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Commentary

USDA Reorganization Should Reduce Biotech Regulation and Feds' Involvement in the Organic Industry

Amanda Maxham

Henry I. Miller

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Observing the missteps in public policy, we're reminded of Ronald Reagan's famous quip that the nine most fearful words in the English language are, "I'm from the government, and I'm here to help." One such occasion was USDA's request last year [2018] for public comments on proposed measures to "improve efficiencies" at the department which were mainly a "reorganization" that merged some agencies and moved boxes around the organizational chart; and the establishment of a Rural Development Innovation Center. The latter is supposed "to identify and develop new tools to better serve rural communities in achieving prosperity."

Perhaps the changes will be better for farmers in some ways, if you have a microscope powerful enough to see things that are very small, but if "prosperity" is really USDA's aim, the department's senior officials should put down the giant bureaucratic pillow they have been using for 30 years to asphyxiate agricultural innovation with excessive, wrong-headed regulation.

Another example of the government not "helping" farmers, consumers, or innovation is USDA's ongoing involvement with setting and enforcing standards for "organic" agriculture. Government officials might not characterize their involvement with organic agriculture as "regulation," but they set and enforce standards and conduct inspections. If it looks, walks and quacks like a duck…

We have two suggestions, discussed below, for changes at the USDA that would actually spur agricultural innovation and free farmers, agricultural scientists and businessmen to prosper, and put an end to government officials' involvement in misleading consumers about "organic" agriculture and food.

END THE UNSCIENTIFIC REGULATION OF MOLECULAR GENETIC ENGINEERING, WHICH PRODUCES "GMOS"

Imagine if in 1987 the emerging technology of cellular telephones was met with a draconian, gratuitous regulatory scheme that required each new model of Motorola RAZR, Kyocera Chocolate and Apple iPhone to undergo untold millions of dollars of unnecessary testing expenses and endure ten years of gratuitous government red tape. There's no way you would be reading this over the internet on your smartphone.

Well, that's what another promising technology has put up with since 1987: USDA's regulation of molecular techniques of genetic engineering, also known as "genetic modification" to produce "GMOs" (genetically modified organisms), has been a disaster since its inception. You can't even calculate a formal regulatory cost-benefit analysis, because the regulated articles are uncommonly benign and the benefits of regulation are zero.

USDA has ignored the long-standing consensus of the scientific community that the new molecular techniques for genetic modification are extensions, or refinements, of earlier, more primitive ones, and policymakers have crafted *sui generis*, or unique, regulatory mechanisms that have prevented the field from reaching anything approaching its potential.

The regulatory burden on the use of genetic engineering is grossly disproportionate to its risk, and the opportunity costs of regulatory delays and expenses are formidable. The public and private sectors have squandered billions of dollars on complying with superfluous, redundant regulatory requirements that have priced public sector and small company research and development (R&D) out of the marketplace.

These inflated development costs are the primary reason that more than 99% of genetically engineered crops that are being cultivated are large-scale commodity crops—corn, cotton, canola, soy, and sugar beets. Hawaiian papayas and non-browning potatoes and apples are among the few examples of genetically engineered "specialty crops," such as fruits, nuts, and vegetables. Regulations are so onerous and approval times so uncertain that Neal Carter, president of the then seven-person biotech company that invented the non-browning apple to remark that he didn't hold out much hope for other small, innovative biotechnology start-ups.

Likewise, the once-promising sector of "biopharming," which uses genetic engineering techniques to induce crops such as corn, rice, and tobacco to produce high concentrations of high-value pharmaceuticals, is moribund. Not surprisingly, few companies or other potential sponsors are willing to invest in the development of badly needed genetically improved varieties of the subsistence crops grown in the developing world.

The seminal question about the basis for regulation of genetic engineering in the 1970s was whether there were unique risks associated with the use of recombinant DNA techniques. Numerous national and international scientific organizations have repeatedly addressed this question, and their conclusions have been congruent: There are no unique risks from the use of molecular techniques of genetic engineering. In fact, because of the high degree of precision and predictability of the technologies, if anything, we are in a far better position to judge potential risks.

Thus, there has been a broad consensus in the scientific community, reflected in statements of federal government policy going back more than 30 years, that the newest techniques of genetic modification are essentially an extension, or refinement, of older, less precise and less predictable ones, and that oversight should focus on the characteristics of products, not on the processes or technologies that produced them. In spite of such guidance, however, regulatory agencies plagued by poor science or devoted to empire-building have often chosen to capture molecular genetic engineering—specifically, recombinant DNA technology and, more recently, gene editing—as the focus of regulation.

The Department of Agriculture (USDA), through the Biotechnology Regulatory Services organization within its Animal and Plant Health Inspection Service (APHIS), is responsible for the regulation of genetically engineered plants. APHIS had long regulated the importation and interstate movement of organisms (plants, bacteria, fungi, viruses, etc.) that are plant pests, which were defined by means of an inclusive list—essentially a binary "thumbs up or down" approach. A plant that an investigator might wish to introduce into the field is either on the prohibited list of plant pests, and therefore requires a permit, or it is exempt.

This straightforward approach is risk-based, in that the organisms required to undergo case-by-case governmental review are an enhanced-risk group (organisms that can injure or damage plants), unlike organisms not considered to be plant pests. But for more than a quarter-century, in addition to its basic risk-based regulation, APHIS has applied a parallel regime that focuses exclusively on plants altered or produced with the most precise genetic engineering techniques. Thus, APHIS distorted the original concept of a plant pest (something known to be harmful) and crafted a new category—a "regulated article"—defined in a way that captures virtually every recombinant DNA-modified plant for case-by-case review, regardless of its potential risk, because supposedly it *might* be a plant pest.

In order to perform a field trial with a "regulated article," a researcher must apply to APHIS and submit extensive paperwork before, during, and after the field trial. After conducting field trials for a number of years at many sites, the researcher must then submit a vast amount of data to APHIS and request "deregulation," which is equivalent to approval for unconditional release and sale. These requirements make genetically engineered plants extraordinarily expensive to develop and test. The cost of discovery, development, and regulatory authorization of a new trait introduced between 2008 and 2012 averaged $136 million, according to Wendelyn Jones of DuPont Pioneer, a major corporation involved in crop genetics.

APHIS's approach to recombinant DNA-modified plants is difficult to justify. Plants have long been selected by nature, as well as bred or otherwise manipulated by humans, for enhanced resistance or tolerance to external threats to their survival and productivity, such as insects, disease organisms, weeds, herbicides, and environmental stresses. Plants have also been modified for qualities attractive to consumers, such as seedless watermelons and grapes and the tangerine-grapefruit hybrid called a tangelo.

APHIS has not shown any willingness to rationalize its regulatory approach, so the regulatory obstacles that discriminate against genetic engineering continue to impede the development of crops with both commercial and humanitarian potential. Many innovative genetically engineered crops foreseen in the early days of the technology have literally withered on the vine as regulatory costs have made testing and commercial development economically unfeasible.

The opportunity costs of unnecessary regulatory delays and inflated development expenses are formidable. As David Zilberman, an agricultural economist at the University of California, Berkeley, and his colleagues have observed, "The foregone benefits from these

otherwise feasible production technologies are irreversible, both in the sense that past harvests have been lower than they would have been if the technology had been introduced and in the sense that yield growth is a cumulative process of which the onset has been delayed."

Instead of meaningful, long-overdue – and obviously needed — regulatory reform, USDA's "reorganization" is focused on shifting boxes around the organizational chart and renaming and merging entities. There's certainly nothing in the USDA's plan that remotely resembles a more appropriate, scientific approach to regulating genetically engineered plants (or anything else, for that matter).

There are far more rational and proven alternative approaches to the current unscientific regulation of genetic engineering – and they don't depend on the existence of the biotechnology regulatory component within USDA – Biotechnology Regulatory Services. It's long past time to get rid of this blood-sucking dinosaur, which consumes $19 million and 96 staff-years annually.

STOP LENDING CREDIBILITY TO ORGANIC AGRICULTURE'S PSEUDOSCIENCE

USDA's involvement with organic agriculture is marked by conflicts of interest and pandering to special interests. You would think by now we would have learned about the problems inherent in the same department simultaneously regulating and promoting an industry – in this case, organic agriculture. Parenthetically, it is an industry that provides an inferior, expensive product.

Speaking of bureaucratic dinosaurs, twice a year something called the National Organic Standards Board meets. The USDA-sponsored group, consisting of 15 farmers, consumer advocates, and organic experts determines which pesticides, fertilizers and other substances and practices are allowed in organic farming and food production. Their decisions are wholly arbitrary and are largely dependent on the needs of organic farmers, whose baseline of allowed practices is primitive.

The Organic Center, an advocacy organization that regularly promulgates fake news about the organic industry and its competitors, explains that one of the top ten reasons to trust organic is that organic foods are "certified." In other words, these are foods produced with ostensibly enlightened techniques that yield superior products. (Leaving aside the widespread cheating that is known to occur.) Many shoppers believe this to be true. According to a survey conducted by the USDA's Agricultural Marketing Service, when they saw the USDA Organic Seal, 65% believed it meant the food was healthier, 70% though it was safer, and 46% believed it was more nutritious than a product not carrying the seal.

But these interpretations of the USDA organic seal are baseless. Organic foods have not been shown by reliable studies to be more nutritious or safer. *Nor were they intended to*: When the first National Organic Standards were issued in 2000, Secretary of Agriculture Dan Glickman said, "Let me be clear about one thing: the organic label is a marketing tool. It is not a statement about food safety, nor is 'organic' a value judgment about nutrition or quality." Another Secretary of Agriculture, John Block, added in 2014, "Yet USDA's own research shows consumers buy higher priced organic products because they mistakenly believe them safer and more nutritious."

Instead, by misinterpreting the USDA organic seal, shoppers are buying into the mystical and unscientific idea that when it comes to food "natural is better." And the USDA is guilty of lending credibility to that misapprehension and to those who wish to snuff out advances in food technology that can make food safer, better, cheaper, and healthier.

Judging by the proliferation of labels proclaiming "natural" in the grocery store, it is a common belief that if a food is produced "naturally," it will be more nutritious or safer. But "natural is better" doesn't stand up to scientific scrutiny. An article in the *American Journal of Clinical Nutrition* in 2009 reviewed 137 food nutrition studies, finding that "On the basis of a systematic review of studies of satisfactory quality, there is no evidence of a difference in nutrient quality between organically and conventionally produced foodstuffs."

Another more recent study, a meta-analysis conducted by Stanford University scientists, examined 237 studies and came to much the same conclusion: "The published literature lacks strong evidence that organic foods are significantly more nutritious than conventional foods." It also debunked the myth that organic foods are safer. The Stanford study found that organic foods were not less likely to be contaminated by pathogenic bacteria like E. coli or Salmonella as compared to conventional. That finding surprised even the researchers. "When we began this project," said researcher Dena Bravata, "we thought that there would likely be some findings that would support the superiority of organics over conventional food."

In fact, organic foods are highly susceptible to contamination. The FDA maintains a list of recalled foods on their website, which indicates that, considering that organic foods comprise just 5% or less of the market in the United States, they are disproportionately represented. According to Bruce Chassy, professor of food science (emeritus) at the University of Illinois, who has looked extensively at food recalls, "organic foods are

recalled 4 to 8 times more frequently than their conventional counterparts."

Even the Organic Trade Association (OTA), a group of hired advocates whose mission is to "encourage and protect organic farming practices," acknowledges that organic foods are no safer than conventional foods: Katherine DiMatteo, former executive director of the OTA, admitted that an "organic label does not promise a necessarily safer product."

Also wrapped up in the idea of food safety is the widely held myth that buying organic reduces your risk of harm from exposure to toxic pesticides. A 2010 poll found that 69% of consumers thought that organic farmers did not use *any* pesticides. That number is even higher among those who buy organic. When the Soil Association, a British food accreditation organization, asked consumers why they buy organic, 95% responded that it was because they wanted to avoid pesticides. Obviously, they are unaware that, as biochemist Bruce Ames pointed out in a seminal article,"99.99% (by weight) of the pesticides in the American diet are chemicals that plants produce to defend themselves."

Plant pathologist Steve Savage set the record straight on exogenously applied "organic" pesticides: "Most consumers believe (erroneously) that organic crops are not sprayed with any pesticides at all. That is not true, and the criterion for what can be sprayed on organic has nothing to do with relative risk — it is simply based on whether the pesticide is deemed 'natural.'" (And, as discussed below, it is also based on what organic farmers, who are forced to use primitive products and practices, need to survive.)

Looking at pesticide residues on both organic and conventional foods, in 99% of cases, residues were below the already extremely conservative levels set by the EPA. Nevertheless, non-organic pesticides are commonly vilified as more dangerous, in spite of evidence to the contrary. "Organic pesticides that are studied have been found to be as toxic as synthetic pesticides, and in general are less effective and so have to be used more often," wrote Steven Novella, president and co-founder of the New England Skeptical Society. He accuses the USDA of "facilitat[ing] this deception with their official seal of approval."

What people believe about organic doesn't hold up to scientific scrutiny, and when looking at how the National Organic Standards Board makes decisions, there's no reason to think it would.

The organic seal identifies foods grown according to the USDA-approved organic farming practices, which define "how the food was created, prepared or raised." In practice, the organic standards include a list of approved and prohibited pesticides and fertilizers, farming and food processing practices.

The organic rules are rife with inconsistencies. Manure can be spread on crops, while synthetic fertilizers that efficiently deliver the same nutrients to plants are prohibited. Soy lecithin, a food preservative, can be created in a mechanical process, but not in a process that uses chemistry to produce exactly the same end product. Milk may be pasteurized – i.e., treated with heat to kill harmful pathogens such as bacteria and viruses — but using light (irradiation) to achieve the same effect is not allowed. Seeds created with highly precise molecular genetic engineering techniques that are designed to grow cheaper, faster and more reliably than ever before are not allowed, but seeds created by the technologies of artificial selection, irradiation mutagenesis, and hybridizations that don't occur in nature are. As we said, organic products and practices are arbitrary.

How does the USDA make the decision as to what makes the list? "The organic standards are designed to allow natural substances in organic farming while prohibiting synthetic substances," according to the USDA's website. But the medical community knows very well that "natural" is not synonymous with safe. Bacterial and fungal toxins are natural, and common foods like licorice and nutmeg are notoriously toxic when consumed in excess. Unsurprisingly, the decisions the board hands down make little sense to scientists or farmers.

Take for example, one farmer who pleaded with the board to "close the loophole" that occasionally allows non-organic lecithin, a food preservative, when organic supplies are low. What's the difference? They are the same product chemically. They smell and taste the same and have the same preservative action within the foods they are added to. But the organic lecithin must be produced with an expensive, time-consuming mechanical process, while the conventional preparation is produced using chemistry. The latter is easier and cheaper to make but is rejected because it is missing a mystical property—it's not "natural."

Organic potato farmers use clove oil to prevent post-harvest sprouting, but Derin Jones, a potato grower, asked the board to allow the synthetic chemical known as 3D2, since it works much better—and he brought photos to help prove his case. His request was denied. Superiority of a product is not the standard by which the board must decide.

Another organic advocate wanted the board to "preserve the exception for ferric phosphate," an effective synthetic chemical used as a slug and snail bait in strawberry fields. Ferric phosphate is generally frowned upon by organic advocates since it is "man made," but is allowed because a "natural" equivalent that effectively does the job simply doesn't exist. Those adhering to the principle of using "what is safest and best" will

use better chemicals not as an exception, but as a rule. That's because scientists (and other people with a rational bent) don't make a distinction between natural and synthetic, which is only a construct of the organic movement. Although (like the Pope), the board does occasionally grant dispensations, it is irrational to believe, in the absence of evidence, that a product is superior simply because it is deemed natural.

Adding an official-looking government seal of approval to organic foods perpetuates these myths, misleading consumers. And it lends credibility to a whole slew of brands such as Dr. Bronner's, Ben & Jerry's, Stonyfield Farm, and Chipotle, among others, who have made it their mission not just to advocate their regressive, cult-like organic ideology but to disparage genetic engineering in every form and at every opportunity. The reason, of course, is that genetic engineering is transforming the yield gap between organic and conventional agriculture into a chasm and threatens the long-term viability of the organic agriculture and food industries.

CONCLUSION

USDA's "reorganization" should include both ending the unscientific regulation of genetic engineering and getting the government out of any involvement with the organic agriculture hoax.

Amanda Maxham is an astrophysicist and science writer. Some of the intellectual content in this article contributed by her was developed as work-for-hire at the Ayn Rand Institute (ARI) and benefited from contributions from ARI staff members. ARI has granted her permission to use this content, errors are her own. Henry I. Miller, a physician and molecular biologist, is a Senior Fellow at the Pacific Research Institute. He was the founding director of the FDA's Office of Biotechnology.

Article

A State of the Art in Genetic Improvement of Asparagus Plants: Patent Based Perspective

Sujit J. Patil
CSIR Unit for Research and Development of Information Products, Pune, India

Swapnil L. Bhalke
CSIR Unit for Research and Development of Information Products, Pune, India

Nishad Deshpande
CSIR Unit for Research and Development of Information Products, Pune, India

ABSTRACT

Asparagus is an important medicinal plant having multiple applications in the various treatment systems. Advances in field of biotechnology has resulted in researchers genetically manipulating medicinal plants to create desired biochemical profile. The present review explores applications of genetic engineering in wild species of *Asparagus*. The search revealed that most of the patents were targeted for yield improvement, followed by nutritional improvement and production of important biomolecules. Yield improvement, was achieved by modifications in plant hormonal levels. For nutritional improvement, popular targeted agents included β-carotene and methionine. Terms annotated for enzymes in patents are depicted using Gene Ontology based map.

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Keywords: Patent; Asparagus; Genetic engineering; Medicinal plants; Yield; Nutrition; Transgenic

INTRODUCTION

The use of herbal medicine is increasing worldwide. According to WHO, more than 80% population of the developing countries rely on traditional medicines for their primary health care, probably due to cultural traditions or lack of alternatives[1,2]. Such medicines are becoming popular in the developed countries as well[2]. Most of the world population is currently consuming the herbal medicine in the form of teas, decocts and extracts in mediums such as water, milk or alcohol.

