** Equivalent to the functional value unit used in life cycle assessment	**Social value** The elements of an organisations mission that impact stakeholders and society more generally
Customer segments The groups of customers using these products or services	**Use phase** The impact of the customer utilising the functional value, e.g. repair and maintenance	**End user** The person or group who 'consumes' the value proposition
Key activities The most important activities the organisation undertakes to deliver their value proposition	**Production** Cataloguing high environmental impact activities which are core to the organisation	**Governance** Capturing the organisational structure including ownership and decision-making policies
Key resources The resources necessary for an organisation to undertake the above key activities	**Materials** What are the Key materials for the organisation and their environmental impact	**Employees** This includes the numbers and types of employees as well as any social programs specifically to advance this stakeholder group
Key partners Partners necessary for the business to undertake some of the businesses core activities	**Supplies and outsourcing** Other activities needed to deliver functional value that are undertaken by partners and suppliers	**Local communities** Here individual communities are considered, this includes communities with an economic relationship (e.g. with suppliers) and the environmental/social impacts
Cost structure Key monetary consequences of the above activities, resources and partners	**Environmental impacts** Key environmental consequences of the above activities	**Social impacts** Here the social cost of the organisation is addressed
Revenue streams The way in which the organisation produces revenue from each customer segment	**Environmental benefits** Any environmental benefits of the organisations including energy/ emissions saving from a baseline	**Social benefits** Any positive social value created by the organisation
Channels The way in which the businesses reaches their customers	**Distribution** Environmental cost of distribution of products	**Scale of outreach** The depth and breadth of relationships the organisation builds with stakeholders
Customer relationships The type of relationship the business has with their customers	**End of life** When the client ends the consumption of the functional value, including the management of the product	**Societal culture** Potential impacts of the organisation on society as a whole

value proposition, environmental value proposition or social value.

The TLBMC as a categorisation matrix is appropriate for this research due to the specific inclusion of the social and environmental canvases, allowing environmental and social credentials of the organisation to be categorised and compared. However, due to the limitations of the content analysis research approach, some organisations did not have explicit or published information on social actions, or environmental impacts or mitigation strategies establishing an accurate and full understanding of the business.

3. Findings

From the analysis, distinct economic-led and environmental-led archetypes were observed. As the TLBMC is structured to be vertically coherent, the archetypes described are evidence of the organisation's core functional value proposition. The archetypes and meta-archetypes are summarised in figure 3.

Of the total 64 organisations, each was categorised into a single archetype. Of these five archetypes, the most frequently occurring was found to be 'Alternative Input', with many organisations utilising bio-based feedstocks to substitute petrochemical processes, a total of nineteen organisations were classified in this archetype. By contrast the least frequent archetype was found to be 'Alternative End-of-Life Processing', occurring in seven organisations.

Each cluster that formed individual archetypes was comprised of organisations across multiple industry subsectors. The proportion of different industry subsectors in each archetype grouping is presented in figure 4. Archetypes which offer an efficiency gain in industrial process tend to arise more frequently in industrial sectors that provide bulk, commodity material supply, including fuels, industrial chemicals and agricultural inputs.

In the following section each of these five archetypes are described, with examples of organisations utilising this archetype and high level value proposition, environmental functional value and social value is presented.

Archetype I: Energy or resource efficient alternatives

The first archetype considers firms substituting an existing industrial process with a biologically-mediated alternative. This is typically associated with chemical production of intermediate chemicals including both fine chemicals including amino acids and bulk chemicals including production of monomers, fuels and lubricant. The rationale for adoption of a biological process over a conventional, industrial chemical approach is to improve energy or resource use, increasing conversion rates to finished products, or reaching finished products with fewer process steps. Also captured within this category are a range of agricultural biotechnology organisations, including animal and plant breeding and genetic modification for farm productivity or resilience. The rationale of biotechnology in this case is similar to industrial applications, to increase the overall efficiency of conversion of agricultural inputs, into products. Due to this these organisations are able to compete on the basis of cost. As the advantage derived is a cost-based advantage this archetype is classified as 'economic-led', the primary advantage of adopting biotechnologies is to reduce costs to be able to compete on price.

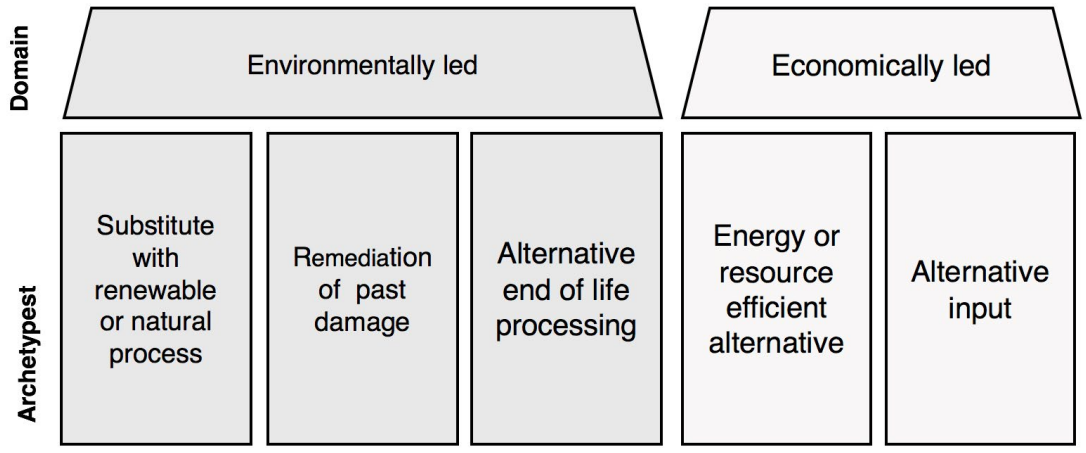

Figure 3: Summary of findings, Sustainable biotechnology-driven business model archetypes