The increasing demand for herbal medicines has accelerated the harvesting of medicinal plants from the wild, which has led to the loss of genetic diversity and habitat destruction[2]. Only 10% of total utilised medicinal plants are being cultivated currently, while majority of the medicinal plants are being collected from wild resources[1]. Domestic cultivation supplemented with biotechnology can serve as a long term viable solution to the above problem as well as the other inherent issues associated with the wild species such as species misidentification, genetic and phenotypic variability of the plant material, minimization of the toxic compounds and/or contaminants, and optimization of desired constitutions[2].

The Himalayan region is enriched with the biodiversity of medicinal plants whose use is mentioned in the Ayurveda, Chinese Herbal Medicine as well as in Unani Medicinal pharmacopoeias. One group of such medicinal plants is the *Asparagus* genus. It includes the species such as *Asparagus racemosus* and *Asparagus adscendens*. These are in high demand and can be domestically cultivated with the help of biotechnological tools. The members of the genus *Asparagus* have been described in the literature to have utility as an antioxidant[3], anti-carcinogenic[4], immuno-stimulant, anti-hepatotoxic[5], antitussive[6], antidiarrheal[7], antibacterial[8], antiulcer[9], antifungal[10], cytotoxic[11], anti-nociceptive, anti-inflammatory[12], estrogenic[13], anti-protozoal[14], spermicidal[15], and molluscicidal[16]. The main pharmacologically active chemical constituents found in the *Asparagus* species include steroidal saponins such as Racemoside A[17], Racemofuran[18], Sarsasapogenin, Kaempferol[19], Shatavarin I, Shatavarin IV[20], Curillosides[21], Aspafiliosides[22], Protodioscin[23],

Asparacoside[24], Asparosides[25], Muzanzagenin[14], and Yamogenin glycosides[15].

The cultivation of *Asparagus* species is variable, as can be inferred from the fact that *Asparagus officinalis* is a commonly grown vegetable for culinary purposes, whereas the commercial cultivation of other species is not widespread owing to their use being limited to the medicinal domain. Although having been cultivated initially for medicinal uses, *Asparagus officinalis* has only recently been found to be a delicacy in culinary dishes. Moreover, *Asparagus officinalis* is known to be the first monocotyledon to be (genetically) transformed and modified[26]. The other species, however are still not commercially cultivated and their availability depends upon the collections from the wild for their utilization in medicinal purposes[27,28]. As stated above, biotechnology can serve as a tool to make the cultivation of such plants more profitable for the farmers by enriching the plants with nutrients or commercial biomolecules or just by increasing the yield of the specific plant[1,2].

Biotechnology is a high technology and diverse domain. From an application perspective for medicinal plants, biotechnology could be applied as a method for biosynthesis and bioaccumulation of desirable natural products along with the product modification in certain cases. Although micro-propagation, cell and hairy root culture as well as gene technology have applications in plant propagation, these tools can also be used to enhance the yield and expression of the desired natural or recombinant products. Micro-propagation has been used for the mass production of plants with the desired traits, while genetic engineering has been used with the main objective to increase the production of pharmaceutically important natural products. As the methods of conventional plant breeding are not notable for the improvement of medicinal plants, genetic engineering might be used instead. Moreover, combinatorial biosynthesis might be utilised for the production of novel natural products as well as rare and expensive pharmaceutically important products. The method of combinatorial biosynthesis involves the combination of different metabolic pathways from different organisms at the genetic level. Hence, genetic engineering can serve as a useful tool in improving medicinal plants by increasing the production of desired natural products and production of pharmaceutically important products as recombinant products[1].

Genetic engineering is technology intensive and involves high investment thus making protection of intellectual property in form of patents a pre requisite for Biotechnology Industry[29]. Latest technological information is hidden in the patents for legal protection of the invention to exclude others from commercial exploiting it. Patents have a wealth of information about the technical details for the particular technological domain, which can be used by a person skilled in the art to replicate the invention or improve up on it. Hence, for understanding the current technological progress and know-how related to genetic engineering, a patent search was conducted in order to find patents concerning the genetic improvement of *Asparagus* species. The patents specifically talking about *Asparagus officinalis* were excluded, as its cultivation is already abundant. This review may serve as an indication of the research already done on *Asparagus* species and as a guide to promote research on domestic cultivation of wild *Asparagus* species and of other wild medicinal plants.

METHODOLOGY

Data mining

A patent search strategy was prepared based on keywords related to the genetic improvement of *Asparagus* species. The keywords included the scientific names and the common names of *Asparagus* as well as indigenous names from the Himalayan region such as "satavar" OR "shatavari" OR "shatamull". For exclusion of the patents related to *Asparagus officinalis,* and those related to the development of abiotic and biotic resistance in plants, the NOT operator along with the keywords (officinalis, vegetable, tolerance and resistance) was used.

The keywords were supplemented by the use of suitable classification codes (IPC and CPC) concerned with *Asparagus* and genetic engineering. The International Patent Classification (IPC) and Cooperative Patent Classification (CPC) are separate hierarchical systems of language independent codes/terms for the classification of patents according to the different areas of technology to which they belong. IPC is divided into eight sections, A-H, which in turn are sub-divided into classes, sub-classes, groups and subgroups. CPC is an extension of IPC providing deeper levels of classification when compared with IPC. Additionally CPC also has one extra section labelled, Y for emerging technologies. For type of biomolecule used as medicine, the patent classification code, 'C08B', was used as it represents the polysaccharides and its derivatives, since the medicinal components from *Asparagus* genus are mostly polysaccharides. The patent classification code, 'C12N9' was used as it is related to enzymes and proenzymes, since the modification of their catalytic activity might result into an improved plant trait. The 'C12N15' class of patent classification code includes the applications of genetic engineering. These classification codes were utilised for patent data mining along with the above mentioned keywords.

INCLUSION AND EXCLUSION CRITERIA

The initial search resulted in 2148 patent records (published online before 1st November 2017) falling within 191 unique INPADOC patent families (Patent families are the set of patents filed in various countries for protecting a single invention; hence one patent per family is considered for further analyses). This result set was screened to obtain the most relevant patent set for *Asparagus* species (excluding *Asparagus officinalis*), with the selection criteria based on the genetic improvement of plant for immediate economic benefits, such as increased yield, production of an economically/nutritionally important biomolecule in the plant etc. The patents related to the development of abiotic and biotic stress tolerance/resistance were excluded from the present analysis, as these patents were only associated with domestically cultivated plants and not with wild plants. The most relevant 46 INPADOC patent families (615 patent records) were grouped together into a set which was utilised for further analysis.

The analysis involved categorising the patents from result set into three major categories based on the application of the genetic engineering. These categories include 1) Yield improvement, 2) Nutritional improvement and 3) Commercial production of economically important biomolecules in the plant. Further analysis also included pathway mapping and analysis as described below.

PATHWAY MAPPING AND GENE ONTOLOGY ANALYSIS

To get an idea of the extent of the use of various metabolic pathway reactions in the patents, the biochemical reactions utilised in the patents were mapped on a "metabolic pathways" reference map from KEGG (http://www.genome.jp/kegg/pathway/map/map01100.html). The enzyme names from the patents were searched on the KEGG database to retrieve their 'KO identifiers', which were then utilised in iPATH2 for tracing the specific enzyme on the reference metabolic pathway map. iPATH2 (interactive pathways explorer), is a web tool from European Molecular Biology Laboratory (EMBL, https://pathways.embl.de/ipath3.cgi?map=metabolic) to locate enzymes and metabolites on a pathway map using their KO identifiers and COG IDs. Since some patents utilised reactions that are not part of the metabolic pathways, these were excluded from the mapping.

The GO (Gene Ontology) terms associated with the enzymes from the patents of the present review were also found and drawn into a DAG (Direct Acyclical Graph). For this, the EC (Enzyme Commission) number of enzymes were used to find the respective gene ontology (GO) ID with the help of IntEnz tool (http://www.ebi.ac.uk/intenz/). The GO IDs were then mapped using QuickGO web server (https://www.ebi.ac.uk/QuickGO/) to get a DAG.

DATA ANALYSIS AND VISUALISATION

Patenting Trend

The first relevant patent was filed in the year 1988 by an industrial entity. As per the overall patent filing trend, the industry is leading as compared to academic institutions. The maximum number of patents filed in a single year by the industry is in the year 2005. Only in the year 2006, 2010 and 2012, were all the relevant patents filed by academic institutions. The top industrial patent filer is Plant Sensory Systems with 5 patent families, while Salk Institute for Biological Studies is the leading patent assignee among the academic institutions with 4 patent families.

Top assignees

Apart from Plant Sensory systems, the top filing industrial members also include the global leaders in plant biotechnology such as Monsanto, DuPont, Bayer Crop Sciences, Syngenta, etc. These global leaders in plant biotechnology are involved mainly in genetic engineering and its application in diverse crops.

Patent filings in countries with respect to assignees and origin of invention

The manner in which the industrial assignees have filed the patents in countries across the globe can be ascertained from the Fig. 3A. The figure shows that US Patent office has received the largest number of patent filings (24), most of which have been filed by Plant Sensory Systems and Monsanto. Australia (20) and European Patent Office (18) follow US in having received the most number of patent filings. Overall, Bayer CropScience leads the way in the number of patent filings throughout the globe, followed by Monsanto and Agresearch. Fig. 3B shows the distribution of patents with respect to the origin country of invention and the countries where these patents were filed. US leads the way in being the origin of the most number of filed patents (164), followed by Germany (31) and New Zealand (17).

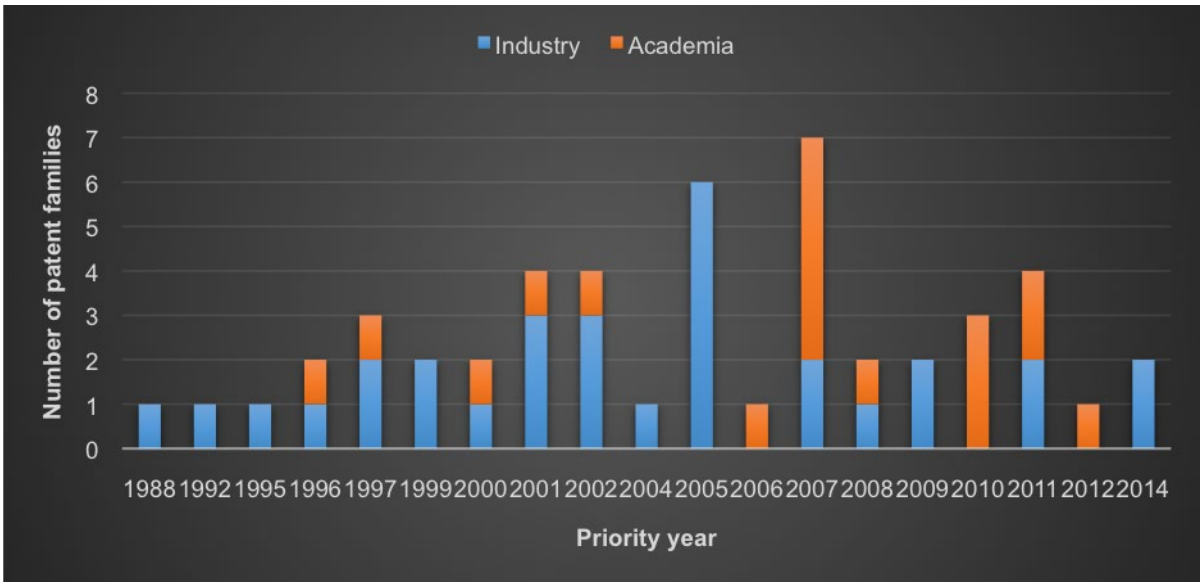

Figure 1: Patent filing trend by entities from industry and academia based on priority year.

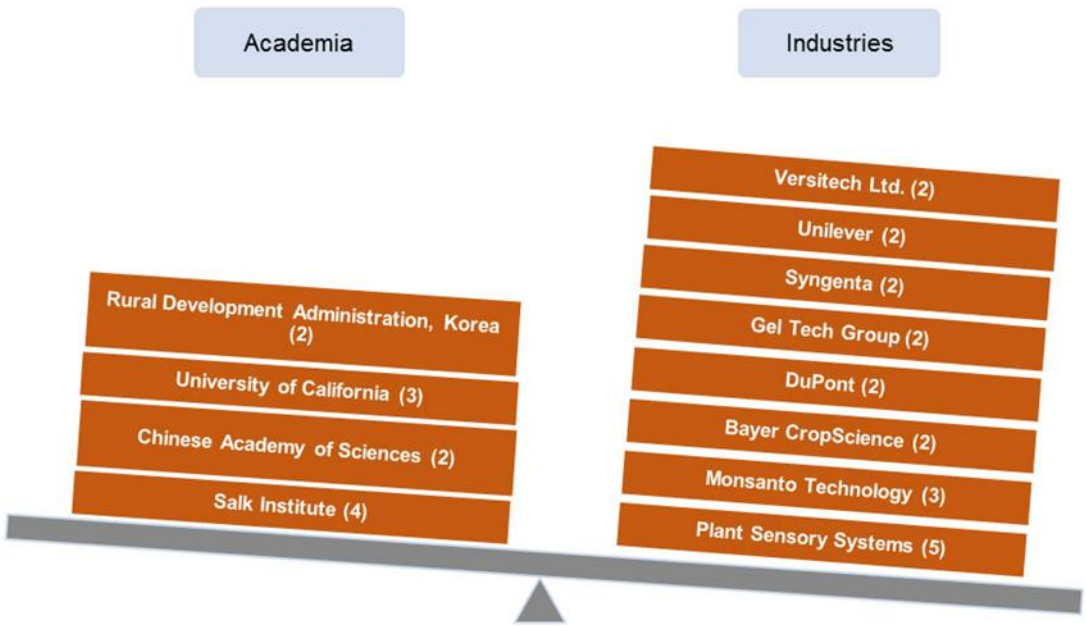

Figure 2: Top 12 assignees in form of academic institutions and industrial entities. The number in parentheses indicate the respective number of patent families.

However, it is important to note here that these number represents the individual patents and not the distinct patent families. In regard to the latter, US leads in being the origin of most number of distinct patent families (30) followed by China, Germany, Great Britain and South Korea with each being the origin of three distinct patent families.

Distribution of patents with respect to IPCs, type of transgene, source of transgene and its mode of expression

As can be seen in the Fig. 4(A), out of 46 representative patents from the respective patent families, 44 patents have been assigned the IPC code C12N00015. The IPC

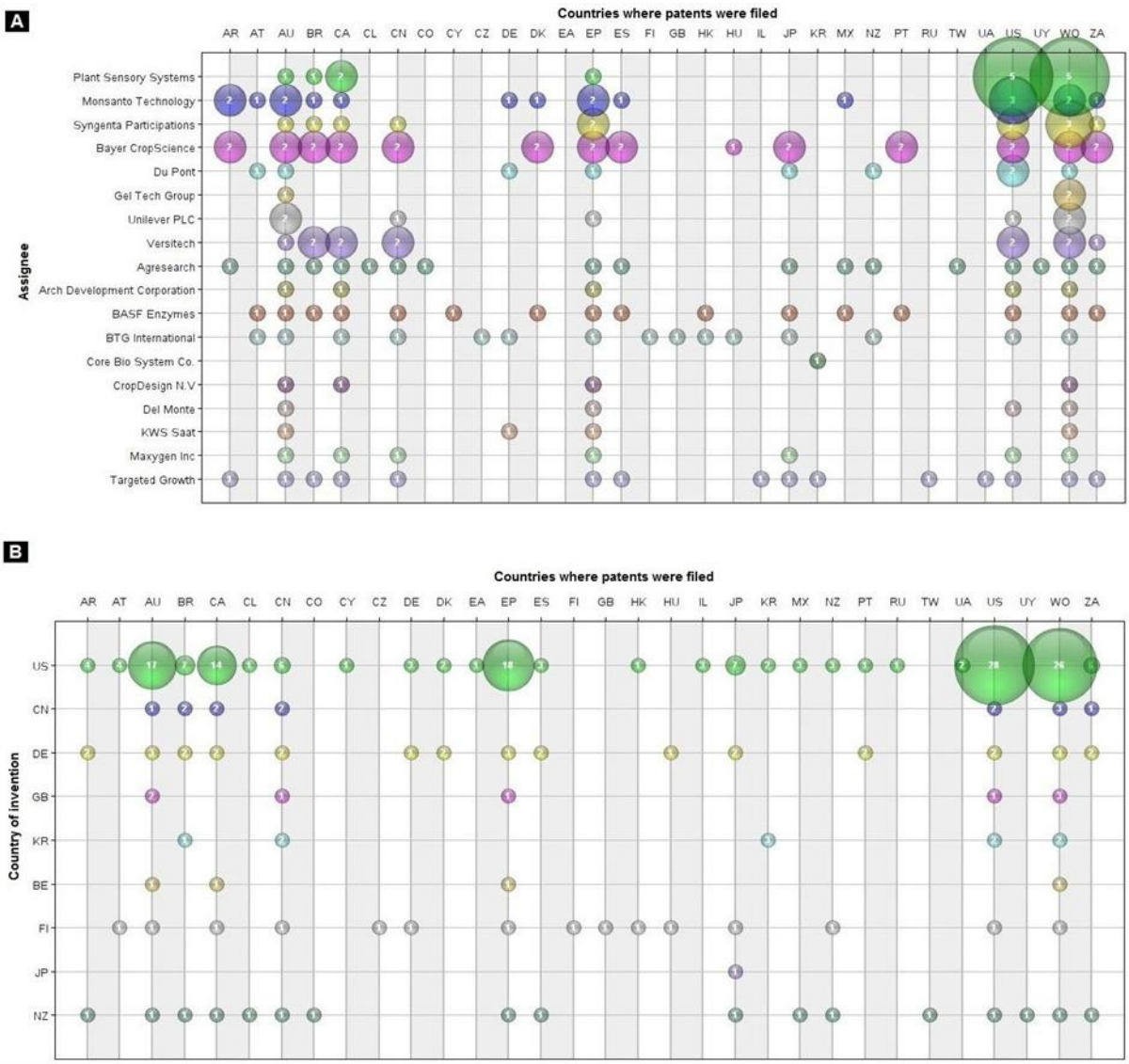

Figure 3: Bubble chart showing the distribution of patent filings with respect to assignee (A) and the country of invention (B).