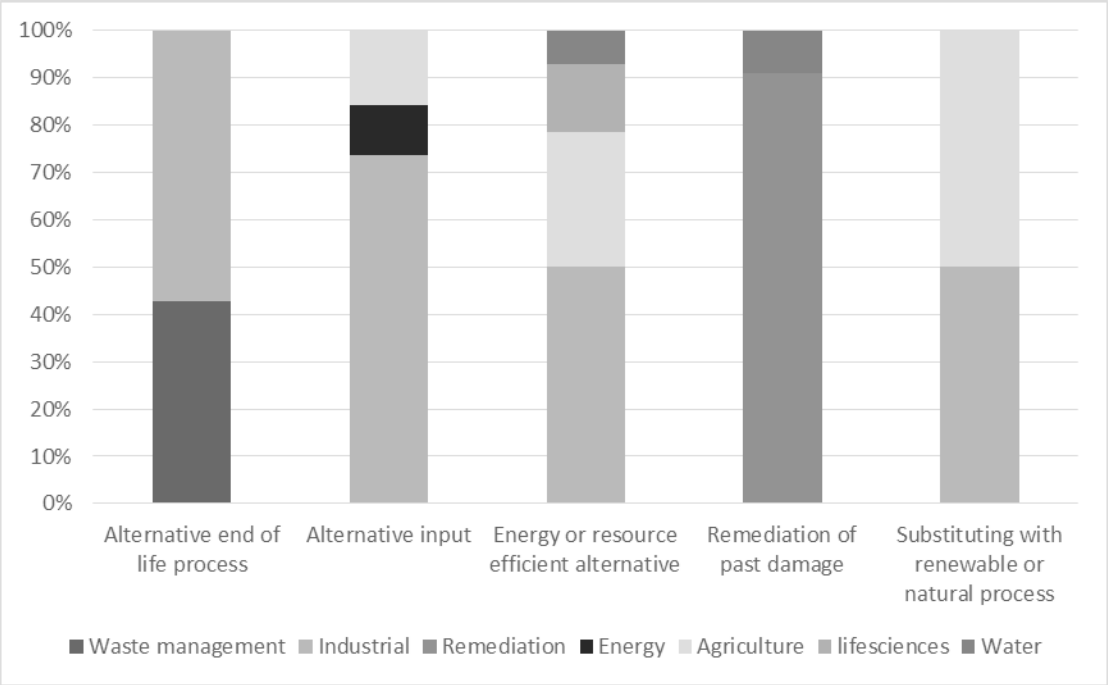

Figure 4: Distribution of industry sectors across archetypes developed in this article

Value Proposition	**Environmental functional value**	**Social value**
Reduction in energy or resource requirements of an established process achieved by utilising a biological alternative to conventional process, typical undertaken at an industrial scale.	Reduced resource requirement for an established process, often savings occur in energy (lower operating temperature), water usage and reduced discharge.	Minimal and not explicit with any included organisations.

Figure 5: Key criteria for the archetype Energy or resource efficient alternative

Examples of organisations in this category include Amyris, a business utilising microbes as an alternative production system for small high value molecules including amino acids. The end product is functionally indistinguishable from conventionally produced materials, however by utilising a microbial production system energy, water and waste discharge are substantially reduced. Amyris produces these chemicals internally, selling bulk chemical to a range of customers, therefore the benefit is realised by outcompeting conventional chemical producers by offering a less resource and energy intensive process. By contrast Novozyme produces bulk enzymes, naturally occurring protein structures that significantly reduce the energy required in chemical reactions. These bulk enzymes are sold to industrial customers in order for the customers to implement a lower energy and resource intensive process in their established operation.

Archetype II: Alternative input

The second archetype considers those businesses applying biotechnology to achieve a known product as an input to an established process, through substituting an input to this process. An example of this is biogas fermentation as an input to energy generation, in this example a fuel product is produced, not from finite fossil fuel resources, instead from the alternative input of a bio-physical feedstock. This archetype may operate as a direct substitution of a fossil fuel product, or, in some cases, organisations operate as a vertically integrates business, encompassing fuel production, energy generation and, in some cases, retail.

A number of biotechnology organisations apply these technologies in order to utilise a non-traditional bio-physical feedstock, in some cases this enables a non-finite resource to be used in place of a finite resource. Examples of organisations utilising this archetype include Neste, which utilises waste biomass as an

Value Proposition	Environmental functional value	Social value
Utilising an alternative source for the production of an intermediate process step. Typically organisations in this archetype utilise a waste stream (e.g. waste biomass) to produce an intermediate product presently derived from petrochemicals or another non-renewable source.	Twofold, alternative management of a waste stream and offering a resource efficient alternative to conventional production.	Minimal and not explicit with any included organisations.

Figure 6: Key criteria for the archetype Alternative input

input, with biologically mediated steps to produce fuels, monomers for the production of plastics and products for the aviation sector. An alternative example is Microsymbiotix, an organisation providing an alternative to prophylactic antibiotic usage in aquaculture by creating microalgae strains that express vaccines. These novel strains can then be incorporated into feed for the aquaculture industry preventing pathogen transmission through vaccination rather than the application of antibiotics. In this case the conventional antibiotic application is substituted for with a low-cost, effectively zero labour vaccination.

As with the previous archetype these organisations operate within the confines of the established industrial value chain.

Archetype III: Substitute with renewables and natural process

The third archetype is observed in organisations that have substituted one or more process steps with biologically mediated alternatives. Typically, these organisations have achieved or are approaching environmental sustainability through incremental action, rather than substantial change to the operating model of the business. Examples of the type of organisations in this category include intermediate chemical production, as well as other industrial organisations. Some businesses in this category include equipment suppliers enabling one or more process steps can be substituted with biotechnology processes.

Value Proposition	Environmental functional value	Social value
Alternative source of commodity products, functionally indistinguishable from (or an improvement over) the established alternatives.	Reduced resource requirement for the production of inputs to processes or materials.	Minimal and not explicit with any included organisations.

Figure 7: Key criteria for the archetype Substituting with renewable or natural processes

A significant number of biotechnology innovations are adopted by existing businesses in order to replace or supplement energy efficient or low efficiency process steps. Thereby adoption of these technologies is aimed at increasing yield, whilst often simultaneously reducing inputs (typically energy, water or fuels). Instances of this archetype are frequently established industrial chemical organisations replacing or supplementing a process step with one employing an enzymatic or microbial process. In these cases, the benefit of the substitution is a reduction in energy requirement, as the reaction often occurs at a lower temperature. In many examples manifestations of this archetype were businesses supplying equipment, materials or knowledge to established industrial-scale producers.

Organisations in this category are frequently offer a functional alternative to an existing commodity produced with a biologically mediated production system. Many examples in this category are bulk material suppliers, producing agriculture chemicals, fuels, polymers and fibres. For instance, Bolt Threads is developing an alternative high technology fibre using yeast to produce spider silk that can then be woven into fabrics. Unlike conventional fibre production arable land is not required and inputs can be, at least partially, derived form sustainable sources. Alternative examples include Perfect Day and PILI, these organisations produce an animal-free milk alternative and microbe-produced pigments respectively.

Archetype IV: Remediation of past damage

The fourth archetype describes companies applying biotechnologies to remediate past damage, predominantly from mining, industrial discharge, ground water pollution and oil spills. Damage management and remediation

Value Proposition	Environmental functional value	Social value
Returning damaged sites to their original state using safe, ubiquitous biology.	As described by several organisations that utilise this business model archetype these organisations are "helping nature to repair itself".	Returning lost land to those that can use it for food production or other commerce.

Figure 8: Key criteria for the archetype remediation of past damage

Value Proposition	Environmental functional value	Social value
Turning waste into valuable products.	Prevention of both waste entering landfill and reduction input costs and resources needed to produce new materials.	Progression toward circular economy, minimising future burden of waste streams.

Figure 9: Key criteria for the archetype Alternative end-of-life processing

is critical for environmental recovery following gradual or acute damage. Extensive discussion in the literature includes application of biotechnologies to damage remediation of oil spills[56], soil contamination[57] as well as industrial pollution management[58]. A large number of commercial ventures are operating offering bioremediation services. The business model of such is presented in figure 8.

Applications of this archetype are observed in mining, agriculture, oil spill management, water management and waste management sectors. For instance, Advanced Microbial Services, KAM Biotechnology and Microgen Biotech utilise comparable technologies and business models. In these cases, the organisation analyses a damaged site to determine contaminants and level of damage. From this initial assessment, a suite of microbes is developed to treat this damage, this culture is expanded to a large quantity then applied to the damaged site, wastewater or otherwise. Through the natural action of the microbes the site is remediated, or environmental stress reduced.

Archetype V: Alternative end-of-life processing

The fifth archetype describes businesses built around alternative end-of-life processing for a range of products/materials. Recycling, polymer processing, replacing a conventional destination, most often this destination would be landfill. The majority of examples in this field are start-ups, with limited or no revenue, indicating this is the most nascent of the five archetypes. Presently there are several areas of scientific enquiry around future waste streams; for instance there are reports of carbon fiber reinforced polymer recycling mediated by a microbial system, an alternative process to the existing energy-intensive pyrolysis recycling process[59].

End of life processing for manufactured goods has significant impact in sustainability of products throughout their lifecycle[60]. Biotechnologies provide a mechanism to reduce the necessary input costs in this recycling process and reduce the overall lifecycle impact of end-of-life processing. Environmental impact, in many cases, is reduced both by decreasing inputs (energy, water, consumable chemicals) and eliminating or reducing any waste products of the end-of-life processing. End of life planning for products remains critical, as biotechnologies are playing a role in reducing the lifecycle energy of products this archetype is likely will play an import role in future lifecycle sustainability planning. This final archetype is summarised in figure 9.

French company Carbios embodies this archetype, developing enzyme-mediate, rather than thermally mediated, recycling processes for PET recycling. By utilising an enzyme-mediated process polymers can theoretically be recycled an unlimited number of times. Ultimately this aims to eliminate petrochemical inputs and create a functioning circular economy for PET containers.

4. DISCUSSION

In this article we sought to answer the question: How do biotechnology-driven sustainable business models differ from previously established sustainable business model archetypes? From the analysis five business model archetypes emerged. These archetypes describe the underlying business logic of sustainable biotechnology-driven firms. The purpose of applying the business model itself as a unit of analysis ensures these archetypes are abstracted from specific products, firms, industries, geographies or networks[19]. In this section the implications of these biotechnology-specific sustainable business model archetypes are considered.

From this study two overarching domains arose; economic and environmentally-led business models, these two domains achieve sustainability through different means. In the case of the former, the leading value proposition of the organisations is economic, by contrast organisations in the environmentally-led domain are

led by environmental value propositions. Though these value propositions are distinct from one another, they both represent a blend of economic, social and environmental imperatives. Consequently, measuring the effectiveness and return of these businesses models require consideration for these distinct value propositions when determining relative returns[61]. In summary, those archetypes in the economically-led domain first and foremost enable a cost reduction, with mostly internal reconfiguration of an organisation, whereas those in the environmentally-led domain typically require reconfiguration of the value chain.

As noted in the results in figure 2 three business model archetypes are included in the economically-led domain. This may be partially explained by the potential premium commanded by bio-based alternatives in some geographies[62], as well as indications of consumer preference for bio-based alternatives where available[63]. The increase in value, either direct economic value in commodity pricing or increase in consumer perception of the products produced from bio-based materials enables a clear economic advantage for these organisations.

A critical finding and a defining aspect of many of the biotechnology business models included in this study is the archetypes classified in the environmentally-led, rather than economically-led, require a deviation from the existing value chain. These organisations offer a product or service that is currently not being serviced within the existing value chain, rather than a direct substitution of an activity already being undertaken by a firm. For example Bolt Threads manufacturing synthetic spider silk as a high performance fibre product for textile applications. In these overarching domains, the nature of the how value is delivered and captured is markedly different, this is highlighted in table 4. These distinctions are reflected in the above described archetypes for each, with greater variances compared to incumbent business models compared with those seen in the environmentally-led archetypes. This is observed across all elements of the business model, including the economic, environmental and social aspects of the organisation. By comparison, those economically led archetypes have more in common with the incumbent businesses, substituting one or more fields of the TLBMC, compared to these incumbents, in order to achieve sustainability.

This article builds on previous literature contributing how biotechnology-driven businesses differ from sustainable business models more generally and offering a set of archetypes for these businesses. Contrasting this to previous work by Bocken et al. (2014) where eight sustainable business model archetypes were identified from the field of sustainability more generally. This study builds on and contributes two additional archetypes found specifically in biotechnology-driven firms. These additional archetypes reflect the differing technology, human and organisational requirements of biotechnology firms. Significantly, in this study, no socially-led business model archetype was uncovered. Bocken et al.[41] developed three socially-led sustainable business model archetypes, broadly the organisations included within these three archetypes falls into five categories: Product Service Systems (PSS), non-profit, advocacy, education and alternate consumer brands. By contrast this study findings highlight that no biotechnology-driven firms fit into the organisational categories Bocken et al.[41] describe for socially-led sustainable business models.

In order to interpret the five archetypes a generalised value chain for the biotechnology industry are included in figure 10. This includes broad critical process steps seen in many of the industry sectors considered in this article including chemical supply, waste management and agriculture. In each case the industry requires inputs into a process, for instance fossil fuels, chemical intermediates; at least one processing stage to produce a product, or offer a service. In the context of this generalised value chain this processing phase considers all of the up and down stream processing from raw material to usable product. Following production is the product use phase and finally disposal. In addition to these core processes potential resultant damage is also included, it should be noted that damage whilst visually represented at the end of the value chain, may occur at any stage, through mismanagement of inputs, for instance an oil spill, improper discharge of waste, or management during use phase of the product.

Interpreting the archetypes through the lens of this value chain allows for interaction between the

Table 4: How domains of business model archetypes provide sustainable advantage and their role in bringing quality innovation to market

Domains	Role of biotechnology	Basis of advantage
Economic	Biotechnology enables more efficient or reliable conversion of products, increasing yield with decreased input cost	Cost-driven, reducing cost, increasing productivity
Environmental	By either offering an alternative means of processing to either use an alternate material or applying a previously unknown means of conversion to a useful final product	Solves an environmental problem, either removing a waste stream, remediating damage or replacing an environmentally costly process step

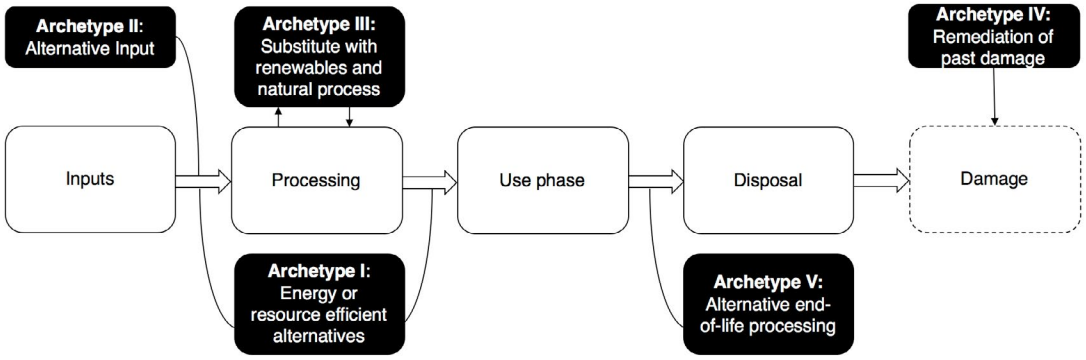

Figure 10: Generalised value chain for biotechnologies, the five business model archetypes typically are included.

archetypes and incumbent business models to be considered. Archetypes I, II and III, all included in the environmental meta-archetype do not compete directly with incumbents. Instead these organisations, address emerging challenges outside the core value chain. These organisations contribute to sustainability by utilising waste sources, providing alternative end-of-life solutions or remediating past damage. These activities do not directly compete against activities of the incumbent organisations in the value chain.