C12N00015 is related to genetic engineering and mutation techniques. In most of the patents, the plants have been genetically modified using *Agrobacterium* mediated gene transfer method. There is only a single representative patent utilising nano-particle bombardment for gene transfer. Besides IPC C12N00015, other major assigned IPCs include IPC A01H0005 and IPC C12N0009 both of which have been assigned to 19 patent families. The IPC A01H0005 is related to the processes for modifying genotypes. These processes includes artificial pollination, hybridisation, selection, production of mutations and production of changes in chromosome number. On the other hand, IPC C12N0009 is related to the use of enzymes and respective proenzymes based on enzyme classification, preparation of the enzyme composition and methods of inactivation using chemicals.

Figure 4(B) reveals the importance of enzymes in biological systems as they have been utilised for all the three transgenic objectives: yield improvement, nutritional improvement and combinatorial bio-synthesis of the high commercial value biomolecules. On the other hand, the expression of biomolecules involved in signal transduction, gene regulation and photoreception has only been associated with yield improvement. Fig. 4(C) shows that yield improvement is the major objective when plants served as the source of transgene; while the transgenes isolated from viral and animal sources have been used only for combinatorial biosynthesis

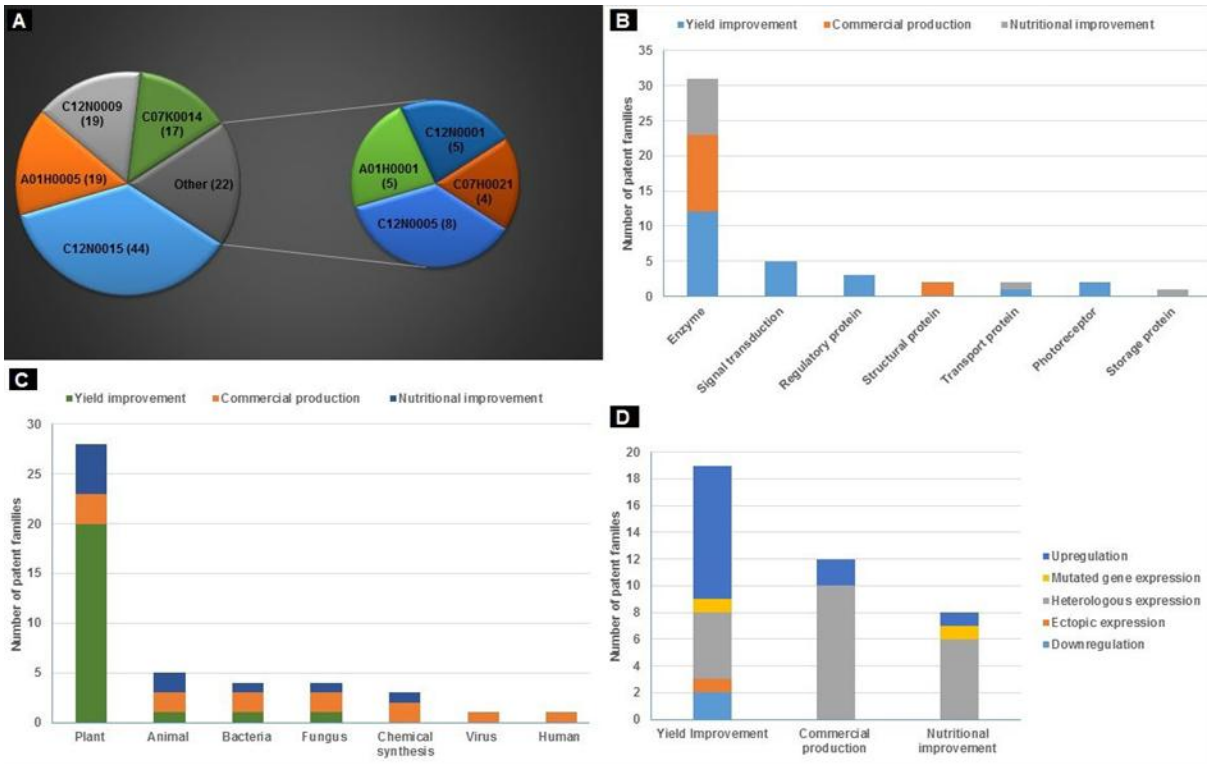

Figure 4: Distribution of patents with respect to various categories. A) Top assigned international patent classification codes (IPCs) to the patent families. B) Distribution of patent families with respect to the type of transgene expressed and the objective of genetic transformation. C) Distribution of patent families with respect to the source of transgene and the objective of genetic transformation. D) Distribution of patent families with respect to the mechanism of transgenic expression and the objective of genetic transformation.

of the commercial important biomolecules. The varying levels of gene expression has resulted into different applications in transgenic plants. The distribution of patents with respect to the gene expression mechanism and the respective objective of genetic engineering is shown in Fig. 4(D). Upregulation refers to the enhancement of the expression of a particular gene found in the plant itself, whereas downregulation refers to the contrary. Heterologous expression refers to the expression of a transgene having a source other than the species in which it is to be expressed. Ectopic expression, here specifically indicates the expression of a gene at a different developmental stage within the same plant. The figure reveals that most of the patents targeted for commercial production employ the heterologous expression of transgenes, whereas most of the patents targeted for the improvement of yield employ the upregulation of endogenous genes.

Figure 5 below provides overview of the gene ontology (GO) annotations assigned to the enzymes utilised in the patents discussed in the present review, in the form of a DAG. The gene ontology is a collaborative project for the organization of biological knowledge to provide a structured vocabulary for annotation of the gene products with molecular functions, biological processes and cellular locations in a highly organized and species-neutral manner with the objective of unified illustration of functional significance of genes across different organisms. GO helps to summarise the current biological knowledge in the form of simple terms and processes. This available knowledge can be applied in organisms in a species-neutral manner with the use of biotechnological tools. GO can also be used to gain gene functional insights in any organism, especially the ones with poorly annotated genomes[30,31]. The wild medicinal plants are considered as such organisms. The functional genomic analysis of medicinal plants is difficult due to the lack of genomic data on them and their genomic sequencing being time consuming and expensive[32]. However, transcriptomics combined with Gene Ontology have emerged as a new tool to interpret the functional role of differentially expressed genes in such plants[33]. According to the method, the set of differentially expressed genes are identified from the transcriptomic data and with the help

of Gene Ontology Enrichment Tools like BLAST2GO (www.blast2go.com), the GO terms being overrepresented in the gene annotations are identified. This can help in the identification and elucidation of the underlying biochemical pathways in medicinal plants, which can then provide information about novel enzymes for their genetic improvement[33].

GO terms annotated to the enzymes utilised in the patents

As the Fig. 5 reveals, in the present analysis, all enzyme genes from the patents were found to have the GO annotations falling under the two domains of 'molecular function' and 'biological process'. Within 'molecular function' domain, all the gene products were observed to have the annotation 'catalytic activity'; which was further sub-divided into 'isomerase activity', 'lyase activity', 'oxido-reductase activity', 'transferase activity' and 'hydrolase activity'. The gene products with isomerase activity were the least utilised one, as only one patent family was observed to have enzyme with this annotation. Overall, most of the patents were found to contain gene products with oxido-reductase activity and transferase activity, with each being involved in 12 patent families. Genes with lyase activity were found in 7 patent families while the gene products with hydrolase activity were found in 5 patent families.

Pathway mapping

Another way to demonstrate the relative positions of the enzymes and the respective reactions/subpathways modified in the patents of the present review, is by tracing them on a reference map of the metabolic pathways from the KEGG database, as shown in Fig. 6. It can be observed from the figure that there are multiple patents utilising biochemical reactions from carotenoid biosynthesis (bottom left), glycosaminoglycan synthesis (top) and taurine biosynthesis (right), while there are only single patents utilising reactions from pathways of xenobiotics metabolism and metabolism of vitamins and cofactors. The modifications in the carotenoid biosynthesis serve as the way to increase the content of beta carotene/lycopene in the plants, and make the plant nutritionally rich which is also achieved by the enhancement of taurine/methionine in plants. The production of hyaluronan (a glucosaminoglycan) has applications in the field of medicine and cosmetics. The figure thus reveals that the utilisation of the various metabolic reactions in the patents is not uniform and there are specific pathways which have been exploited more than the others owing to their economically important end products.

DISCUSSION

Yield Improvement

Plant yield improvement has been the most common application of genetic engineering for cultivated plants.

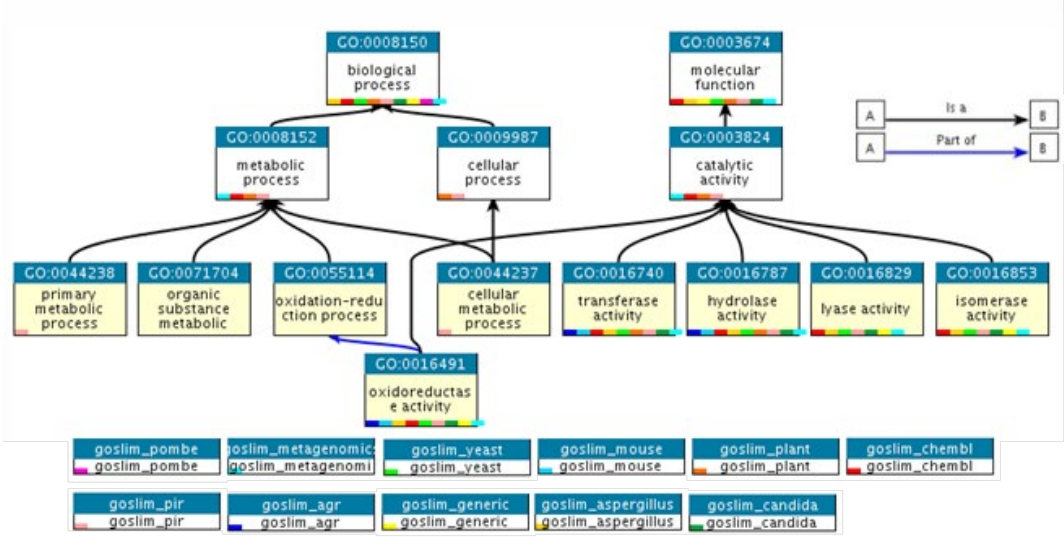

Figure 5: Overview of the GO terms (up to 3 levels) associated with the enzymes utilised in the patents.

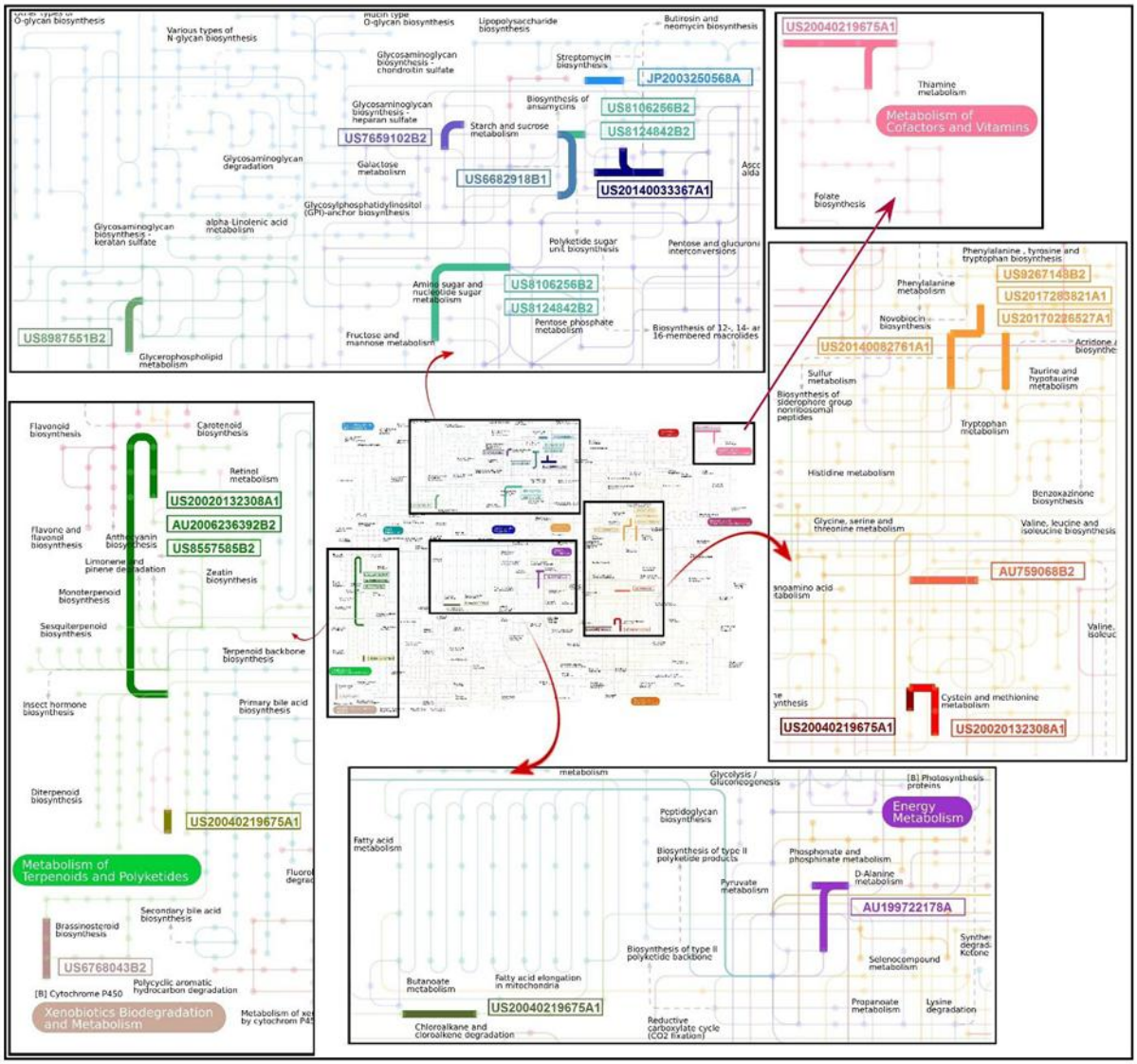

Figure 6: Map of biochemical reactions utilised in the patents. A panoptic view of the metabolic reactions occurring in eukaryotes is represented in a KEGG map (centre). The enzymes/reactions discussed in the patents here were traced on this map and are shown in the surrounding images.

Wild medicinal plants are also now being targeted for yield improvement as the amount of medicinal compounds can be increased by improving the yield. Most of the patents in the present review deal with the improvement in yield.

Modification of the plant hormonal levels

Phytohormones are the one of the most common agents to enhance the yield of plants. Phytohormones are involved in the physiological effects and biochemical pathways. Modification of their biosynthesis or signal pathways can lead to an increase/decrease in their quantity, which can have significant effects on the growth of plants.

Amongst phytohormones, brassinosteroids have been commonly targeted via genetic engineering for yield improvement due to their wide range of effects in plant morphology. Patent US6768043B2 describes the increase in plant yield by increasing the overall plant size. It reveals the discovery of the das5-D mutant, which was created by insertional mutagenesis and activation tagging, wherein a T-DNA containing a transcriptional enhancer is randomly inserted into plant genomes. These mutants were observed to be larger than the wild type plants. Activation tagging results in an increased

Table 1: Summary of the patents targeting yield improvement

Method used	Patent no.	Assignee
Modification of the plant hormonal levels	US6768043B2	The Salk Institute for Biological Studies
	US8008542B2	
	US7994402B2	Monsanto Technology LLC
	US7105654B1	
	US20140033367A1	Current: National Institutes of Health (US) Original: University of Central Florida Research Foundation
	US20090288226A1	DuPont
	US8581041B2	Plant Sensory Systems LLC
Cell cycle modification	AU200043960A	CropDesign N.V.
	US6696623B1	The Salk Institute for Biological Studies
	US9637754B2	Targeted Growth, Inc.
Modification of plant architecture and photosynthesis	CN101597610B	Institute of Genetics and Developmental Biology, Chinese Academy of Sciences
	WO2011097816A1	
	US9150875B2	Gyeongsang National University
	US9695437B2	Monsanto Technology LLC
	AU199919672A	KWS Saat AG
	EP354687B1	DuPont
Modification of Transpiration	US9505811B2	Current: National Institutes of Health (US) Original: The Regents of the University Of California
	US20130326734A1	The Regents of the University of California
	US20150315606A1	
Promiscuous expression of SAD gene	US20140082761A1	Plant Sensory Systems LLC
Phosphatase expression	US9476058B2	Versitech Limited
	US9238819B2	
Arabidillo-1 expression	WO2007060514A3	Syngenta Participations AG

expression of the protein which has been "tagged" and subsequently, the position of this tagging was discovered to be upstream of the DAS5 gene coding for a cytochrome P450 enzyme. Hence, it was concluded that the overexpression of DAS5 gene can be used as a strategy to increase the yield of plants. The overexpression causes an increase in several brassinolide precursor molecules which subsequently enhance the growth of the plants.

Brassinosteroid biosynthesis involves steroid reductases, some of which have been hypothesised to be expressed by the gene SAG13 (Senescence-associated gene), according to the patent US7994402B2. In the patent, SAG13 was overexpressed in *Arabidopsis thaliana*, which resulted in an increase in the size of the seed and lateral root by 100%. The patent mentions that the putative expression of the steroid reductase involved in the biosynthetic pathway of brassinosteroids might be involved in the increased size of the plant organ.

Apart from overexpression, downregulation of the inhibitory molecules has also been used as the strategy to increase the levels of a particular phytohormone in the plant. As it can be seen in the patent US8008542B2, the downregulation of the negative brassinosteroid regulator, BKI1 (BRI1 kinase inhibitor 1) by RNAi leads to a decreased inhibition of BRI1 by BKI1 and hence improved availability of the receptor to bind to the hormone, brassinolide. Greater binding of brassinolide to BRI1 causes improvement in the yield of the plant.

Receptor binding was also modified in the patent US7105654B1. This patent describes the heterologous expression of a mutated form of ethylene receptor (ETR1) gene to increase the plant yield. The ETR1 receptor in the form of an active dimer is involved in the regulation of plant response to gaseous ethylene (phytohormone). Expression of a mutated form of the ETR1 gene causes its binding to the indigenous ETR1 of the plant to form an inactive dimer and hence its inactivation. This inactivation can cause the plant to be insensitive to ethylene and delay the abscission of flowers, fruits, leaves and pods, which can lead to an increase in the plant yield.

Most of the phytohormones are initially present as inactive conjugates of ester or ether linked-glucosides and need to be cleaved by enzymes to make them active[34]. Patent US20140033367A1 discusses the expression of a

beta glucosidase gene, *bgl1* from the fungus *Trichoderma reesei* for enhancing the release of the phytohormones from their conjugates and hence enhance the plant yield. The patent indicates that the improved features were correlated with the increase in gibberellic acid (GA) levels in the transgenic plant, leading to the conclusion that most of the exogenously expressed beta glucosidase was used up in converting the GA conjugates into their respective active form.