Vermeulen and Witjes[11] explain the difficulty of transitioning to a SBM, requiring significant changes from production process to modes of operation. With many organisations being equipped to manage incremental change and innovation[11]. This may also be due to the fact the research field of SBM is still emerging and presently there are few tools and resources available to assist companies with sustainable business modelling. A further contribution of this article is as a formative tool for biotechnology businesses looking to apply sustainable innovation. For an organisation looking to apply this as part of a sustainable innovation process a twofold application is suggested, by first considering the value chain above and considering where the organisation would presently fit in the core value chain (marked in black boxes in figure 9). Secondly the organisation can consider the adjacent archetypes uncovered in this study as initial inspiration for business model experimentation[43]. For instance, if a conventional industrial chemical production organisation was seeking to undertake a sustainable innovation project they would first identify their position in the current value chain, in this case they would classify as *Processing*. From there the organisation would consider the adjacent sustainable biotechnology archetypes described in this article. In this example Archetype I and Archetype III are adjacent to the *Processing* link in the traditional value chain, these would then be selected as the basis of experimentation for the firm to support transition toward sustainability.

Limitations and future research

This study provides insight into sustainable biotechnology-driven business models; however, several limitations of this study are acknowledged. The mode of data collection focused on companies from listings of sustainable organisations, this, by the nature of said listings, focuses on industrial biotechnology companies. This largely eliminates medical, pharmaceutical and some agricultural biotechnology organisations. Accordingly, if this study were to be further developed a separate data collection mode seeking sustainable biotechnology business models from these related models could be included. A further limitation of this approach is the content analysis methodology, requires published information, meaning private organisations without a published presence, or organisations working with some degree of secrecy (for instance early stage start ups) have been excluded due to lack of available data. In future, studies could apply ethnographic data collection, in order to capture unpublished data regarding these organisations. Avenues for future research include:

- Are these same archetypes found through primary data collection in biotechnology firms?
- Does applying the value chain, presented in figure 9 in the discussion, as a formative tool to assist in sustainable innovation?

5. CONCLUSION

This article questions how the business model of sustainable biotechnology-driven firms differs from other

businesses. By developing on the archetypes suggested by Bocken et al.[41] and utilising a detailed, multi-layered analysis of sustainable biotechnology business models using the triple-layer business model canvas as the analysis matrix[13] this article provides detail around how biotechnology-driven sustainable businesses function across economic, social and environmental domains this article supports the realisation of future, sustainable, biotechnology innovations. Historically organisations are led by capitalist values, with social and environmental outcomes considered secondary.

Based on the findings of this study sustainable biotechnology-driven businesses can reach a sustainable business model through either operating as an environmentally-led archetype or economically-led archetype. The mechanism of value creation, delivery, capture and sustainable operation differs in each case. Broadly organisations operating an environmentally-led business model archetype facilitate some reconfiguration of the industry value chain they operate in, utilising biotechnology to offer a product or service distinct to those previously available. Whilst those operating an economically-led business model directly substitute an existing offering.

In spite of enthusiasm for biotechnologies to enable sustainability, especially to support the supplementation or even replace finite resources (for instance through the development of biofuel alternatives or the combustion of biogas for energy production) large-scale implementation faces a number of hurdles in the coming decades. Overall this article bridges this gap contributing a set of archetypes specifically related to sustainable biotechnology companies. These offer exemplars and inspiration to those seeking to commercialise biotechnologies for mass impact.

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Article

Regulation and Market Influences on Innovation in Biotechnology

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ABSTRACT

In today's competitive landscape innovation in biotechology is a necessity as there is a continuous increase in chronic diseases globally such as cancer, cardiovascular diseases, diabetes and hepatitis B that is driving this demand. Biotechnology is one of the fastest growing industries with a growing demand for precision medicine and biosimilars, with bioinformatics expected to experience exponential growth in the coming years as a result of substantial innovation in the field. Innovation gives biotechnology companies the opportunity to grow faster and more competitive and ultimately influence the direction of the industry by developing drugs, medicines and therapeutics as well as environmentally friendly chemicals, fuels and materials that address the growing needs of society. Despite the continuous need for innovation in biotechnology, companies are influenced by a number of issues, in the development and commercialization of their innovations. In this paper the focus is on regulation and market influences on innovation in biotechnology. First, the influence of regulation and governments on innovation in biotechnology is discussed. Second, examines the role of marketing on innovation in biotechnology. Third, the impact of market and patient analysis on innovation in biotechnology is examined and a framework is proposed. Following that final conclusions are drawn.

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REGULATION AND GOVERNMENT INFLUENCE ON INNOVATION IN BIOTECHNOLOGY

Regulatory conditions are recognized as important factors influencing the innovation activities of companies, industries and whole economies (Blind, 2012). Biotechnology companies are subject to significant scrutiny for example; The Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Occupational Safety and Health Administration (OSHA) to ensure regulatory compliance. Regulators, governments and healthcare professionals want to ensure that patients have access to new and innovative drugs that are affordable within available resources. But the affordability aspect of an innovative drug makes this a challenging calculus. Innovation and competition are the biggest drivers in delivering better value drugs to patients. But "value" is subjective in terms of which diseases and patient populations are to be given the benefits of this rationed innovation in healthcare. Therefore, while most regulators and governments understand the critical role of biopharmaceuticals in enhancing the healthcare system, and they are supporting alternative ways to fulfill demand for these products, it often becomes incumbent on these regulators and governments to determine where the scarce resources are applied in terms of which basic innovations are to be funded. For example, some governments are actively supporting the development of their biosimilars industries. Yet, regulatory concerns can significantly impact the development and potential revenue generated from biosimilars. Additionally, FDA's safety and efficacy requirements may demand larger studies providing more evidence of the drugs safety that results in major

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development costs that may not be recovered by the manufacturers (Miller, 2017).

Biosimilars are essentially generic therapeutics based on reference products that have come off patent. Biosimilars today can be up to 30 per cent cheaper than other drugs. Furthermore, in some markets, including the US, which is the major target for biosimilars being developed today, many developers are targeting 50 per cent discounts. As patent protection on more complex biopharmaceuticals expires, there will be greater opportunities within the market for biosimilars. In June 2013, the European Union (EU) approved Remsima, Celltrion's biosimilar version of the monoclonal antibody Remicade. As the patent protection of leading drugs expire biosimilars will drive the innovators to accelerate research for superior products (biobetters) that will allow these innovators to maintain their high product prices. Introduction of biosimilars will increase pressure on the overall industry to decrease the cost of life changing drugs, and there will be as many as 5-8 new biologics manufacturers producing the same biologic for the same indications. Over time, discounts may decrease even further than the currently targeted 50 per cent for biosimilars in segmented markets. Many of these new manufacturing entrants will leave the market if they are unable to produce or distribute their products cost-effectively. Biosimilars are an example of where innovation in biologics manufacturing and cost reduction will facilitate production efficiencies. However, it is difficult to translate these late-stage, production-related innovations to the basic research, patient-related, needs.

Biotechnology companies recognize the reality that a biotechnology business is based on marketed products that generates revenue for shareholders (Rajamäki, 2008). The primary objective in regulation and government intervention in this industry is to ensure that innovation is not surpressed yet society is protected from potentially unsafe or ineffective products. The company's valuation is a result of innovative products, meeting patient needs, adhering to regulatory and government requirements with an extended patent life. Thus, new challenges have emerged as a result of extensive knowledge coupled with regulatory challenges and increasing pressure for scientific innovation and profitability.

THE ROLE OF MARKETING ON INNOVATION IN BIOTECHNOLOGY

Marketing is the commercialization engine that generates revenue to fund and develop new biological products. It is this development funding from sales of existing products that fills the new product pipeline and enables the next generation of products to reach the market. These next generation biologics increase a company's value to society, while increasing its market share, and its value to shareholders. Effective marketing strategy contributes to companies achieving their core purpose. Marketing provides various ways through which companies can understand patient needs such as broad market research, market and patient analysis, patient interactions, and consultants as innovators. Effective marketing requires the ability to translate the expert knowledge of scientific discovery to meeting an existing patient, and market need so the true value of the product can be established. It is estimated that in the biotechnology industry, only one in 5,000–10,000 therapeutic innovations survive through to product commercialization (Stremersch and Van Dyck, 2009). Biotechnology companies need to clearly identify their target market users in the different geographic locations they are addressing. Marketing biotechnology products is very different from marketing other consumer products in this regulated environment. Because of its regulated nature, marketing must be effectively integrated into the ethos of the company and the ethics must be embedded in the culture and emanate from the top-down.

Since patient needs are constantly changing, the marketing approach undertaken needs to create value. Value is created by tapping into unique opportunities and being highly sophisticated in the use of modern marketing techniques. This enhances the company's market position by identifying and exploiting novel opportunities that meet patient requirements. The role of marketing in biotechnology companies must start at the very earliest stages when a drug must first be evaluated based on alternative therapeutic indications for which clinical trials must be developed. Decisions on which indications to target are made based on disease incidence and prevalence, revenue potential, competition, reimbursement situation, among other factors. The marketing role becomes more apparent once a new drug application (NDA) or biologic license application (BLA) is submitted to the U.S. Food and Drug Administration (FDA) [or to the EMA]. The timeframe to effectively prepare for a product launch for a biologic that has gone through clinical trials is typically 12 to 18 months. Biotechnology companies recognize that a successful product launch is closely linked with a comprehensive understanding of the marketing and commercialization issues related with the product and its potential competitive market. They think strategically about the diverse value that their products may hold in different markets, most significantly when the industry is in an earlier stage of development and when acquiring fundamental technology may provide greater value.

Many smaller biotechnology companies are forming alliances with (or being acquired by) pharmaceutical companies that are traditionally recognized as having a strong marketing and sales infrastructure. Research-based biotechnology companies are generally resource-constrained, and have neither the budget nor sales staff to become more marketing and sales oriented and directly compete with pharmaceutical companies for example: Amgen, Genentech, Biogen-Idec, Genzyme, and Millennium. While all of today's biotechnology giants started as smaller companies, the business situation today has changed, and most smaller companies develop 'exit strategies' that may include having their intellectual property (their innovations) acquired by larger biotechnology companies that are starved for innovative pipeline products. Genentech has made the successful transition from a small biotechnology to a leading biotechnology company by both understanding the importance of marketing and cleverly integrating it with the science.

In the later stages of the marketing process, effective marketing requires the ability to clearly communicate and have an in-depth understanding of the target markets and end users. These target markets and end-users differ by geographical markets. For example, in the US and New Zealand, direct-to-consumer marketing opens a large variety of media for communication to patients and populations. Other regions require much more intensive communication with regulators, government agencies, insurers, or other third-party payors. The biotechnology company's marketing efforts must be focused on facilitating and enabling the innovation's survival.

MARKET AND PATIENT ANALYSIS FOR INNOVATIONS IN BIOTECHNOLOGY

Both market and patient focus should be the foundation for a biotechnology company's innovative efforts. A biotechnology company differentiates itself in its target markets by exceptional execution in understanding the market and meeting patients' needs today while also developing a mind-set for future innovations. Amgen is very innovative in their efforts to meet patients' needs, they aim to create superior value for patients primarily focused on new drug development, continuously innovate to be increasingly more efficient and effective in discovering new medicines that will enhance patients' lives while at the same time increasing the value of the company for its shareholders.

Biotechnology companies must clearly identify their target patients and the core market that they will address. Biotechnology products focus on specific and limited markets because they are designed to treat specific patient illnesses. The market is challenging and complicated because the patients whom the treatments are designed are not the individuals that decide to purchase the product. The decision makers are the consultants, physicians or the clinics and hospitals treating these patients. Therefore the key decision makers are central to the product approval and must be convinced that the specific product is appropriate and effective for the illness before they would prescribe the product to any patient. It is fundamental that the biotechnology company identifies the appropriate market for its product in order to determine who the specific patients are and decide the geographic scope of its marketing strategy.

In analyzing the market and its patients, it is essential for biotechnology companies to think about the following:

- What is the specific illness that needs more innovative medicines?
- How big is the market (number of patients suffering from this illness nationally and globally per annum) for the new innovation to help patients?
- What are the patients' needs in treating this illness?
- Why would consultants and physicians decide to use this product to treat patients' rather than existing products in the market?
- What are the benefits of this new product compared to other competing products on the market?
- Will the product be affordable to patients'?
- Who are the competitors and what is their competitive position in the market?
- What is the best route to market?

In addressing the above questions this paper proposes a market and patient analysis framework set forth in Figure 1. Such as model understands the innovation of the biotechnology company to be strongly influenced by the need for an in-depth market and patient analysis.

As indicated in Figure 1 above, market and patient analysis in biotechnology is an assessment of the overall appeal of the market and patients for the proposed innovation. This requires the following:

- An analysis of the key factors influencing the market in the short, medium, and long term.