Although not directly relating to the increased levels of phytohormones, patent US20090288226A1 reports increased plant growth rate by the overexpression of cis-prenyltransferase genes. It hypothesises that enhanced IPP flux due to improved cis-prenyltransferase activity in the plant may result in altered hormone biosynthesis in the transgenic plants as IPP is involved as a precursor of many classes of plant hormones such as gibberellins, brassinosteroids, cytokinins etc.

Although, γ-aminobutyric acid (GABA) is not considered a major plant hormone, but it might be an intracellular signalling molecule in plants, as it has been reported that intracellular and/or extracellular GABA concentrations increase rapidly in response to a range of stresses[35]. GABA is also reported to have a positive effect on the growth of plants[36]. There are three known metabolic pathways that have an effect on the GABA levels in plants, among which the latest to be discovered in plants involves the catabolism of polyamines such as putrescine. The enzyme, PAT (putrescine aminotransferase) converts putrescine and alpha-ketoglutarate to gamma-aminobutyricaldehyde and glutamate. The gamma-aminobutyricaldehyde is then reduced by gamma-aminobutyricaldehyde dehydrogenase (GABAIde DeHase) to form GABA. Patent US8581041B2 describes the overexpression of PAT and GABAIde DeHase genes in plants to increase the production of GABA, thereby increasing the plant seed yield.

Cell cycle modification

Besides the modification in plant hormonal levels, another way to accelerate the plant growth involves changing the cell cycle dynamics. The regulatory molecules involved in this case which can be targeted include cyclins and cyclin-dependent kinases (CDKs). Overexpression of these molecules can lead a cell to a quick exit through the various regulatory check points of cell cycle and hence rapid cell multiplication leading to improved growth rate.

This strategy was utilised in the patent AU200043960, where the co-overexpression of *cdc2a* and *cycB1;1* caused an enhancement in the growth rate of transgenic plants. On similar lines, patent US6696623B1 illustrates the overexpression of a cyclin, *cyc1aAt* under control of the *cdc2aAt* promoter which causes an increase in the main and lateral root growth rate, along with a proportional increase in dry mass.

An indirect strategy to increase the levels of cyclin-CDKs in plant cells is demonstrated in the patent US9637754B2, which involves the downregulation of cyclin-dependent kinase inhibitors (called CKIs). It shows that the expression of a mutated CKI can lead to the downregulation of the endogenous wild type CKI by the process of competition. This leads to an increase in the activity of cyclin-CDK complexes and hence rapid progression through the cell cycle.

Modification of plant architecture and photosynthesis

Plant architecture refers to the shape of the aerial part of a plant. It can allow the plant to maximise the amount of light that is received, for the purpose of photosynthesis. Modification in the architecture can also lead to plants being able to grow at higher plantation density and hence to an increase in yield per unit area being cultivated.

Erect panicles has many advantages for plants such as increased lodging resistance, improved circulation of CO_2 and moisture, and enhanced availability of light to the leaves. *DEP1* and *DEP2* genes are known for *d*ense and *e*rect *p*anicle type, which were expressed, as per the patent CN101597610B and WO2011097816A1, respectively, to produce plants with erect panicles and hence with increased dry weight.

In addition to panicles, the tiller angle is also a good candidate for modifying the plant architecture. The patent US9150875B2 describes the overexpression of a nuclear protein with four zinc finger motifs, OSMPT1 (*Oryza sativa* Modifier of Plant Type) in plants to create plants with narrow tiller angles and hence higher yield when grown at high plantation density.

High density plantation can sometimes face problems due to a response found in plants called, "shade avoidance", which allows the plants to avoid shade by altering stem elongation, flowering time etc. This response involves considerable changes in the reproductive strategies, and hence affects the commercial yield. Patent US9695437B2 alleviates this problem by reducing the expression of a gene, constitutive photomorphogenesis 1 (COP1), responsible for shade avoidance, in order to increase the yield of the plant.

Photosynthetic rate in plants can also be improved by overexpression of the photoreceptors, as described in the patents, AU199919672A (Phytochrome b) and EP354687B1 (Phytochrome a3, a4).

Modification of Transpiration

The alteration in the intake of CO_2 by leaves comprises another method of controlling the rate of photosynthesis. The intake process is regulated by CO_2 sensors present in the guard cells and the genes coding for these sensor proteins have been identified in the following three patents, which have utilised the overexpression of these genes in order to increase the accumulated biomass of the plant. These patents include US9505811B2 (CORP1, CO_2-Response Protein), US20130326734A1 (Open Stomata 1, SnRK2.2, SnRK2.3, or carbonic anhydrase), and US20150315606A1 (Subtilisin-like serine endopeptidase family protein, ATSBT 5.2-like protein).

Other miscellaneous methods

SAD (sulfinoalanine decarboxylase) gene is not found in plants and its expression has resulted in improved overall plant yield as per the patent application, US20140082761A1, which states that the promiscuous enzyme activity of SAD creates end-products like beta-alanine, 4-aminobutanoate, and 2-aminoethane sulfonate that have been shown to promote plant growth and production.

Overall plant yield was also improved according to the patents, US9476058B2 and US9238819B2, which describe the overexpression of a gene coding a phosphatase with C-terminal transmembrane domain (AtPAP2, *Arabidopsis thaliana* purple acid phosphatase 2) in plants.

The exclusive enhancement of lateral root development was achieved in the patent WO2007060514A3 by overexpressing the gene, Arabidillo-1 (Armadillo repeat-containing protein). The possible mechanism suggested for this effect includes the regulation of downstream genes and/or 26S proteasome targeted degradation of the inhibitor(s) of lateral root development.

Nutritional improvement

Humans and animals depend on plants for various important nutrients such as proteins, vitamins, minerals etc. However, the concentration of these nutrients in plants is generally low and hence there have been consistent human efforts to fortify edible plants with these nutrients. Conventional breeding has been utilised for this purpose but the success achieved has been limited due to the limited gene pool and the process being time consuming. Genetic engineering provides efficient tools for making nutritionally rich plants in a short amount of time[37] and the following patents demonstrate this principle.

Beta (β-) Carotene (Vitamin A)

Beta carotene is the precursor of Vitamin A, which is essential for the process of visual photo-transduction, occurring in some animals including humans. US20020132308A1 outlines the preparation of a single nucleic acid transcript containing four β-carotene biosynthetic enzymes (including phytoene synthase, phytoene desaturase, ζ-carotene desaturase, and lycopene cyclase) for expression in transgenic plants, in order to augment the plant β-carotene and lycopene levels.

A similar method consisting of bi-cistronic expression of the genes, phytoene synthase and carotene desaturase was demonstrated to increase the beta-carotene levels in transgenic rice according to the patent, US8557585B2.

AU2006236392B2 describes the use of pineapple epoxide hydrolase promoter and ubiquitin terminators for the enhanced expression of carotenoid biosynthesis genes intended for increasing the content of β – carotene or lycopene in the transgenics.

Table 2: Summary of the representative patents targeting nutritional improvement

Nutrient(s) enhanced	Patent no.	Assignee
β-carotene	US20020132308A1	Maxygen Inc.
	US8557585B2	Rural Development Administration, Korea
	AU2006236392B2	Del Monte
Taurine	US9267148B2	Plant Sensory Systems LLC
Methionine	US20170226527A1	
Taurine and Methionine	US2017283821A1	
Isoleucine	AU759068B2	Purdue Research Foundation
Vitamin C	AU200059790A	Unilever
Lipids	US8252973B2	The Salk Institute for Biological Studies
Glutamine-rich protein	US7119255B2	Syngenta Participations AG
Thiamine, lysine, iron, Vitamin E, Vitamin A, and protein	US20040219675A1	

Amino acids

Taurine is an important osmolyte present in vertebrate brains and the ocular region and also serves a substrate for the synthesis of bile salts. The pathway involving the synthesis of taurine from methionine and cysteine has not yet been found in plants, and its transgenic expression serves as the objective of the patent US9267148B2. The patent utilised the genes, cysteine dioxygenase (CDO), sulfinoalanine decarboxylase (SAD), glutamate decarboxylase (GAD), cysteamine dioxygenase (ADO), taurine-pyruvate aminotransferase (TPAT), sulfoacetaldehyde acetyltransferase (SA), taurine dehydrogenase (TDeHase), and taurine dioxygenase (TDO) in multiple combinations to increase the content of taurine in plants.

CDO and SAD overexpression was also surprisingly found to increase the level of the essential amino acid, methionine in transgenic cells, as per the patent US20170226527A1. The same genes were again overexpressed to increase the amounts of both methionine and taurine in the patent, US2017283821A1.

The amount of another essential amino acid, isoleucine was enhanced in transgenic cells by expressing a feedback-insensitive threonine dehydratase according to AU759068B2.

Although glutamine is not an essential amino acid, still, it is required in certain physiological stresses and can be acquired through dietary sources. The patent US7119255B2 achieved the enhancement of glutamine-rich protein content in plants by the overexpression of a storage protein gene, labelled as Q-protein.

Other vitamins and fatty acids

AU200059790A cites the fact that humans have lost the ability to synthesise their own Vitamin C owing to the presence of a defective L-gulono-1, 4-lactone oxidase gene in the genome, and hence depend on plants for its dietary supply. The inventors created transgenic plants rich in Vitamin C by the expression of D-arabinono-1, 4-lactone oxidase (ArLO) gene isolated from yeast (*Saccharomyces cerevisiae*).

Similarly, the improvement in lipid production was achieved according the patent US8252973B2 by expressing chalcone isomerase-like fatty acid binding protein genes, which is involved in fatty acid binding and transport, present at the loci, At3g63170 and At1g53520.

In contrast to the patents on enrichment of a single nutrient, patent US20040219675A1 identified multiple nutrient genes. The mentioned genes include phosphormethyl-pyrimidine kinase, di-hydro-di-picolinate synthase, ferritin, gamma-tocopherol methyltransferase, 4-diphosphocytidyl-2-C-methyl-D-erythritol kinase, and bZIP transcription factor for improving the content of thiamine, lysine, iron, Vitamin E, Vitamin A, and protein, respectively.

Commercial production of economically important biomolecules

The production of pharmaceutically and economically significant molecules through combinatorial biosynthesis could be achieved via recombinant biotechnology. Plants can be used as bioreactors for the synthesis of recombinant products, as they have advantages such as low production cost, easy scale up, eukaryotic post-translational modifications, direct usage of plant organs as feed or food supplement, absence of human pathogen as possible contaminants etc.[38]. Medicinal plants such as *Asparagus* species could be utilised as a bioreactor for production of high value compounds.

Enzymes

Enzymes have a huge demand in certain industries such as pharmaceuticals, chemical production, biofuels, food & beverage, and consumer products. Enzymes can be produced in large quantities with the use of genetic engineering technology. Production of enzymes in transgenic plants has been described in patents e.g. amylases (in US7659102B2), alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) (in AU199722178A). Amylases have various industrial applications such as in liquefaction of starch, in alcohol production, in detergents, in baking applications, in animal feed etc., whereas ADH and ALDH has applications in dietary supplements and pharmaceutical industry, according to the respective patents.

Glucosaminoglycans

Although, proteins are the major targets for production via recombinant technology owing to their ease of expression, other biomolecules have also been produced in plants. For instance, the production of glucosaminoglycans (long unbranched polysaccharides containing a repeating disaccharide unit) molecules has been described in US8124842B2 and US8106256B2. The mentioned disaccharide units contain either of two modified sugars: N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc), and a uronic acid such as glucuronate (GlcA) or iduronate (IdoA). They are usually found as components in the extracellular matrix of animal tissues, where they serve as lubricators and shock absorbers in joints. They have applications in medicine and cosmetics. In the aforementioned patents,

Table 3: Summary of the representative patents targeting commercial production of economically important biomolecules

Biomolecule(s) produced	Patent no.	Assignee
Amylase	US7659102B2	Current: BASF Enzymes LLC Original: Verenium Corporation
Daidzein	US7501556B2	Unilever
Hyaluronan	US8124842B2	Bayer CropScience AG
	US8106256B2	
SQDG	US7479387B2	Michigan State University
Tissue plasminogen activator	KR100887367B1	Rural Development Administration, Korea
ADH and ALDH	AU199722178A	Gel Tech Group Inc.
Collagen	WO1997004123A1	
Trehalose	US6323001B1	BTG International Ltd
Methanol	JP2003250568A	Osaka Industrial Promotion Organization
Oil	US8987551B2	Agresearch Limited
Sucrose	US6682918B1	Current: National Institutes of Health (US) Original: Arch Development Corporation

the glutamine:fructose 6-phosphate amidotransferase (GFAT), UDP-glucose 6-dehydrogenase (UGDH), and hyaluronan synthase (HAS) genes have been expressed for synthesis of glucosaminoglycans such as hyaluronan in plants.

Biomolecules for pharmaceutical applications

The transgenic production of daidzein is described in the patent US7501556B2, which also lists its potential use as a medicament in the treatment/prevention of osteoporosis, cancer, menopausal symptoms etc. The multi-gene expression of isoflavone synthase (IFS), chalcone isomerase (CHI), and chalcone reductase (CHR) genes was utilised in the production of daidzein, according to the patent.

Another potential anti-cancer biomolecule, 6-sulfo-α-D-quinovosyl diacylglycerol (SQDG) was produced in plants by the expression of UDP-sulfoquinovose synthase (SQD1) gene as per the claims of the patent US7479387B2.

Tissue plasminogen (tPA) factor was the target molecule for transgenic production in the context of the patent KR100887367B1. It has applications in the treatment of diseases that feature blood clots, such as pulmonary embolism, myocardial infarction, stroke etc.

Production of collagen and trehalose in transgenic plants was claimed in the patents WO1997004123A1 and US6323001B1, respectively, by the respective expression of *COL1A1*, *COL1A2* (from *Bos taurus*) and trehalose-6-phosphate synthase (from *Saccharomyces cerevisiae*) genes.

Other biomolecules

In search of alternative energy sources, biofuel has emerged as a promising option. Hence there have been efforts to increase the calorific value of plants, which can be observed in the patents JP2003250568A and US8987551B2. These outline the expression of pectin methyl esterase (PME) to produce methanol and the expression of diacylglycerol acyltransferase 1 (DGAT1), oleosin to increase oil content of the plants, respectively.

Other patents concerning the transgenic production of biomolecules include, US6682918B1 (expression of sucrose synthase to produce sucrose), and US20040219675A1 (expression of adenylate transporter gene to increase the production of starch).

CONCLUSION

The global herbal medicine market was valued at $71.19 billion in 2016 and is expected to reach a size of $86.74 billion by 2022[39,40]. The increasing demand has led to a rapid loss in wild populations of medicinal plants including that of the species belonging to *Asparagus*, due to their unmanaged harvesting. Also, species misidentification and variability in the active pharmaceutical component's concentration are other problems commonly faced in the utilisation of medicinal plants. In order to overcome these problems, it is necessary to make the domestic cultivation of wild species more common and profitable for the farmers. As the methods of conventional breeding are not much helpful in case of medicinal plants and are also time-consuming, as well as their use to create hybrids is limited to members of the same genus, they have been superseded by the use of genetic engineering[1]. Genetic engineering can be used to enhance the domestic cultivation of wild medicinal plants and to increase

the economic value associated with them. The present review can also help in exploring the applications of genetic engineering to produce plants with traits having immediate economic value along with the production of active pharmaceutical components in medicinal plants, particularly, wild *Asparagus* species. The present analysis reveals, enzymes have been primarily targeted to be genetically modified for improving plant traits. It has also been observed that genetic engineering has been utilised for yield improvement, nutritional improvement and commercial production of high commercial value biomolecules. The highest number of patent families (23) have been involved in yield improvement; followed by nutritional improvement and commercial production of biomolecules.

For yield improvement, the alterations in phytohormone levels such as that of brassinosteroids and ethylene using genetic engineering was utilised in 7 of the patent families. Moreover, the modification in levels of GABA, an intracellular signalling molecule, was also utilised for yield improvement. Next popular method for yield improvement was cell cycle modification. In case of nutritional improvement, the major nutrients fortified into plants included beta-carotene (precursor of Vitamin A), amino acids and fatty acids. Most of the gene expression involved in this case was heterologous in nature.

Plants can also be used as bioreactors for producing biomolecules as recombinant products, especially the ones which require post-translational modifications. Various biomolecules which have been claimed to be produced in the patents of this review includes enzymes (amylase, ADH, ALDH), glucosaminoglycans (hyaluronan), tPA, daidzein, SQDG, trehalose, collagen, methanol, sucrose and starch.

From the above analysis, it can be concluded that there are technologies available for improving the economic value of *Asparagus* plant species, in addition to their medicinal value. The available application of biotechnological tools can be helpful in maximising the financial gain obtained from medicinal plants. The wild species of *Asparagus* can be cultivated domestically and their exploitation from wild resources can be avoided as has already been done in case of *Hypericum perforatum* and *Gingko biloba* in Europe and America[1]. Yet currently there is a lack of such genetically engineered cultivars and hence additional work needs to be done in order to enable the maximal exploitation of these important plant resources.

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Note: Mr Sujit Patil and Mr Swapnil have contributed equally in this review.

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Article

Accessing Continuous Glucose Monitoring (CGM) Sensors in France and the Us: A Comparative Case Study of Abbott's Freestyle Libre (FSL) System

Lucie Perrier
Is a J.D./Master en Droit Candidate at Cornell Law School/Université Paris 1 Panthéon-Sorbonne

ABSTRACT

Blood sugar monitoring is at the heart of every type one diabetic's treatment. Because patients need make 500,000 decisions over a lifetime on average, reliability on monitoring devices is vital. Thus, the development of Continuous Glucose Monitoring (CGM) systems came as a revolution, as patients need not prick their fingers anymore and now have access to previously unavailable blood sugar trends. This note uses Abbott's *FreeStyle Libre* (FSL) as a CGM case study comparing the patenting strategies, regulatory and pricing obstacles this biotechnology company had to face to market its product in both France and the United States.