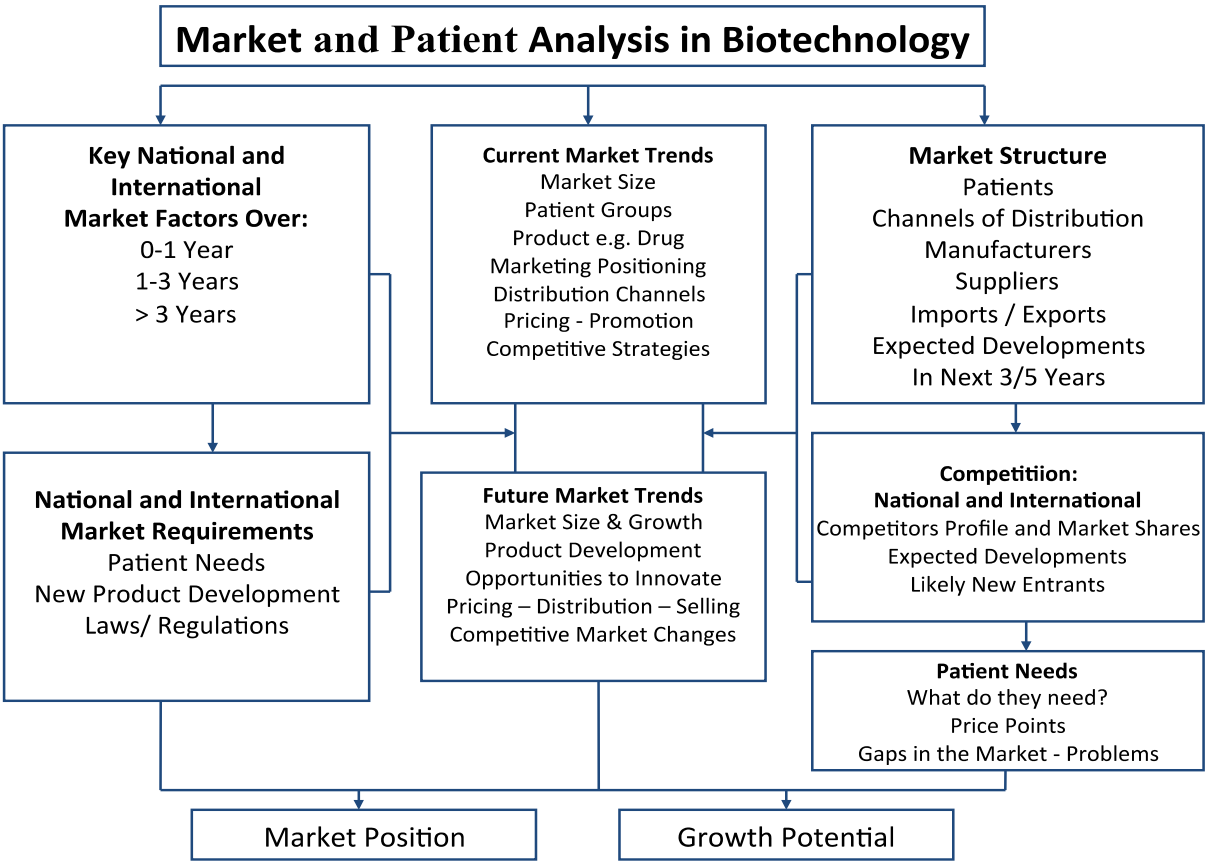

Figure 1: Market and Patient Analysis Framework

- Understanding the national and international market requirements and in particular identifying:
  - What is happening in the leading and most innovative biotechnology markets?
  - What are patient needs in these markets?
  - How are products adapting and further developing to meet and exceed the urgent needs of patients?
  - What laws, regulations and standards are governing the market and the products?
- Assessing the current and anticipated market trends in terms of market size, patient groups, product development, market positioning, distribution, price, innovation and the competitive market.
- Understand the market structure and if the product is viable within that structure.
- Identify the key competitors both nationally and internationally.
- Understand the patients' illness and their real needs.
- Determine a realistic price point for the product.
- Continued R&D is essential to develop further innovations to address the market needs.
- Know the growth potential in the short, medium, and long term.

Interpreting the insights gained for market and patient analysis provides insights into seeking new ways of evaluating the company based on the analysis as follows:

- Implications of trends in drug development, patient needs, and expected changes in the short, medium, and long term.

- Identify the key issues to be addressed through:
  - Ensuring innovation from individuals and teams inside the organization,
  - Engaging in open innovation opportunities, and
  - Identifying patients' who are the end users of the drug or treatment and whose current needs will extend even further in identifying drugs and/ or treatments that are not just treating the specific illness but are able to facilitate in providing a permanent treatment to give the patient a live as normal as possible. Since patients are familiar with conditions that will be evident in the future, they can be an effective *need forecasting laboratory* for marketing research (Von Hippel, 1986).
- Understand the sources of what will improve a patients' quality of life.
- Identify the key obstacles that are affecting the opportunities of increasing drug or treatment quality, service, sales, profits, growth, and competitiveness.
- Identify any shortcomings vis-à-vis the Key Success Factors.
- Reverse roles and step into the shoes of: i) competitors; ii) consultants; iii) healthcare professionals and most importantly iv) patients' to provide new insights and perspectives.

In-depth R&D should provide important insights for analyzing markets and patients provide biotechnology companies with opportunities to seek connections and bridge gaps by looking at the following:

- Gaps that can be filled in existing product ranges.
- Possible combinations – novel combinations of products for example, in Ireland introducing a bill to make cannabis available to those with chronic pain, epilepsy, cancer, MS, fibrmyalgia and, under a doctor's recommendation to help to alleviate symptoms of illness.
- Know what competitors are doing and how your company can do better.
- Analyze beyond the industry for ideas that could be transferred from other industries that would benefit patients and society at large.

When a biotechnology company is market and patient focused the knowledge they gain through their R&D, patients, market analysis and competitor analysis results in more innovative product development, more effective market targeting and positioning, thereby creating opportunities for increased innovative drug development targeting specific illnesses that will result in time to greater competitiveness and sustained competitive advantage. Such organizations as Amgen, Allergan, Biogen, Gilead Sciences, Novo Nordisk, Regeneron are market leaders with an outstanding knowledge of the market and patients resulting in groundbreaking innovations.

The traditional model of a pharmaceutical company fully integrated from drug discovery, to development, to distribution has now changed in the way today biotechnology companies depend on a complex network of for example healthcare professionals and consultants, academic/ universities, industry specialists, patients, government, policy makers, marketing, and distribution relationships. Successful biotechnology companies are looking for new ways to become more innovative and competitive while increasing value for society. Innovative products are not only evaluated in how well they perform, but if they represent substantial improvements over existing products and are cost-effective in the process.

CONCLUSION

Doing what has always been done is not sustainable in today's biotechnology environment as it will only achieve a system that is inefficient, ineffective, inequitable and unaffordable. While new scientific knowledge and innovation is generally slow to disseminate, regulators and governments must call on biotechnology companies to develop its best ideas and innovations to do better for society. Regulation is essential to ensure innovations have adopted appropriate clinical trials and repeated testing of practical application so that safe, quality products that meet market demand are being produced. Biotechnology companies operate in a dynamic environment and therefore need to invest, to adapt, and to manage their market environment to satisfy the needs of current and potential patients while operating effectively within a stringent regulatory environment. Innovative activities that are compliant with regulatory and government requirements, market and patient focused are major sources of intelligence that facilitate opportunity recognition and innovation within biotechnology companies. While innovation is essential for biotechnology to create economic and societal prosperity, it is a commercial necessity for individual companies.