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I. INTRODUCTION

A. Diabetes: A Worldwide Burden

In its first Global Report on Diabetes, the World Health Organization (WHO) stated that an estimated 422 millions adults were living with diabetes in 2014, compared to 108 million in 1980.[1] This increasing global prevalence should continue to rapidly increase, with the prospect of exceeding 500 million cases in 2030,[2] making it one of the most important public health issues facing healthcare systems today.[3] Indeed, there were approximately 30.3 million American diabetics in 2015 (or 9.4% of the US population),[4] and the Europe region counted 58.9 million diabetics (or 9.1% of the European population) that same year.[5] But while diabetes numbers are impressive, its costs are even more dramatic.

Just as the prevalence of diabetes widely varies across the Europe area, the range of average diabetes-related healthcare spending is also very broad: from about $10,083 per diabetic per year in Luxembourg to just $122 in Tajikistan.[6] Aggregating all this data allowed the International Diabetes Foundation (IDF) to conclude that diabetes alone was the cause of 9% of the region's total health expenditure in 2015—that is 156 to 290 billion dollars, which averages out to $2,610 to $4,854 per person per year.[7] Diabetes in America, too, creates an exorbitant economic burden. It amounted to $245 billion in the form of higher medical costs ($176 billion) and reduced productivity ($69 billion) in 2012.[8] That total estimated cost of diagnosed diabetes in the US skyrocketed five years later—to $327 billion.[9]

B. Diabetes: Different Types, One Goal

While diabetes numbers are usually estimated on a global scale,[10] not all diabetes are alike. It is true that the term "diabetes" generically describes the inability to effectively regulate levels of glucose in the blood properly,[11] but the condition comes in different forms. The main ones are type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes.[12]

Gestational diabetes solely occurs during pregnancy.[13] However, the general population is more accustomed to the most publicized T2D, whose onset usually occurs late in life after progressive deterioration.[14] Type 2 diabetes is usually triggered by prolonged bad daily habits (ie. physical inactivity and an unhealthy diet) and is defined by an inefficient action of insulin on patients.[15] Type 1 diabetes or "juvenile diabetes", on the other hand, usually occurs before the age of forty and results from the pancreas' total inability to produce insulin.[16] Its exact causes are still unknown to the medical community but endocrinologists generally agree that it results from a complex interplay between one patient's genetic heritage and external environmental factors.[17] This particular type of the condition is less familiar because T1D patients usually make up for only 5 to 10% of the diabetic population.[18]

Just as the different types of diabetes differ in their causes, their treatments vary as well. Because of type ones' total lack of insulin secretion, their treatment can only be constituted of exogenous administration of insulin–either through the use of an insulin pump or multiple daily injections.[19] On the other hand, T2D patients' treatment mainly consists of diet, physical exercise and/or drug therapy, but only if the former is not effective.[20] Nonetheless, both kinds of treatment have the same goal: keeping the patient's concentration of blood glucose (BG) in the safe range.[21] If not, hyperglycemic events (when BG is too high) can lead, in the long run, to very serious complications and premature death. Possible complications include retinopathy that may lead to blindness, cardiovascular disease, kidney failure, leg amputation and nerve damage.[22] Hypoglycemia (when BG is too low), on the other hand, can be dangerous in the short term by potentially inducing a coma or even death.[23] Because T1D patients are more prone to hypoglycemia, just because they exclusively rely on insulin therapy,[24] and since the dosing of insulin primarily relies on a patient's capability to measure BG levels accurately, this paper will solely focus on T1D blood glucose management.[25]

C. Blood Sugar Management: Then and Now

The discovery of insulin by Frederick Banting and Charles Best,[26] then later its marketing in the 1920s were a true medical breakthrough.[27] Instead of being doomed to survive for three years only, newly diagnosed T1D diabetics could now dream of living a longer and healthier life.[28] Yet, it presented a risky drawback for patients—the management of insulin-induced hypoglycemias.[29] The only way to prevent such an event requires regular blood sugar testing. And monitoring blood sugar levels is undeniably not straightforward! Starting with cumbersome urine tests, the pharmaceutical industry continually brought more and more innovations in diabetes management during the 20th century.[30] As a result, self-monitoring BG (SMBG) became possible in the 1970s when SMBG meters were put on the market.[31] It was a first drastic transformation in a patient's life, as one could take action after only waiting a few seconds to have a reading of her BG level. For patients with T1D, doctors recommend to repeat this operation at least four times a day.[32] To do so, patients need to prick their fingers with a lancet, put a drop of capillary blood on a test strip and wait for the meter to reveal the reading.[33] However, due to the insufficient sampling frequency, the results of a SMBG meter cannot indicate critical episodes in a patient's life.[34] This shortcoming was however revolutionized by the development of Continuous Glucose Monitoring (CGM) sensors.[35] Such wearable sensors are minimally-invasive devices that measure BG concentration almost continuously (1-5 sampling period) for several consecutive days or weeks.[36] By measuring in the interstitial fluid that is in the subcutaneous tissue, sensors provide patients and health care professionals (HCP) data on blood sugar fluctuations that was simply inaccessible before.[37]

By swiping the reader over the sensor for a one-second scan, a patient can visualize trends (ie. going low or high, and at what speed) and learn from patterns. As a result, he or she can treat hypo – and hyper-glycemias that would have gone undetected with a SMBG meter, even if used multiple times a day.[38] From previously focusing on a sole BG reading to now seeing a trend, patients' quality of life improved and they can thus more effectively prevent complictions in the long run.[39]

The three main competitors in this industry are Dexcom Inc, Abott Laboratories and Medtronic.[40] While the latter released the first CGM device in 1999,[41] Abbott made the latest advance with its FreeStyle Libre (FSL) system. It got rid of a major complaint: calibration.[42] That step requires users to collect one or more SMBGs a day so as to enable the conversion of raw measurements to glucose values to be used as basis for operating the sensor .[43] The FSL, on the other hand, is the only CGM system which is factory-calibrated.[44] As a practical matter, this means that the FSL provides the first reading one hour after the sensor has been activated.[5]

While the clinical benefits of using the FSL have been proven,[46] one may wonder why it was first available on the European market in 2014, before reaching American patients four years later.[47] Before delving into a comparative approach to medical devices' pricing on both sides of the Atlantic (III), let us scrutinize the obstacles Abbott Laboratories had to pass in order to market its FSL technology in both France and the US (II).

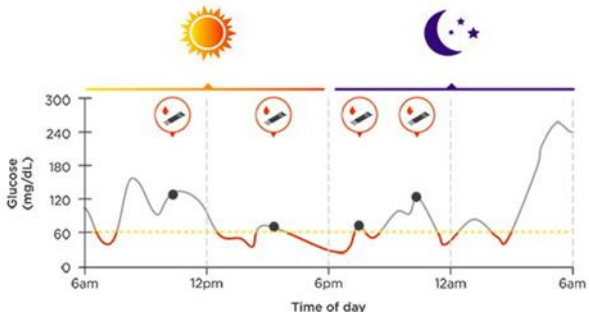

Figure 1: Illustrative comparative graph of a T1D patient's BG levels over 24 hours. The dots represent SMBG meter readings, while the graph is what a patient would see on her reader when using a CGM sensor.

Figure 2: The FreeStyle Libre Flash Glucose Monitoring System has two on-body parts: a handheld reader and a disposable sensor that a patient is advised to insert on the back of her upper arm.

II. MARKETING THE FSL IN FRANCE AND THE US

For pharmaceutical companies, especially ones producing medical devices, the most important form of intellectual property protection is patents.[48] A patent provides a negative right to its owner allowing him to prevent others from making, using, offering for sale or selling his patented invention.[49] However, while patents are critical to the economic success and future growth of a company, it is important to remember that patents alone do not do all the work.[50] It does not automatically give a pharmaceutical company the ability to sell its technology on a specific market.[51] Countries place regulatory "obstacles" blocking certain products, including medical devices, from entering its market. This is especially true in the biotechnology industry where products must first obtain approval from a national regulatory body before they can be sold to patients.[52]

Prior to conducting a comparison of pre-market approval processes in both France and the US (B), we must first consider the patentability of the FSL system (A).

A. Patenting the FSL

To use the FSL system, a patient must first apply the sensor in the back of her upper arm.[53] To do so, Abbott Laboratories developed an applicator that permits this insertion.[54] One must first open the sensor pack and the applicator pack then combine them together to assemble the sensor. The FSL system therefore comprises three elements in total: a sensor pack, an applicator and a reader.[55]

What was Abbott's strategy to protect this technology so as to gain and keep its market share?

a. In the US

Through its Article 1, Section 8, Clause 8, the US Constitution provides that "Congress shall have the power… To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries". To further this command, Congress enacted the Patent Act of 1790, a year after the Constitution's ratification and set up the Patent Board, the US Patent and Trademark Office's ancestor (USPTO).[56] The idea behind the award of patents is to reward inventors for the fruit of their labor. That is, in exchange for disclosing their inventions, they can legally exploit them in a monopolistic manner for a period of twenty years.[57] However, research and development (R&D) in the pharmaceutical industry is an uncertain, expensive and, most of all, time-consuming process that approximately take 8 to 10 years to carry out.[58] To make up for this "lost time", big pharma companies do not hesitate to resort to borderline immoral strategies to exploit loopholes in patent laws so as to extend their invention's market exclusivity.[59]

i. Evergreening

When trying to maximize its monopoly over a drug or medical device beyond the life of its original patent, a company is engaging in "evergreening".[60] That is, a company seeks to obtain multiple patents covering various aspects of its invention.[61] In the biotechnology industry, that usually means filing patent applications covering the active ingredient, formulations, methods of manufacturing, mechanisms of actions, packaging, screening methods, ect.[62] Abbott claims that the FSL system is currently covered by 92 US patents[63] but most of them "only" cover *methods*.[64] While this observation might imply that Abbott is limited by the nature of its invention (as in the FSL system is not a drug), the latter still managed to cover most, if not all, aspects of its technology.

The basis of the FSL sensor is Abbott's "method of detecting a level of an analyte [a chemical substance that is the subject of chemical analysis] in a bodily fluid".[65] However, the manufacturer's legal counsels adopted a wider view of what this invention meant. Indeed, they applied for patents covering the necessary insertion of the sensor for its use. That means the sensor assembly itself, which includes "a sensor and a connector for coupling the sensor to the electronics assembly".[66] That particular application is comprised of 65 images illustrating the packaging, loading systems, applicators and elements of the on-bod device itself.

Abbott truly took evergreening to the next level by also obtaining patents covering its "swipe system" that permits the patient to get a reading by simply swiping the reader over the sensor,[67] but also its system providing a power supply to the device,[68] its method allowing the display of graphical representation of BG data[69] and arrows indicating trends on the reader,[70] its processing method to generate those actual trends,[71] and even the method for determining the "elapsed sensor life" (that is, the number of remaining days during which the FSL will be working).[72] However, before being able to swipe and read the corresponding BG level on the reader's screen, a reaction must take place in the sensor to convert the raw reading into a BG reading. To that end, Abbott also patented "novel polymeric transition metal complexes", which can be used as "electron transfer mediators in enzyme-based electrochemical sensors",[73] its calibration technology, as well as the method for generating wireless communication.[74] This proactive initiative seems to be working for Abbott, as it owns 50% more patents than its competitor Dexcom on its rival product the G4 Platinum System.[75]

ii. Secondary Patent Applications

Another defensive strategy used to maximize the longevity of Abbott's portfolio is "secondary patent applications". Secondary or follow-on-patents, also known as "reformulations", are "the most popular and, arguably, the most effective way to prolong a product's commercial life",[76] as it delays competition between developed innovations based on the same original invention.[77]

For example, Abbott currently owns ten different patents that cover the composition of its FSL's biosensor membrane.[78] According to its patent application, this membrane is "useful in limiting the flux of an analyte to a working electrode in an electrochemical sensor so that the sensor is linearly responsive over a large range of analyte concentrations and is easily calibrated".[79] As a result, sensors equipped with such membranes "demonstrate considerable sensitivity and stability, and a large signal-to-noise ratio, in a variety of conditions".[80] Even though

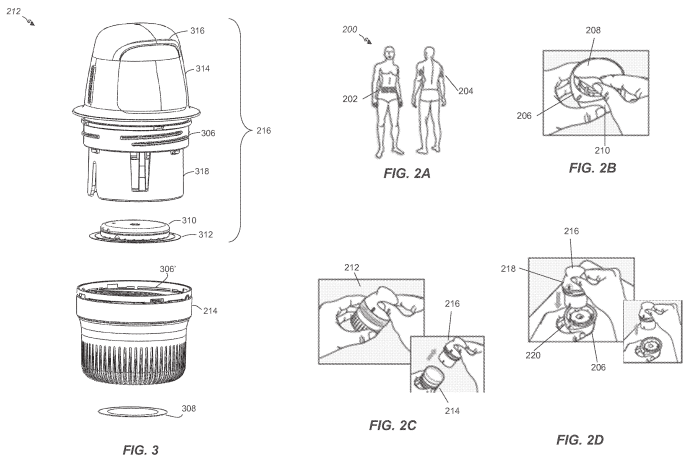

Figure 3: These technical drawings illustrate how to connect the applicator pack (212) with the sensor pack (214), allowing the patient to assemble the sensor (310). Once this step is complete, the patient must apply the applicator pack on her skin (containing the assembled sensor) and press firmly for the spring to insert the sensor into her upper arm.

it abandoned three additional patent applications covering this membrane, what is striking is the period of time during which Abbott worked on it. Its first membrane patent application was filed sixteen years ago, in 2002, and was granted in 2005.[81] Yet, it still applied for another nine patents, the latest one being granted in 2017.[82]

iii. Brand Migration

Finally, as a leader on the CGM market, Abbott has engaged in "brand migration", also known as "product hopping", a patent-maximizing technique wherein the innovator company releases a successor product with a different brand name and with minor changes such as changes in design, small features, ect. to extend the overall term of its monopoly.[83] In fact, the FSL system is the daughter product of Abbott's prior CGM system: the FreeStyle Navigator. Marketed in 2008, it was later withdrawn from the market in 2013 due to the FSL's much awaited arrival.[84] The Libre was therefore not a per se revolution as it uses the same enzyme glucose sensing technology as the FreeStyle Navigator.[85]

The first piece of Abbott's brand migration evidence is the set of FSL versions available in the US: the professional one and the first patient variation. While the former was approved by the Food and Drug Administration (FDA) in 2016,[86] the latter was approved a year later.[87] Both look exactly the same design-wise but the professional reader is white, while the patient version is black.[88] The only functional difference is that the pro version is indicated for use only by health care providers, so that the reader component of the system stays with them.[89] As a result, it is no surprise that both are covered by the same patents.[90] Yet, the most striking evidence of branding migration is the arrival of a second patient version of the FSL on the US market in 2018. While the first FDA-approved patient system lasts 10 days, the latest version lasts 14 days (like the pro version).[91] Moreover, the first BG reading can now be done after an hour post-insertion versus 12 hours in the 10-day system.[92]

That means that Abbott has put on a the US market a slightly-improved version of the FSL every year since 2016. This tactic might be explained in part by the easier FDA approval process for devices used by professionals only.[93] It probably wanted to "test" the FSL out with professionals and wait for feedback from the European market before investing in the more stringent FDA approval process for the patient version.

b. In France

Because Abbott is a global company, this patenting strategy was replicated all over the world, especially through the strategic use of the non-unitary European and international patenting systems.[94] Indeed, the Patent Cooperation Treaty (PCT) provides a unified procedure for filing applications in each of the contracting states of the treaty,[95] just like the European Patent Convention (ECP) provides a similar unified procedure for its own contracting states. However, the latter may only be filed with the European Patent Office (EPO), while a PCT may be filed with both the EPO or the World Intellectual Property Organization (WIPO).[96] When searching for a patent on the French *Institut National de la Propriété Intellectuelle*'s database (INPI),[97] one will only find that Abbott obtained its patents in France through the EPO or WIPO, not the INPI.[98] The company clearly made use of these international pathways for patenting its biosensor membrane, or its cornerstone analyte monitoring system repeatedly over time.[99] As such, it is clear that Abbott is also involved in evergreening in the EU. However, that does not seem to be a problem as there are no such prohibition in the EU and the patent laws there are still quick permissive.[100] Indeed, while evergreening may be deemed anti-competitive behavior under the scope of Article 102 of the Treaty on the Functioning of the European Union (TFEU),[101] its application is still unclear. Because patent laws are Member State-specific, a piece of EU law such as Article 102 cannot challenge a country's patent laws, here France's.[102]

On the other hand, Abbott did not engage in brand migration in France. Its sole version of the FSL there is, and from the start, a 14-day patient version that provides a first BG reading after one hour post-insertion. It was available in 2014 already, while this exact same version was only available in 2018 for Americans. What could account for such a difference?

B. Getting Market Approval for the FSL

Obtaining a patent does not mean that a patient will access the technology. While it definitively helps pharmaceutical companies compensate their R&D costs,[103] they also need regulatory approval, especially as to the safety of their products before they can sell them to patients. They depend as well on future profits from the technology that will actually reach the market in order to recoup their investments.[104]

In the US, the process is conducted by the FDA, which grants pre-market approval (PMA) (a). In European Union, any Member State's notifying body may grant the CE Mark (b).

a. Approval by the American Food and Drug Administration

i. Pre-Market Approval (PMA)

The agency's Center for Devices and Radiological Health (CDRH)'s role is to protect the public's health by ensuring that medical devices are effective, safe, reliable and that they work in a consistent manner.[105] Applying the Medical Device Amendments of 1976, the CDRH must first verify to which class of devices the one under consideration is part of, based on the risk it could expose the patients to.[106] Class I devices that are low-risk are subject only to "general controls".[107] Class II devices are subject to additional informational requirements—mandatory performance standards, guidance documentation, or additional labelling—also called "special controls". These are usually reviewed and cleared via the premarket notification pathway. Generally referred to as the 510(k) pathway, it requires applicants to show that their new device is substantially equivalent to a pre-existing or predicate device.[108] Lastly, because class III devices are considered to support or sustain life, prevent impairment of health, or present a potential, unreasonable risk of injury,[109] "special controls" are not enough to insure efficiency, safety reliability and consistency.