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Article

The Opportunities to Develop a Successful Entrepreneurship and Business Model in Biotechnology: an Overview

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ABSTRACT

Biotechnology is an incredible technology promising a better future worldwide and proved to be genera of great outcomes. Since its inception it has been projected to bring fantastic advances along with huge economic rewards, in short it promises more for less. Involvement of molecular biology in biotechnology lead its way into the various aspects of science based industries. Pharmacogenomics, drug discovery and drug delivery are the emerging tools in health industry which can only be possible due to the onset of biotechnology. Worldwide, pharmaceutical companies pursued research in the medicines and diagnostics by implementing biotechnology. Biotechnology is a major tool for improving human life by improving agriculture, human health and environment. Developing countries tend to have growing needs but scarce resources, therefore, such claims naturally appeal to those in power. The practical applications of Biotechnology extend from widely separated fields, creative minds, these ideas need to be researched and developed. Extent of scope in the field offer opportunities for great industrial growth. A novel product as a result of intensive research often leads to a business model. Past has seen several industries established by scientists to make a difference through their product by understanding the need of people and market potential. Entrepreneurial potential in biotechnology is governed by factors like development of technology as an only solution for the problem or the better solution for the currently available technologies. Critical testing and regulatory agency approval must be received prior to commercial production and marketing. Although the field has immense opportunity but the level of uncertainty and failure is also high. So, an efficient and well organized strategy should be followed to develop and deliver a successful business model for biotechnology. The paper presents an illustration about the business potential in biotechnology from incubation of an idea and its transformation into a value aided product or technology through various demanding and formative steps like financing, human resource and marketing.

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INTRODUCTION

Biotechnology is an age old science, which focus on the human welfare through the involvement of living organisms. Commercial aspects of biotechnology are vast and scope of the technology is also diversified, from medical

to industrial, plants to animals and to food to beverage industry. Technology has its contribution in baking and fermentation in conventional practices since the ancient times. Modern day biotechnology has more to offer than breeding of plants and domestication of animals due to the involvement of molecular biology. Biotechnology has entrusted potential to affect the society as well as the economy greatly.

Progress that occurred in the field during last few decades sent a message which is quick and loud that the future wealth creation will be through the knowledge based industry and this knowledge era will be incomplete without biotechnology that has fascinated the entire world (**Konde, 2008**). Because, biotechnology involves the use of living organisms, cells or tissues or materials derived from them, the motion of ownership and exploitation of resources for projects has been and will continue to be of great importance to the development of industry.

Market potential of various stream of biotechnology such as Agricultural ('green') biotechnology is predicted to increase to USD 28 billion by 2019. The cultivation of genetically modified plants now account for 13 % of the arable land available worldwide giving a hope for development of industries based on the manufacturing of GM seeds. While industrial ('white') biotechnology, could allow for total revenue of more than USD 500 billion worldwide by 2020 by changing more of the chemical processes to the biotechnological processes. Key segments of industrial biotechnology are the enzyme market and biofuels. Medical ('red') biotechnology offers an increase to 27 percent by 2020, which is equivalent to a worldwide sales volume of almost USD 280 billion. In 2015, 23 percent of the revenue in the global pharmaceutical industry was achieved with bio-pharmaceuticals. Pharmaceutical industry is expecting more from the biotechnology by producing biosimilars for diagnostics and therapeutics for oncological research.

With the expansion of biotechnological capabilities, enormous opportunities have opened up for potential commercialization. Once ideas become available, those ideas with best possibility for commercial success must be identified and converted into new or improved product, process and service, which is the essence of innovation. The innovation led growth, innovation led recovery, and innovation led competitiveness are not mere slogans but they are a hard reality of the present and the future. Beyond mere research in laboratories it includes idea incubators; technology parks; a conducive intellectual property right regime; enlightened regulatory systems ; academics who believe in not just "publish or perish" but "publish, patent and prosper"; potent inventor—investor engagement; adventure capital and passionate innovation leaders (**Deeds and Coombs, 2000**). This process involves a combination of scientific research to determine how difficult it may be to engineer the product and thorough market research to establish the likely demand for the product. The business of inventing discovering of new products and procedures are time consuming, tiresome and often risky. From very beginning governments worldwide have recognized the value of rewarding those who have invested in these dating and adventurous acts and have made technological advancements and discoveries. A patent granted by government protects investors or developers for a certain number of years and provides a legal means to ensure economic reward for creativity, research and development and above all, the perseverance and patience involved. In India, biotechnology sector is on a crossroad where on one hand it must find affordable solutions to the pressing national needs in agriculture, health and energy, and on the other hand it must be competitive enough to take advantage of the lucrative international market (**Parmar, 2005**).

THE COMMERCIALIZATION OF BIOTECHNOLOGY

Entrepreneurial activities in life sciences started in the late 1970s and some of the notable early players were established in 1983. During that year an estimated $500 million was invested by venture capitalists into biotech startup companies. In 2000, investment into the biotech industry was estimated at $ 5 billion. At present there are over 1200 companies in United States alone. As with all types of business ventures there are certain unique approaches in biotechnology business. The five basic concepts in the establishment of a business venture include idea; scientific development and market research; first production of capabilities; testing, approval and marketing; and finally production **(Shimasaki, 2014)**.

In order for biotech products to become reality the new ideas and discoveries must be brought out of the laboratory setting into an industrial setup. Many of the outstanding discoveries originate in public funded academic and research environments which are traditionally not business oriented; therefore, entrepreneurs with business acumen developed the concept of a biotechnology company. Market research or economic forecasting is a tricky process but is a fundamentally important corporate tool. Usually before any business venture is attempted, substantial research is done to access the feasibility of the proposed service or product. Like is there a market? Why produce something that cannot be sold? It is critical to demonstrate a good understanding of the immediate and the flume market for the products or the services to be provided. Making economic forecasts that address the questions

like these is central to business planning. Besides, it is also important to discuss the competition that exists and how competitive the product or service would be. Along with it a market survey must be conducted to know the strengths and weaknesses of the existing competition and in what ways the new product is superior.

The foundation of a successful business lies in a business model but the fact is that there is no universal model instead universal business principles do exists. Further considering the diversity and dynamics of the market place, the business model may have to be appropriately modified to adapt to the prevailing business climates. A good business model or plan should calculate a return on investment as well as a net present value.

There are two biotechnology business models that characterize biotech companies:

i. Product development companies.
ii. Platform technology development companies.

PRODUCT DEVELOPMENT COMPANIES

These focus on commercializing a product usually an agricultural product (including food) and the products of some therapeutic value. During last twenty five years a number of life sciences companies capitalized on new technologies to mass produce a number of beneficial, small biomolecules that had not been considered by the giant pharmaceutical companies. A sample of such companies and their products is given in Table 1. The product based biotechnology business model has certain advantages. The market for some of the products, especially therapeutic products is large and sustainable for the very fact that diseases are seldom eradicated and thus sickness persists in the population, generating a constant and perpetual need for medicine, Secondly, the business is very profitable the total margins reaching up to the range of 80-90 percent (**Afzal et al. 2009**). Further, there is no or if, any, then it is only very little pricing pressure, while the patent for the product remains valid. Besides, it is very difficult for competitors to encroach because of favorable conditions for obtaining a patent for the product, this leads to protecting the huge investment of the creators of products.

The major disadvantage of the product based Biotechnology business model is its huge risk, the reason behind this stipulated risk is the estimation that only one out of ten companies that invest and are evaluated in clinical trials, receive approval for a new drug application (**Deeds et al. 2000**). Above all the product development is characteristically of long duration i.e. from 5 to more than 10 years and is very exhaustive along with being expensive.