As the first FDA-approved FSL system, the pro version was classified as a Class III device and approved on September 23, 2016.[110] Getting pre-market approval means that Abbott met with the agency to discuss available preclinical data so as to determine the least burdensome approach for the collection of clinical evidence. That discussion boils down to a cost-benefit analysis–the issue being the appropriateness of time, effort and resources invested by the inventor that would "guarantee" him a probable likelihood of PMA by the FDA.[111] Then, Abbott filed for an investigational device exemption (IDE), which triggered the formal review process. This application is composed of evidence exposing prior research (e.g., preclinical evidence, outside the US data), manufacturing processes (e.g., sterilization, packaging), and study protocol (e.g., risk analysis, monitoring procedures, consent materials). And upon approval of this IDE application, the FDA allowed the company to work on its device according to the proposed clinical trial plan. Here, the FSL pro system relied on one study only, which involved only 75 participants.[112] The next step was for Abbott to prepare its PMA submission. Its main elements are similar in form and content to the IDE application: additional studies, proposed labelling and intended use.[113] However, the focus of the FDA's scrutiny shifted at that stage to the safety and effectiveness of the device. After seven amendments over a year, the FDA approved the pro system.[114]

As for the first 10-day patient system, it just took another year for Abbott to obtain PMA. However, the FDA relied on four clinical studies this time.[115] It might be explained by the possibility of user bias by the now real-time availability of data to patients.[116] Indeed, they can now see the trends themselves and can take action (ie. inject more insulin or go for a walk to lower their BG level or eat to compensate for an approaching hypoglycemic event).

Considering that a T1D has to make over 500,000 decisions over a lifetime on average, a patient's reliability on the FSL system may turn out to be dangerous if one is not trained to use it.[117] The FDA's stringent procedure is therefore not only understandable but also desirable for patients on the other end.

ii. PMA Supplement

On the other hand, the 14-day patient version was FDA-approved through a PMA supplement application.[118] One manufacturer may decide to submit such an application if it wants to update or modify an already FDA-approved class III device.[119] They are required for incremental changes that are "accepted part[s] of a device's life cycle".[120] Here, Abbott solely sought approval for the expansion of the sensor wear period to 14 days, and the decrease of the sensor warm up time to one hour.[121] It is a very beneficial procedure for the manufacturer as the FDA's involvement prior to implementation of the change is very limited or inexistent.[122] Moreover, it took the FDA one fourth of the time it had needed to approve the initial device–that is, approximately three months versus one year.[123]

The FDA is therefore clearly "needed" at every change made to a medical device. For instance, it just approved a mobile app for use with the FSL 10-day and 14-day systems, allowing patients to monitor BG trends on their compatible iPhone devices.[124]

b. Through the EU's Decentralized Approval System

Abbott did not follow this three-step marketing tactic in France. It directly sought safety approval for a 14-day patient version, which was obtained in September 2014,[125] exactly four years before its equivalent in the US and two years before the US professional version.

In the EU, every medical device on the market must carry a *Conformité Européenne* (CE) mark indicating that it complies with relevant safety standards set forth in the Medical Device Directives (MDD).[126] A device with a CE mark can be marketed in any EU member state after a national notifying body's approval, such as France's *Agence nationale de sécurité du médicament et des produits de santé* (ANSM).[127] By adopting the MDD,[128] the EU has defined the minimum safety standards

required for such devices depending on the severity of the risk posed on the patient, just as in the US. As such, the European framework provides for four classes of devices leading to four pathways to the CE mark: classes I, IIa, IIb and III.[129] The FSL system was considered part of class IIb.[130] A device in this class requires clinical and/or non-clinical evidence to support approval. As in the US, if a device is shown to be substantially similar to an already approved device, data from the predicate device may be used to support an approval application, and new clinical testing may not be needed.[131] Whatever studies Abbott used to support its application, it obtained approval by the British notifying body in a very short period of time.

Because of the EU's decentralized approval system and the more stringent FDA PMA process, a "device lag" of three years has been reported between the EU, thus France, and the US.[132] In fact, the lag has been of four years for the 14-day FSL system. This is probably why Abbott decided to issue a professional version first on the US market, knowing it would be easier and faster to get a regulatory approval for this simplified system.[133] But at the end of the day, European patients still enjoyed earlier access to this diabetes management breakthrough over US patients.

III. AFFORDING THE FSL SYSTEM IN FRANCE AND THE US

However, safety approval alone does not equate to availability to patients.[134] Another factor is the device's actual cost (a) and if too high, the efforts to render it affordable (b).

a. Raw Cost of the FSL

Marketed in France first, Abbott set the reader's price at 50,10€ (as part of a starter package including two sensors for 169.90€) and a sensor's at 59,90€.[135] If used all year round, it required a T1D to budget 1487.70€ all taxes included, which is approximately $1,687.[136] This was considered very cheap and market disruptive, as the average yearly cost for CGM usage for Europeans was of 4,000€/year before the FSL.[137]

The 10-day FSL system has been available in US pharmacies since December 2017 for a cash price ranging from about $36-$53 per 10-day sensor.[138] The reader costs about $70-$97 (more pricy than in France).[139] People in the diabetes community had predicted that it was unlikely that the sensor pricing–$120/month with most insured people paying $40-75/month–would change with the arrival of the 12-day version.[140] They were right.[141]

b. Making the FSL Affordable–Reimbursement

Though initial raw costs of the FSL were similar on both sides of the Atlantic, patients did not have actual access to it due to inexistent reimbursement. Analysis shows that although time for pre-market approval review may actually take longer in the US on average, the timeline from application to clinical studies results render the availability of devices in the US similar to or even shorter than in the EU.[142] And this is largely because, once a device is approved in Europe, it is still subject to reimbursement approval (at national level) before becoming available for patient use.[143] This is quite logical since most EU member states have Social Security agreements, generating multi-party negotiations as to the drug or medical device's pricing. Therefore, reimbursement decisions take considerably longer in the EU Member States than in the US.

In May 2017, the French government approved the total reimbursement of the FSL system by Social Security.[144] It decided so after a scientific evaluation of the device by the *Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé* (CNEDiMTS),[145] which reported the advantages of the system versus its risks for the 300,000 target T1D patients.[146] The second step to effective reimbursement came down to reaching an agreement on pricing between the manufacturer, the government and interested third parties,[147] such as the *Fédération française des diabétiques*, representing French diabetic patients.[148] From an initial cost of 59,90€ per sensor, negotiations efforts initially led to a final cost of 50€/sensor.[149] However, since July 2018, that cost has been scaled down to 45€/sensor.[150] As a result, the government limited this advantage to T1D patients, for a total of 26 sensors per year.[151] That simply meant that, as of June 2017, each and every T1D in France could choose to switch to the FSL system for the whole year and free of charge.[152] A victim of its own success, French pharmacies and therefore T1D patients currently suffer from a shortage of sensors (and must sometimes resort to their old SMBG meters...).[153]

There is no such social security system in the US, nor can the government negotiate pricing.[154] As a result, reimbursement of the FSL or any other CGM system is subject to one's insurance policy, if any.[155] However, Abbott has not changed its economic model that is often used in the diabetes market, like for SMBG readers. In other words, Abbott priced its reader cheaply so as to get patients to use its system. In doing so, it projected that once patients were "hooked", the price elasticity of demand would decrease and it could make more profit by having patients buy the product it needs often: the

sensor.[156] A sensor is in fact almost as expensive as a reader. US patients are thus facing a much more random outcome than their "carefree" French counterparts.

IV. CONCLUSION

There is no doubt that the FSL system marked a new step in the CGM revolution, despite being not equally accessible to patients around the globe. However, the CGM market is not done impressing T1D patients. Abbott just got the CE mark for its next generation FSL. It would include Bluetooth technology allowing patients to set alarms to warn them about potential hypo – or hyperglycemia without having to swipe–another evergreening strategy though.[157] But Abbott is not the only one interested in this juicy market.[158] Roche too, in partnership with Senseonics, invested in another type of sensor: the Eversense.[159] Totally implanted under a patient's arm for six months, this CGM system would solve a major pitfall: sensors that are ripped off from patients' arms.[160] Subject to a shorter "device lag", it got its CE mark in 2017[161] but only got FDA-approved this summer–almost a year later.[162] Better yet, the most awaited diabetes management innovation is the "closed-loop" system. It would include a CGM device as well as an insulin pump, which would administer pre-set amounts of insulin over the course of the day depending on the CGM results, just as a healthy person's pancreas works.[163] This "artificial pancreas" would alleviate patients from the mental load of calculating carbohydrates amounts to insulin ratios multiple times a day. Surprisingly, the most advanced company in the field is not one of the big three. It is French medtech company Dialoop, which is the pioneer in the field, as it got a CE mark for its "DBLG1 system" mid-November 2018.[164] While no price has been announced for this next revolution, let us hope that this three-years-old company will disrupt the diabetes management market–a market currently controlled by three giants only.

ENDNOTES

1. World Health Org., Global Report on Diabetes 6 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf.
2. Giacomo, C. et al., *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65 (2017). Some even project that by 2040 the number of people with diabetes will have risen to 642 million as the population ages. Erica Richardson et al., Joint Action Chrodis, *National Diabetes Plans in Europe: What lessons are there for the prevention and control of chronic diseases in Europe?* 9 (2016), http://www.euro.who.int/__data/assets/pdf_file/0009/307494/National-diabetes-plans-Europe.pdf. Others are more alarming, estimating that over 700 million adults worldwide would be affected in 2025. David Olczuk & Ronny Priefer, *A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus*, 12 Diabetes & Metabolic Syndrome: Clinical Res. & Rev. 181, 181 (2018).
3. Erica, R. et al., Joint Action Chrodis, *National Diabetes Plans in Europe: What lessons are there for the prevention and control of chronic diseases in Europe?* 9 (2016), http://www.euro.who.int/__data/assets/pdf_file/0009/307494/National-diabetes-plans-Europe.pdf.
4. Am. Diabetes Ass'n, Statistics About Diabetes, http://www.diabetes.org/diabetes-basics/statistics/?loc=db-slabnav (last visited Nov. 10, 2018).
5. The Europe region includes diverse populations, from Norway in the North, the Russian Federation in the East, Turkmenistan in the South and Iceland in the West. It is not limited to the European Union. World Diabetes Found., *IDF Diabetes Atlas: 7th Edition, Diabetes by Region: Europe, 75* (2015), https://www.worlddiabetesfoundation.org/sites/default/files/Europe.pdf. The number of diabetic patients increase by 2.9% each year in France. Solveig Godeluck, *Assurance-maladie : le coût du diabète risque de s'envoler [Health-insurance : The costs of diabetes might skyrock]*, Les Echos (Aug. 24, 2016), https://www.lesechos.fr/24/08/2016/LesEchos/22261-018-ECH_assurance-maladie---le-cout-du-diabete-risque-de-s-envoler.htm.
6. World Diabetes Found., *IDF Diabetes Atlas: 7th Edition, Diabetes by Region: Europe, 75* (2015), https://www.worlddiabetesfoundation.org/sites/default/files/Europe.pdf.
7. *Id.* In France, nineteen billions of dollars have been spent on diabetes in 2015. World Diabetes Found., *IDF Diabetes Atlas: 7th Edition, Diabetes by Region: Europe, 59* (2015), https://www.worlddiabetesfoundation.org/sites/default/files/Europe.pdf. It averages out to 5,000€ per year per person. INSEE, *Les coûts humains et financiers du diabète sont très élevés [The Human and Financial Costs of Diabetes are Very High]*, 131 Econ. de la Réunion 16, 16 https://www.insee.fr/fr/statistiques/1289738 (last visited Nov 10, 2018).
8. Wanya, Y. et Al. Am. Diabetes Ass'n, *Econ. Costs of Diabetes in the U.S. in 2017*, Diabetes Care 1, 2 (2018).
9. *Id.* at 1 (including medical and productivity costs).
10. *See* World Health Org., *Global Report on Diabetes* 6 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf. It was not possible to estimate the number of adults with type 1 and

type 2 diabetes separately, as most of the studies used did not report these groups independently. Katya Ogurtsova et al., *IDF Diabetes Atlas: Global Estimates for the Prevalence of Diabetes for 2015 and 2040*, 128 Diabetes Res. & Clinical Prac. 40, 46 (2017).

11. Courtney, D., & John, A. (2011). The Socio-political Roots of Pharmaceutical Uncertainty in the Evaluation of 'Innovative' Diabetes Drugs in the European Union and the US. *Soc. Sci. & Med*. 72: 1574, 1574.
12. World Health Org., *Global Report on Diabetes* 12–13 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf.
13. *Id*. at 13.
14. *See* Courtney D., & John, A. (2011). The Socio-political Roots of Pharmaceutical Uncertainty in the Evaluation of 'Innovative' Diabetes Drugs in the European Union and the US, *Soc. Sci. & Med*. 72:1574, 1574.
15. Giacomo, C. et al., *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65, 65 (2017). This T2D definition is grossly simplified for the purposes of this paper. Its risk is determined by a wider interplay of genetic and metabolic factors such as ethnicity, family history of diabetes, and previous gestational diabetes combined with older age, overweight and obesity, unhealthy diet, physical inactivity and smoking. *See* World Health Org., *Global Report on Diabetes* 12 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf.
16. *See* Courtney, D., & John, A. (2011). The Socio-political Roots of Pharmaceutical Uncertainty in the Evaluation of 'Innovative' Diabetes Drugs in the European Union and the US. *Soc. Sci. & Med*. 72:1574, 1574.
17. Yet no specific risk factors have been shown to cause a significant number of cases. World Health Org., *Global Report on Diabetes* 12 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf
18. Giacomo, C. et al. (2017). *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65, 74 (2017).
19. *Id*. at 65; *Type 1 Diabetes Treatments*, JDRF, https://www.jdrf.org/t1d-resources/about/treatment/ (last visited Dec. 2, 2018).
20. Giacomo, C. et al., *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65, 66 (2017). *See generally* Charlotte Hayes & Andrea Kriska, *Role of Physical Activity in Diabetes Management and Prevention*, 108 J. Am. Dietetic Ass'n S19-S23 (2008); Sylvia Ley et al., *Prevention and Management of Type 2 Diabetes: Dietary Components and Nutritional Strategies*, 383 Lancet, 1999–2007 (2014).
21. Managing BG levels means getting as close to a normal (nondiabetic) BG level as you safely can. This usually means a patient's readings should be between 70 and 130 mg/dl before meals, and less than 180 mg/dl two hours after starting a meal, with a glycated hemoglobin (A1C) level less than 7%. However, those targets are generally individualized by a doctor depending on a variety of factors. Am. Diabetes Ass'n, Tight Diabetes Control: What Does Blood Glucose Management Mean?, http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/tight-diabetes-control.html (last visited Dec. 2, 2018).
22. World Health Org., *Global Report on Diabetes* 6 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf. Poorly controlled BG levels may increase the risk of fetal death during gestational diabetes. *Id.*
23. Giacomo, C. et al., *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65, 65 (2017).
24. It may also occur in people with T2D treated with insulin. *See* Am. Diabetes Ass'n, Hypoglycemia (Low Blood Glucose): Causes of Low Blood Glucose, http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html (last visited Dec. 2, 2018). An average T1D patient usually experiences up to two episodes of mild low blood glucose each week. This estimate only counts episodes with symptoms. This number would certainly be higher if it included lows without symptoms and the ones taking place during the night. *Id*.
25. This does not mean BG management is not important in T2D patients. Quite the contrary: lifelong management and regular follow-up enables people with all types of diabetes to live longer and happier lives. World Health Org., *Global Report on Diabetes* 77 (2016), http://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf. However, T1Ds are typically diagnosed way earlier in life than T2Ds. *See supra* note 16. They are therefore at a higher risk of complications due to the length of their condition. Type ones are also subject to harmful hypoglycemic events that type twos are usually not experiencing because of their insulin regimen. Giacomo Cappon et al., *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65, 65–66 (2017).
26. Florence Rosier, « *Evergreening* », *stratégie à but lucratif ["Evergreening", a for-profit strategy]*, Le Monde (Apr. 13, 2015), https://www.lemonde.fr/sciences/

article/2015/04/13/evergreening-strategie-a-but-lucratif_4615100_1650684.html.

27. David,O., & Ronny, P. *A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus*, 12 Diabetes & Metabolic Syndrome: Clinical Res. & Rev. 181, 182 (2018). Its discovery was the closest thing to a miracle in the history of medicine. Thea Cooper, Breakthrough : Elizabeth Hughes, The Discovery of Insulin, and The Making of Medical Miracle (St. Martin's Press, 1st ed. 2010).

28. *See* Diapedia: The Living Textbook of Diabetes, Historical Aspects of Type 1 Diabetes, https://www.diapedia.org/type-1-diabetes-mellitus/2104085134/historical-aspects-of-type-1-diabetes (last visited Dec. 2, 2018). Thus statistic refers to a more late-onset type of T1D, which physicians could distinguish from a more aggressive form of diabetes. The latter, appearing in medical literature in the 19th century, was a very rare form of the condition terminating in a fatal ketoacidosis (a life-threatening build-up of acids in the blood due to prolonged high BG levels). A starvation regimen could potentially prolong a patient's (miserable) life but the children typically died of ketoacidosis, tuberculosis or starvation within days or months of diagnosis.

29. David, O. l., & Ronny, P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus. *12 Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 181, 182.

30. *See id.*

31. *See* S. F. Clarke & J. R., *A History of Blood Glucose Meters and their Role in Self-Monitoring of Diabetes Mellitus* 69 Br. J. Biomed. Sci. 83 (2012). That is testing before every meal and going to bed. But doctors usually advise to also check two hours post-meals. So T1D patients can use SMBG meters up to 8–10 times a day, especially is they are involved in physical activity.

32. David, O., & Ronny, P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus, *Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 12:181, 183 (2018).

33. *See id.*

34. *See id.* Indeed, while SMBG results show BG readings in the safe range, the continuous glucose monitoring sensor's result reveals the fluctuations between each finger prick. For an illustration, see Figure 1.

35. David, O., & Ronny, P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 12:181 (2018).

36. *See generally* Eun-Hyung, Y., & Soo-Youn, L., *Glucose Biosensors: An Overview of Use in Clinical Practice*, 10 Sensors 4558 (2010); David, Klonoff, *Continuous glucose monitoring*, 28 Diabetes Tech. & Therapeutics, 1231 (2005); Sandeep Kumar Vashist, *Continuous Glucose Monitoring Systems: A Review*, 3 Diagnostics 385 (2005); Nelly Mauras et al., *Continuous Glucose Monitoring in Type 1 Diabetes*, 43 Endocrine 41 (2013); Daniel DeSalvo & Bruce Buckingham, *Continuous Glucose Monitoring: Current Use and Future Directions*, 13 Current Diabetes Rep. 657 (2013).

37. *See id.* It involves inserting a filament that is 5 mm long and 0.4 mm wide just under the skin. *Abbott's FreeStyle Libre Pro Continuous Glucometry System for Professionals FDA Approved*, Medgadget, https://www.medgadget.com/2016/09/abbotts-freestyle-libre-pro-continuous-glucometry-system-professionals-fda-approved.html (last visited Dec. 3, 2018).

38. Type one patients report a 38% reduction in time in hypoglycemia with the FSL system. Jan Bolinder et al., *Novel Glucose-Sensing technology and Hypoglycemia in Type 1 Diabetes: A Multicentre, Non-Masked, Randomised Controlled Trial*, 399 The Lancet 2254 (2016).

39. Giacomo, C. et al., *Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment*, 6 Electronics 65, 70 (2017) ("From a clinical point of view, the use of real-time CGM showed meaningful improvements in glycated hemoglobin (HbA1c) and a reduction of hypoglycemic events. Moreover, the use of CGM sensors was demonstrated to improve quality of life, e.g., by reducing fear of hypoglycemia, and resulted in being cost-effective in long-term projections. Although all these benefits have been extensively proven, there are still many other factors that influence patient and clinician confidence in the use of CGM, such as accuracy, reliability, usability, duration of sensor life, and calibration requirements.").

40. David, O., & Ronny, P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 12:181, 183. *See also* Amanda Pedersen, *Is DexCom Really Winning on the CGM Battlefield?,* Medical Device and Diagnostic Industry, https://www.mddionline.com/dexcom-really-winning-cgm-battlefield (last visited Dec. 3, 2018); Gary Scheiner, What CGM systems are available in 2018?, Integrated Diabetes Services, https://integrateddiabetes.com/choosing-a-cgm-3-heads-are-better-than-one/ (last visited Dec. 3, 2018).

41. *See* David, O., & Ronny, P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 12:181, 184.

42. *See id*. at 185.

43. Giacomo, C. et al. (2017). Wearable Continuous Glucose Monitoring Sensors : A Revolution in Diabetes Treatment. *Electronics* 6:65, 70–71.

44. *Id*. at 71.

45. Jeemin, K. et al., *FreeStyle Libre in US Now Approved for 14-Day Wear and 1-Hour Warmup*, Diatribe, https://diatribe.org/freestyle-libre-us-now-approved-14-day-wear-and-1-hour-warmup (last visited Dec. 3, 2018). This one hour warmup period is an improvement the first available patient version of the FSL system that required 12 hours to warmup, that is a 12 hours calibration time period. *See* Adam Brown & Kelly Close, *Abbott's FreeStyle Libre Approved in US to Replace Routine Fingersticks*, Diatribe, https://diatribe.org/abbotts-freestyle-libre-approved-us-replace-routine-fingersticks#warm-up%20time (last visited Dec. 3, 2018).

46. It has especially be shown to prevent severe hypoglycemias. *See* Haute Autorité de Santé [High Authority for Health], *Avis de la Commission Nationale des Dispositifs Médicaux et Technologies de Santé [Report by the National Commission on Medical Devices and Health Technologies]* (July 12, 2016), https://www.has-sante.fr/portail/upload/docs/evamed/CEPP-5113_FREESTYLE%20LIBRE_12_juillet_2016_(5113)_avis.pdf; B. Bonora et al. *Head-to-head Comparison Between Flash and Continuous Glucose Monitoring Systems in Outpatients with Type 1 Diabetes*, 39 J. Endocrinol. Invest. 1391 (2016).

47. This question triggered this paper, especially since Abbott Laboratories is an American pharmaceutical company. *See* Adam Brown & Kelly Close, *Abbott's FreeStyle Libre Approved in US to Replace Routine Fingersticks*, Diatribe, https://diatribe.org/abbotts-freestyle-libre-approved-us-replace-routine-fingersticks#warm-up%20time (last visited Dec. 3, 2018).

48. Joanna Brougher, Intellectual Property and Health Technologies: Balancing Innovation and the Public's Health 2 (Springer, 2014).

49. *Id*. at 40.

50. *Id*.

51. *Id*.

52. *See id*.

53. On how to apply the sensor, see FreeStyle Libre Getting Started, Youtube, https://www.youtube.com/watch?v=0cXwO9YBJxE (last visited Dec. 3, 2018).

54. Abbott describes this step as a "sensor application", but it seems more proper to call this a "sensor insertion" as it involved the actual insertion of a filament in the patient's skin. *See supra* note 37.

55. To see how the parts look like, see *Introducing the new FreeStyle Libre 14 day system!*, FreeStyle Libre, https://www.freestylelibre.us/system-overview/freestyle-14-day.html (last visited Nov. 30, 2018).

56. *See* Eddy Ventose, Patenting Medical and Genetic Diagnostic Methods 50 (Edward Elgar Pub. Ltd., 2013).

57. *See About IP: Patents*, WIPO, https://www.wipo.int/patents/en/faq_patents.html (last visited Dec. 3, 2018).

58. Arun, K. & Arun, N. (2017). Ever-greening in Pharmaceuticals: Strategies, Consequences and Provisions for Prevention in USA, EU, India and Other Countries, *Pharmaceutical Reg. Aff*. 6:1, 1.

59. *See id*. at 1-6.

60. Joanna Brougher, Intellectual Property and Health Technologies: Balancing Innovation and the Public's Health 145 (Springer, 2014).

61. *Id*. at 145–146.

62. *Id*. at 146.

63. Some other patents may currently be pending or may have been issued in the meantime. *See Diabetes Patents,* Abbott, https://www.abbott.com/patents/diabetes-patents.html (last visited on Nov. 10, 2018).

64. *See id*.

65. U.S. Patent No. 9,753,746 (filed Jan. 2, 2001). You can notice as well the broadness of the description of this method, allowing Abbott to protect itself in future litigation.

66. U.S. Patent No. 9,931,066,B2 (filed Sept. 21, 2017); but also the apparatus for insertion in the skin and the method of inserting. *See* U.S. Patent No. 9,402,544, B2 (filed Dec. 23, 2010); U.S. Patent No. 9,693,688, B2 (filed Nov. 12, 2015).

67. That is a method of "establishing a communication range between a data processing unit and a control unit by placing the control unit within a predetermined distance from the data processing unit". U.S. Patent No. 8,514,086,B2 (filed Aug. 11, 2011).

68. U.S. Patent No. 7,620,438,B2 (filed Oct. 4, 2007).

69. U.S. Patent No. 8,514,086,B2 (filed Aug. 11, 2011).

70. U.S. Patent No. 9,532,737,B2 (filed Sept. 27, 2012).

71. U.S. Patent No. 9,314,195,B2 (filed Mar. 10, 2011).

72. U.S. Patent No. 9,574,914,B2 (filed June 26, 2014).

73. U.S. Patent No. 6,605,200,B1 (filed Nov. 14, 2000).

74. U.S. Patent No. 9,949,639,B2 (filed Oct. 12, 2017).

75. Compare *supra* note 63 with *Patents*, Dexcom US *available at* https://www.dexcom.com/patents (last visited Dec. 6, 2018).

76. Nicoleta Tuominen, *Patenting Strategies of the EU Pharmaceutical Industry Crossroad Between Patent Law and Competition* Policy, 1 Res. Papers in L. 15 (citing Robin Mitchell & Debra Bingham, *Rules to Live or Die By For Life Cycle Management*, *available at* http://aei.pitt.edu/44320/1/researchpaper_1_2011_tuominen.pdf.

77. *Id*. at 13 (citing Mavroghenis, *Article 82 EC and Strategic Patenting – Patent Thickets, Defensive Patents, and Follow-on Patents*, 4, *available at* http://www.droit.ulg.ac.be/ieje/fileadmin/IEJE/Pdf/Mavroghenis_Strategic_Patenting_and_Article_82_EC.pdf.

78. It abandoned three applications in that process. *See Biosensor membranes*, Google Patents, *available at* https://patents.google.com/patent/US9014774B2/en?oq=9%2c014%2c774 (last visited Dec. 2, 2018).

79. U.S. Patent No. 9,014,774,B2 (filed Nov. 7, 2013).

80. *Id*.

81. U.S. Patent No. 6,932,894,B2 (filed Mar. 6, 2003).

82. U.S. Patent No. 9,713,443,B2 (filed Feb. 2, 2017).

83. Arun, K., & Arun, N. (2017). Ever-greening in Pharmaceuticals: Strategies, Consequences and Provisions for Prevention in USA, EU, India and Other Countries. *Pharmaceutical Reg. Aff.* 6:1, 2 (2017).

84. David, O., & Ronny, P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 12:181, 184.

85. *Id*. at 185.

86. *Id*. at 184.

87. *See News: Abbott FreeStyle Libre Now OK'd for 14-Day Wear*, Healthline (Aug. 6, 2018), https://www.healthline.com/diabetesmine/freestyle-libre-14-day-wear#1 (last visited Dec. 3, 2018).

88. Compare the pro version with the latest patient version. *See FreeStyle Libre Pro System*, FreeStyle Libre US *available at* https://www.myfreestyle.com/freestyle-libre-pro-cgm-system (last visited Dec. 3, 2018); *My FreeStyle*, FreeStyle Libre US *available* at https://www.freestylelibre.us/?source=www.myfreestyle.com (last visited Dec. 3, 2018).

89. David, O., & Ronny P. (2018). A History of Continuous Glucose Monitoring (CGMs) in Self-Monitoring of Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Res. & Rev.* 12:181, 184–185 (explaining that the aim is to avoid user bias); *see also Difference between FreeStyle Libre and Libre Pro,* Diabetes Views, http://diabetesviews.com/2016/11/difference-between-freestyle-libre-and-libre-pro/ (last visited Dec. 3, 2018).

90. *See Diabetes Patents,* Abbott, https://www.abbott.com/patents/diabetes-patents.html (last visited on Nov. 10, 2018).

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Article

Valuing NOL Carryforwards for the Small Cap Biotechnology Subindustry

Robert Beach
East Tennessee State University, Department of Economics and Finance, Johnson City, TN

ABSTRACT

Under the 2017 tax law, carryforward rules for net operating losses (NOLs) allow corporations to apply these losses forward for up to twenty years of taxable income. Startup corporations primarily engaged in basic research or that require rapid growth to be sustainable can go a number years with no positive earnings and thus accumulate net operating losses. These losses can be used to reduce tax obligations in the future. This paper estimates the value of NOLs across firms in a specific subindustry: small cap biotechnology. A valuation method based on ARIMA estimates of future income is used to calculate the value of the NOLs that can be carried forward. The results indicate that even for a subindustry which typically has net operating losses for many years in a startup phase, the expected value of the future benefit of a reduction in taxes is actually fairly modest.

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INTRODUCTION

Under the 2017 tax law, carryforward rules for net operating losses (NOLs) allow corporations to apply these losses forward for up to twenty years of taxable income. Startup corporations primarily engaged in basic research or that require rapid growth to be sustainable can go a number years with no positive earnings and thus accumulate significant net operating losses on their books. These losses can be used to reduce tax obligations in the future. This paper estimates the value of NOLs across firms in a specific subindustry: small cap biotechnology.[i] Small cap is usually defined as any firm with a market capitalization between $300 million and $2 billion. Since the market capitalization of a firm varies day to day with changes in its stock price, the firms included in this group are those captured in a snapshot taken on a specific date, May 24, 2018.

A valuation method based on autoregressive integrated moving average (ARIMA) estimates of future income is used to calculate the value of the NOLs that can be carried forward. Given the data for operating losses, this method forecasts the expected earnings before taxes (EBT) and an upper bound and a lower bound based on a projected 95% confidence limit. An algorithm based on the carryforward rules then applies the losses forward for up to 20 years. The results indicate that even for a subindustry which typically has net operating losses for many years in a startup phase, the expected value of the future benefits of a reduction in taxes is actually fairly modest. This is because for many firms in this subindustry, based on the ARIMA analysis, expected future earnings are not often positive.

i The classification structure used here is the Global Industrial Classification System (GICS).

LITERATURE REVIEW

Most OECD countries have some form of operating loss carryforward rules. These usually allow for carrybacks from one to three years and carry forwards of up to 20 years (see Cooper and Knittle, 2006). In the recent past U.S. losses could be carried back two years and carried forward up to 20 years. However, these parameters are subject to change based on issues related to the performance of the economy. For instance, the carryback period was extended in the wake of the nine-eleven crisis in 2001 and after the financial crisis in 2008 (BTA portfolio 593, 2017). In both cases it was extended to five years. This softens the blow to corporations by providing tax refunds and liquidity during a time of crisis (for a discussion of these effects see Grahm and Kim, 2009). The 2017 tax law specifies that going forward from 2018. NOLs cannot be carried back but carried forward for 20 years.

Investment and capital structure decisions can also be impacted by the state of a firm's NOLs. As an example, Auerbach and Poterba (1987) argue that as carryforwards

go up investment in assets with longer term depreciation should go up since the reduced depreciation is offset by the carryforwards. They also argue capital structure should shift more towards equity since the impact of the tax shield is reduced.

The issue addressed here is valuation of the firm's NOLs based on projected future earnings. Valuation of NOLs is an issue since it is contingent on the uncertainty of positive earnings in the future. Cooper and Kittel (2006) argue that because the loss to be carried forward is often not used until many years later, the realized present value is much less than the book value would indicate.

Although it can be argued that not only does the firm's NOLs affect investment and capital structure decisions as in Auerbach and Poterba, but also firm value through its impact on free cash flow, the more common approach is to calculate directly the present value of the expected tax savings. Taking this approach, both Streitferdt (2013) and Sarkar (2014) use option pricing models similar to the Black-Scholes model. Streitferde employs a collar strategy much like that used in options trading in which the long call option has an exercise price of zero and the short call has an exercise price equivalent to the NOL. This is essentially a one period model. To implement in a multi-period framework a Monte Carlo simulation is used under the assumption of a normal distribution of future earnings. Along the same line, Sarkar uses a valuation method based on a contingent claim framework that assumes a normal distribution of future earnings and uses a numerical method to implement in a multi-period framework.

More consistent with the approach used here, De Waegenaere et al. (2003) use a projection of future steady state income given its historical earnings as a basis of valuation of its NOLs. Likewise, in this paper historical earnings are used, but here an ARIMA model captures the inherent cyclicality of the data to predict future earnings.

METHODOLOGY

The earnings data used in the analysis comes from the Security and Exchanges Commission (SEC) Edgar database. The data collected begins with the firm's S-1 report, which includes typically up to three years of financial data previous to going public with an IPO, and includes the annual 10-K financial reports through 2017. For each of the firms under consideration, this data is used to estimate future earnings before taxes for 20 years (specifically, 2018 through 2038). Note that any NOLs from the last year of data would expire at this point.

An ARIMA model is used for these estimates. One advantage of the ARIMA model is that even if there are few years of positive earnings in the data, any cyclicality, volatility, or upwards trend is captured and there can be future years with expected positive EBT. Using the algorithm in Appendix A, NOLs from the data are distributed based on projected EBT. Distributions are also made for a minimum and maximum forecast based on the 95% confidence interval.

This approach has advantages over the methods discussed above. The options approach of Streitfort and Sarkar does not lend itself to a multi-period model and requires numerical simulations to estimate an intertemporal solution; and the approach of De Waegenaere is based on the assumption that future earnings will be a constant steady state value and does not capture the volatility of future income.

ARIMA MODELS

ARIMA models have three parameters, usually designated as *p*, *d*, and *q*. *p* represents the auto regressive degree, *d* represents the degree of differencing, and *q* represents the moving average degree. The theoretical model can be expressed as

$$EBT_t = a + \sum_{p=1}^{P} EBT_{t-p} + \sum_{q=1}^{Q} \varepsilon_{t-q}$$

where EBT_t is earnings before taxes if positive and a loss if negative for year *t* and ε_t is the error term for year t for an ARIMA model. If differencing is included in the model (represented by the *d* parameter) there is an additional term expressed as:

$$DIFT_t = EBT_t - EBT_{t-1}$$

where $DIFF_t$ represents, in this case, first differencing. There could also be higher degrees of differencing. In the ARIMA model used in this paper, second differences were sometimes used. That is:

$$DIFF_t = (EBT_t - EBT_{t-1}) - (EBT_{t-1} - EBT_{t-2})$$

An ARIMA model allows for each set of data to be estimated separately and for the autoregressive, integrated, and moving average parameters to be chosen to obtain the best fitting statistical model. Figure 1 represents a plot of the typical forecast produced by the ARIMA estimate. This is based on the parameters that produce the best fit. The goodness of fit is captured by the Ljung-Box portmanteau statistic which has a chi-square distribution. Roughly

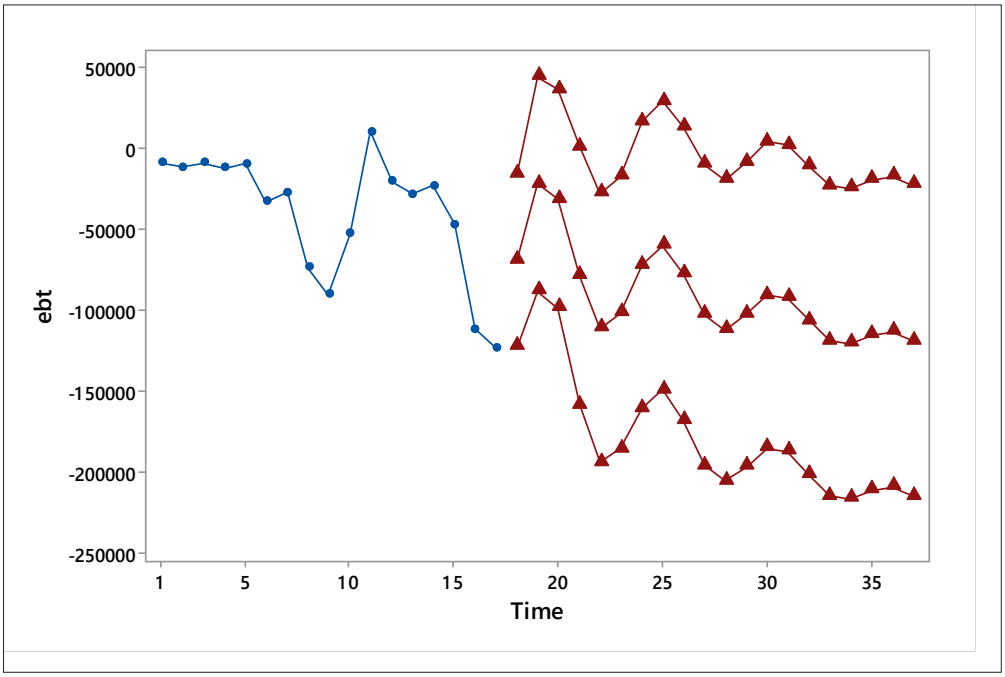

Figure 1: Typical example of actual (dots) and projected (triangles) EBT with 95% confidence intervals.

speaking, this means based on the number of observations the smaller the statistic the greater the p-value and the better the goodness of fit. That is, the null hypothesis of no correlation among the residuals is rejected.