PLATFORM TECHNOLOGY DEVELOPMENT COMPANIES

These focus upon making existing technology (or tools) more efficient i.e. better, faster and cheaper. Earlier, tool companies engaged in activities such as the enhancement of the delivery of existing therapeutics, currently, numerous companies have been formed not only in drug delivery but also in hot areas like gene discovery, gene therapy, proteomics, bioelectronics, and combinational chemistry. A sample of such companies and their activities are presented in the Table 2. The major advantage of platform

Table 1: Product based companies and some of their specific products

S.No	Company Name	Product	Use
1	Eli Lilly	Humulin	For treatment of diabetes
2	Genentech	Pulmozyme	For treatment of cystic fibrosis
3	Amagen	Epogen	For treatment of anemia
4	Centeon	Helixate	For treatment of hemophilia
5	Centocor	Retavase	For treatment of myocardial infraction
6	Höchst	Lantus®	For long term treatment of diabetes
7	Hoffmann La Roche	Herceptin	For the treatment of Breast cancer targeting HER2 gene
8	Merck	BCG vaccine (TICE® strain)	For the treatment of tuberculosis
9	DuPont	Bio-PDO®	Bio-propanediol, first synthetic biomaterial for biofuel production
10	Monsanto	Round Up Ready	Herbicide resistant transgenic crops
11	Genentech	OCREVUS®	Monoclonal Antibody treats multiple sclerosis (MS)
12	Cetus corp	Proleukin	Interleukin 2 for the treatment of kidney cancer
13	Biogen	AVONEX® (Interferon β – 1A)	For the treatment of relapsing multiple sclerosis (MS)

Table 2: Some platform based companies and some of their specific products

S.No.	Company Name	Selected Product or Tool
1	Rosetta	DNA Chips
2	Perspective Biosystems	Sequencing Instruments
3	Kiva Genetics	SNP Genotyping
4	Aiza	Drug Delivery
5	Millenium	Gene Discovery
6	Xyomix	Proteomics, Protein chips
7	Illumina Inc.	Microarrays
8	Agilent Technologies Inc	Capillary electrophoresis, FISH probes
9	Oxford Nanopore Technologies	Nanopore DNA sequencer
10	Pacific Biosciences	PacBio RS DNA sequencer
11	Raindance Technologies	Digital PCR

technology development companies is that it takes only a very short time for the product to reach the market the reason being that the FDA approval is often not required, since an existing and previously approved product is being improved. Secondly, the technology is not being developed from the beginning so the risk of product failure is lowered. The major disadvantage includes the risk of competition that is almost inevitable, since quality is never ending; it is likely that sooner or later-some better cheaper and faster technology will emerge on the market. The adverse effects are more significant when the technology being used to enhance existing ones is not patentable.

STARTING A BIOTECHNOLOGY BUSINESS

In order to commercialize an idea, it needs to be nurtured in a business culture. Traditionally, businesses are created to fulfill the needs in a society and in the process financial rewards accureto the owner of the business. To fulfill a need a business must either add value to something by making a product or by adding value of someone by providing a service. This suggests that, for many traditional businesses, the needs existed before certain companies fulfilled them. Furthermore, biotechnology is rapidly evolving, posing a significant challenge to business based on it (**Shimaski, 2008**). To develop any business plan in biotechnology, one needs to be fully aware of the technology with a strategy involving the market research. Market trends lead to the development of a novel product which is either significantly superior to the currently available technologies or the only solution to the persisting problem. There are few key aspects which should be taken care of while creating a successful Biotech company.

FINANCE AND CAPITAL INVESTMENT

The business plan in biotechnology needs more capital in comparison to other areas of entrepreneurship. On average, it costs between $25 million to $100 million to develop new medical diagnostics and devices, and more than $1 billion to take new drugs from the laboratory through regulatory approval to sales. Biotechnology companies can access capital from the same pool that other business do. A business may be financed in one of the two ways debt financing and equity financing. In debt financing the company obtain capital by securing it against an asset or group of assets. The company incurs debt through loans, bank overdrafts, and other such transactions. The lender charges interest on any outstanding balance regardless of whether the company makes or loses money. The main source of capital in debt financing is banks and other commercial lenders. Equity financing entails the element of risk, with the investor standing to lose the invested capital, should the company be unprofitable or unsuccessful. Assets that may be placed at risk include plant, machinery, and stocks. The primary sources of equity capital are venture capitalists and the general public. Equity funders receive dividends only when the company has accrued distributable profits. Such dividends can change over the life of the investment.

THE TECHNICAL ASPECT

Irrespective of the business model, the technology involved should be proven to be technically feasible and workable. Investors are not interested in funding scientific ideas or concepts; they will fund only what is realistic and can be commercialized for profitability. The

Figure: Flow Diagram representing the steps for a successful business development strategy

technology may be completely developed or may be in various stages of development; therefore, it is important to disclose the technical status to the potential investors. Another aspect of interest to investors is the range of application of the technology. This will determine whether the market base for the company would be narrow or broad. Further, it is advantageous if the technology has the room for further development and expansion to include new product opportunities. A caution with technology in a fast developing industry like biotechnology is the issue of patents which should be dealt properly to avoid unnecessary and costly litigations at later stages. While developing a business plan, feasibility and reproducibility of the technology should be carefully observed. If a technology comes under IPR (Intellectual Property Rights), proper details should be taken from the concerned regulatory bodies.

THE HUMAN RESOURCE

A biotechnology company thrives on quality human and nonhuman resources. Biotechnology based business models depends on the scientific concepts and principles so it is highly recommended to recruit qualified scientists, especially biochemists, geneticists, microbiologist, and chemists. Management should be prepared to provide an attractive salary package with quality incentives to build a stable team (**Schoemaker and Schoemaker, 2003).** For example, being from academia, such scientists would like to publish their research in peered journals, on the other hand the company may want to keep certain discoveries secret for at least a period of time. Academics would love to have a good library resource. Some companies may offer stock option to scientists and other key staff.

Apart from scientists, a biotechnology company needs accountants, marketing personnel, public relation personnel, laboratory technicians, administrative staff, and personnel for housekeeping. Top notch personnel can be hired only if the company has adequate financial resources. Biotechnology is a very capital intensive business that depends on investors to start and sustain the operation. It is not uncommon for biotechnology companies, especially the entrepreneurial ones, to operate in a deficit mode during the early years of existence, because during these years, the company is engaged in the development of their first products.

MARKETING STRATEGY

It is repeatedly said that the three factors to consider in establishing a new business are market, market and market. It is important to conduct market research to determine market outlets for the product, the size of the market, the distribution, the presence of competitive products, stability, profitability, and opportunities for growth. Presence of competitors in the field is also a good sign for the economical prospects and market opportunities of the product and the service. Once the markets have been firmly decided upon, the company needs to plan on how to actually deliver the goods and services to the customers. This has to do with the mechanics of moving the product. The alternatives are many, but the company needs to identify the most effective and profitable ones. A product is unprofitable unless it is marketed efficiently. As part of the business, a company should try to define and develop a unique identity by which it wishes

to be known in the business community. It should be unambiguous and easy for customers to associate with. It is important to be consistent in keeping the standards set in order for a loyal customer base to grow.

Market strategy also involve the need to search for potential partners working in similar field as biotech companies often hand off late stage development to larger companies with deeper pockets. News of mergers and acquisitions are quite common in the field of biotechnology as it prove to be a significant financial as well as marketing strategy to sell your product under a banner name of some parent organization which is well established. Knowing customer with their habits and making an effort to deal with pricing and distribution of the product along with justification lead to the guaranteed success.

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