RESULTS

Of the 122 firms that fell into the biotechnology subindustry, 31 were not included because the numerical method used by the software could not determine a solution for firms with less than nine years of earnings data. In addition, 14 were not included because of various miscellaneous reasons.

Of the remaining 77 firms 15 were included in the ARIMA analysis, For the remaining 66, these firms had no positive earnings over the last nine years. Preliminary analysis indicated these firms were highly unlikely to have any positive future earnings. This was confirmed by performing an ARIMA analysis on ten firms across the range of small cap biotechnology from $300 million to $2 billion market cap. None projected future positive earnings. The assumption then for these firms is that the present value of the NOLs is zero for the forecasted values, and for the upper and lower bounds for the 95% confidence interval. The summary values in Table 1 are based on these 77 firms. Appendix B is a status table of all the firms in the biotechnology subindustry. It indicates which firms were omitted and which firms were used in the analysis.

The results of the ARIMA analysis are given in Table 1. Each firm in the analysis is listed, along with its ticker symbol, the present value of the firm's forecasted reduction in EBT given its NOLs; plus the forecasted reduction in EBT for the lower 95% confidence interval and the upper 95% confidence interval.[ii] Also listed is the Ljung-Box chi-square portmanteau statistic and its p-value.

The totals include the present value of the total forecasted reduction in EBT from applying the NOLs, plus present value of the total for the lower and the upper 95% confidence intervals; the present value of the NOLs calculated by applying a tax rate of 21% (based on the 2017 tax law) to the these reductions in the EBT; and the NOL value as a percentage of the market cap of the small cap biotechnology subindustry.

In summary, the present value of total reduction in future EBT is $750,888 thousand; the present value of total tax savings is $126,149 thousand; and tax savings as a percent of the market cap of the biotechnology subindustry is 0.1837%.

CONCLUSION

Operating losses that accrue during the early development phase of a startup can shelter future taxes for a number of years. NOL carryforwards provide a

ii Present value is based on an overall weighted average cost of capital for the biotechnology subindustry estimated in Damodaran, 2018.

Table 1: Present value of total NOL valuation in $1,000 for the small cap biotechnology subindustry. *** indicates the numerical method cannot compute the chi-square statistic, usually a result of a smaller number of years of EBT data

Name	Symbol	Market Cap ($million)	Forecast ($thousand)	Lower ($thousand)	Upper ($thousand)	Chi Squre	p-value
Biospecifics	bstc	309	0	0	0	09.56	0.387
GTx, Inc.	gtxi	426	0	0	2485	2.44	0.982
Cytokinetics	cytk	472	0	0	294561	6.3	0.506
Progenic	pgnx	562	0	9	54006.6	19.52	0.012
Chemcentryx Inc.	ccxi	643	122949	65541	159961	***	***
Sorranto	srne	701	21496	0	62539	***	***
Access Pharmaceuticals	abeo	759	0	0	96379	9.87	0.196
Advance Magnetics	amag	795	13345	0	463398	7.99	0.239
Geron Corp.	gern	810	0	0	555842	14.1	0.079
Vanda Pharmaceticals	vnda	881	35727	0	250326	6.05	0.642
Mimeds Group	mdxg	996	2086	297	2086	***	***
Retrophin	rtrx	1200	0	0	226474	***	***
Genomic Health	ghdx	1400	3194	0	126291	13.57	0.094
Madrigal Pharmaceutical	mdgl	1700	297990	0	654116	9.78	0.281
Momenta Pharmaceuticals	mnta	1900	254101	0	528906	4.22	0.896
Present Value of Reduction of EBT			750888	65838	2948467		
Total Tax Value			126149	11061	495342		
Value as a percent Market Cap			0.1837%	0.0161%	0.7212%		

government subsidy for startups and other firms and buffer them from the costs of starting an enterprise or downturns in the economy. This subsidy, though, is only available to firms that at some point become profitable and have positive earnings before taxes.

The results show that across the small cap biotechnology subindustry, the aggregate value of the NOLs is surprisingly small. This can be attributed to the fact that these firms are primarily engaged in some form of medical research and typically go many years with losses until a pipeline of marketable products can be developed. Based on past performance, many cannot expect to be profitable in the future. Indeed, of the 77 firms used in the analysis, only 15 passed the filter that there be at least one year of positive earnings in the last nine years. Thus, taken as a percent of total market cap for the subindustry, the aggregate value of NOLs in the small cap biotechnology subindustry is 0.1837%.

This suggests that for subindustries primarily engaged in basic research such as small cap biotechnology, the book value of NOLs considerably over represents its realized value. Further, for these subindustries any effects on investment and capital structure, as discussed above in Auerbach and Poterba would be minimal.

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APPENDIX A: DISTRIBUTION OF NOLS

For the expected EBT for 20 years and projected upper and lower 95% confidence intervals derived from the ARIMA analysis:

1. Distribute NOLs for any positive EBT through 2017.
2. Distribute remaining unexpired NOLs starting with year 2018.
3. Continue distributing NOL and calculating tax savings for year *t* until it is used up or reaches the 20 year limit.
4. Sum the reduction in EBT.
5. Multiply by tax rate.
6. Sum up value of tax savings.

APPENDIX B:

Status Table

Ticker Abbreviation	Company Full Name	Market Cap ($m)	Status
CBMG	Cellular Biomedicine Group, Inc.	300	9 yrs < 0
VSTM	Verastem, Inc.	313	9 yrs < 0
ABUS	Arbutus Biopharma Corp	323	9 yrs < 0
CRVS	Corvus Pharmaceuticals, Inc.	324	9 yrs < 0
ATHX	Athersys, Inc.	327	9 yrs < 0
AGEN	Agenus Inc.	349	9 yrs < 0
CPRX	Catalyst Pharmaceuticals, Inc.	353	9 yrs < 0
ADVM	Adverum Biotechnologies, Inc	389	9 yrs < 0
SYRS	Syros Pharmaceuticals, Inc	389	9 yrs < 0
SGYP	Synergy Pharmaceuticals, Inc	395	9 yrs < 0
ALBO	Albireo Pharma, Inc.	396	9 yrs < 0
MNOV	Medicinova, Inc.	396	9 yrs < 0
IDRA	Idera Pharmaceuticals, Inc.	415	9 yrs < 0
PDLI	PDL BioPharma	432	9 yrs < 0
SVA	Sinovac Biotech Ltd.	434	9 yrs < 0
SIGA	Siga Technologies Inc.	504	9 yrs < 0
ACHN	Achillion Pharmaceuticals Inc.	509	9 yrs < 0
NVTA	Invitae Corp	519	9 yrs < 0
VCEL	Vericel Corp	523	9 yrs < 0
PRTA	Prothena Corp plc	570	9 yrs < 0
CASI	CASI Pharaceuticals, Inc.	584	9 yrs < 0
BCRX	BioCryst Pharmaceuticals, Inc.	585	9 yrs < 0
STML	Stemline Therapeutics	587	9 yrs < 0
AKBA	Akebia Therapeutics	589	9 yrs < 0
FATE	FATE Therapeutics, Inc.	596	9 yrs < 0
VYGR	Voyager Therapeutics, Inc.	612	9 yrs < 0
KERX	Keryx Biopharmaceuticals, Inc.	615	9 yrs < 0
BYSI	BeyondSpring Inc.	618	9 yrs < 0
ZIOP	Ziopharm Oncology, Inc.	625	9 yrs < 0
RIGL	Rigel Pharmaceuticals, Inc.	646	9 yrs < 0
NVAX	Novavax, Inc.	649	9 yrs < 0
DRNA	Dicerna Pharmaceuticals, Inc.	725	9 yrs < 0
GLYC	GlycoMimetics, Inc.	755	9 yrs < 0
LJPC	La Jolla Pharmaceutical Company	831	9 yrs < 0
ARWR	Arrow Electronics, Inc.	856	9 yrs < 0
DVAX	Dynavax Technologies Corporation	1000	9 yrs < 0
CTMX	CytomX Therapeutics, Inc.	1000	9 yrs < 0
FLXN	Flexion Therapeutics, Inc.	1000	9 yrs < 0
LXRX	Lexicon Pharmaceuticals, Inc.	1000	9 yrs < 0

ESPR	Esperion Therapeutics, Inc.	1000	9 yrs < 0
ALDR	Alder Biopharmaceuticals	1100	9 yrs < 0
TGTX	TG Therapeutics, Inc.	1100	9 yrs < 0
MRTX	Mirati Therapeutics, Inc.	1100	9 yrs < 0
KPTI	Karyopharm Therapeutics Inc.	1100	9 yrs < 0
QURE	UniQure N.V.	1200	9 yrs < 0
ALSE	Alseres Pharmaceuticals	1200	9 yrs < 0
ADAP	Adaptimmune Therapeutics plc	1200	9 yrs < 0
EPZM	Epizyme, Inc.	1300	9 yrs < 0
MYOV	Myovant Sciences Ltd.	1300	9 yrs < 0
BHVN	Biohaven Pharmaceutical Holding Co Ltd.	1300	9 yrs < 0
RDUS	Radius Health Inc	1300	9 yrs < 0
BOLD	Audentes Therapeutics, Inc.	1300	9 yrs < 0
IMGN	ImmunoGen, Inc.	1400	9 yrs < 0
IOVA	Iovance Biotherapeutics Inc	1500	9 yrs < 0
RGNX	Regenxbio Inc.	1500	9 yrs < 0
SGMO	Sangamo Therapeutics Inc	1600	9 yrs < 0
EDIT	Editas Medicine Inc	1700	9 yrs < 0
PBYI	Puma Biotechnology Inc	1900	9 yrs < 0
INSM	Insmed Incorporated	2000	9 yrs < 0
XON	Intrexon Corp	2000	9 yrs < 0
SPPI	Spectrum Pharmaceuticals, Inc.	2000	9 yrs < 0
OPK	Opko Health Inc.	2,000	9 yrs < 0
NK	NantKwest, Inc.	301	Data < 9 yrs
TTOO	T2 Biosystems, Inc.	316	Data < 9 yrs
PIRS	Pieris Pharmaceuticals	326	Data < 9 yrs
MCRB	Seres Therapeutics, Inc.	330	Data < 9 yrs
NERV	Minerva Neurosciences, Inc.	331	Data < 9 yrs
BLCM	Bellicum Pharmaceuticals, Inc.	341	Data < 9 yrs
SBBP	Strongbridge Biopharma plc	342	Data < 9 yrs
CRBP	Corbus Pharmaceuticals Holdings, Inc.	346	Data < 9 yrs
MRUS	Merus N.V.	370	Data < 9 yrs
ARQL	Arqule Inc.	376	Data < 9 yrs
JNCE	Jounce Therapeutics, Inc.	377	Data < 9 yrs
CDNA	CareDx, Inc.	413	Data < 9 yrs
INO	Inovio Pharmaceuticals, Inc.	442	Data < 9 yrs
ZYME	Zymeworks, Inc	453	Data < 9 yrs
CNCE	Concert Pharmaceuticals	473	Data < 9 yrs
INSY	Insys Therapeutics	529	Data < 9 yrs
CARA	Cara Therapeutics, Inc	542	Data < 9 yrs
NTRA	Natera, Inc.	624	Data < 9 yrs
ADRO	Aduro BioTech, Inc.	646	Data < 9 yrs
FPRX	Five Prime Therapeutics	15	Data < 9 yrs

Table continued.

Ticker Abbreviation	Company Full Name	Market Cap ($m)	Status
ADMS	Adamas Pharmaceuticals	791	Data < 9 yrs
KHTRE	Knight Therapeutics	906	Data < 9 yrs
MGNX	MacroGenics, Inc.	921	Data < 9 yrs
CHRS	Coherus BioSciences, Inc.	936	Data < 9 yrs
URGN	Urovant Sciences Ltd.	951	Data < 9 yrs
NTLA	Intellia Therapeutics, Inc.	1100	Data < 9 yrs
PTCT	PTC Therapeutics, Inc.	1400	Data < 9 yrs
GTHX	G1 Therapeutics Inc	1600	Data < 9 yrs
XLRN	Acceleron Pharma Inc	1700	Data < 9 yrs
AIMT	Aimmune Therapeutics Inc	1900	Data < 9 yrs
ANAB	AnaptysBio	1900	Data < 9 yrs
RCAR	RenovaCare Inc.	377	Misc
AUPH	Aurinia Pharmaceuticals Inc.	491	misc
MRSN	Mersana Therapeutics, Inc.	496	misc
AKAO	Achaogen Inc.	529	misc
MESO	Mesoblast Limited	573	misc
KURA	Kura Oncology, Inc	584	misc
ACIU	AC Immune S.A.	596	misc
AMRN	Amarin Corporation plc	881	misc
EGRX	Eagle Pharmaceuticals	977	misc
ATNX	Actinium Pharmaceuticals, Inc	1100	misc
ACOR	Acorda Therapeutics	1100	misc
CLLS	Cellectis S.A.	1100	misc
RGEN	Repligen Corporation	1900	misc
ENTA	Enanta Pharmaceuticals	1900	misc
BSTC	Biospecifics	309	X
GTXI	GTX Inc	426	X
CYTK	Cytokinetics	472	X
CCXI	Chem Centryx Inc.	643	X
PGNX	Progenics	562	X
SRNE	Sorranto	701	X
ABEO	Abeona Therapeutics Inc.	759	X
AMAG	Advance Magetics	795	X
GERN	Geron Corp.	810	X
VNDA	Vanda Pharmaceuticals	881	X
MDXG	Mimeds Group	996	X
RTRX	Retrophin	1200	X
GHDX	Genomic Health, Inc.	1400	X
MDGL	Madrigal Pharmaceuticals Inc	1700	X

MNTA	Momenta Pharmaceuticals, Inc.	1900	X
TOTAL		103289	

Status

9 yrs < 0: No positive earnings over 9 years previous to 2017.

Data < 9 yrs: Less than 9 years of earnings data.

Misc: Miscellaneous such as a non-US corporation.

X: Indicates corporation that had at least 1 year of positive earnings in the last nine and enough data so the software could compute a solution.

Article

Patents and Diagnostic Methods in the U.S.: the Subject Matter Eligibility Trap

Javier Saladich Nebot
is a Law & Global Governance graduate, ESADE Law School (Barcelona, Spain). Brief experience in healthcare and Life Sciences Law as a legal intern working for a research institute based in Washington D.C. and for various international law firms.

ABSTRACT

Diagnostic methods have been gaining medical recognition and social importance as innovations that can be useful to provide individuals with a diagnosis, a prognosis or a prediction with regard to a condition that they currently have or that they are in risk of developing. Despite the great amount of resources deployed to produce these health technologies and their potential benefits for healthcare systems and patients or prospective patients alike, their exclusive protection in the United States has recently faced resistance from patent examiners and courts on the basis that diagnostics constitute a dubious innovation. Inconsistent arguments used for the refusal of patent protection led to a labyrinth where innovators in the diagnostics sector could not reasonably expect their patent application would be allowed or after the patent was issued.

This paper aims to convey the doctrine of subject matter eligibility as applied to diagnostic methods by the relevant administrative guidances and case law. In doing so, it aims to depict the pitfalls resulting from the general application of a non-patentability rule to diagnostics, and to suggest opportunities still available for innovators to overcome uncertainty by filing compliant applications while maximizing the likeliness of enjoying protection once the patent is awarded.

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Keywords: Biotechnology; Diagnostics; Patentability; Subject matter

INTRODUCTION[1]

Medicine has been traditionally practiced following trial and error. Under this model, physicians have reacted to disease providing a standardized treatment, only introducing changes based on known conditions of the patients or side effects of the prescribed therapy. However, coinciding with the fast growth of new technologies, innovation in healthcare shows that the "one size fits all" approach could be a thing of the past in the next few years, paving the way instead for another model known as personalized medicine, individualized medicine or precision medicine.

Personalized medicine, as commonly referred to in academia and also in the news, is defined as "the prescription of specific treatments and therapeutics best suited for an individual taking into consideration both genetic and environmental factors that influence response to therapy.[1]" Although tailored medicine was first formulated in 1957[2], it was not a real possibility until late 1990s. The first time "personalized medicine" appeared in the literature was in 1998[3]. But it gained momentum after the mapping of the human genome was completed in 2003[4], and the "omics" studies –genomics, among other–[5] allowed to determine both the susceptibility to disease

1 Fifth-year Law & Global Governance student at ESADE Law School (Barcelona, Spain). Formerly a JD exchange student at Cornell Law School (Ithaca, United States) and currently a Political Science & Diplomacy student at Yonsei University (Seoul, South Korea). Experience in Healthcare and Pharma Law as a legal intern at one foundation based in Washington D.C. and one international law firm.

and the response to medications of each individual based on their genetic information[6].

Personalized medicine, thus, has revolutionized medicine in two ways: as a diagnostic and as a therapeutic method[7]. In this paper, we are going to focus on the diagnostics side of this phenomenon. Molecular diagnostics, meaning any method which uses biomarkers to assess disease risk or presence, has the potential to enable healthcare providers to shift the standard of care from reaction to prevention[8]. Therefore, it presents the benefit of lowering healthcare costs[9], and this should provide a strong reason to incentivize innovation in this realm. However, we see that, besides the "valley of death" inherent in any biotechnological development[10], there is a landscape that further discourages rather than encourages investment in molecular testing. Lately, researchers and diagnostic testing companies have been facing unnecessary difficulties in terms of "FDA regulation, patent law and healthcare regulation[11]".

For the purpose of this paper, we are going to deepen into the patent law aspects of personalized medicine. Patent protection for diagnostic methods is of paramount concern to innovators in the field because it is supposed to help them recoup their investment in research[12]. Also, it is important for public health because it provides innovators with an incentive to undergo the costly process of bringing diagnostic tests to the clinic, and patients with the chance to receive an individualized care[13]. Unfortunately, the incentive of patent protection has been undermined during the last ten years and is now in jeopardy after diagnostic methods patents have been rejected and invalidated in some landmark decisions.

I. MEDICAL DIAGNOSTICS IN PERSONALIZED MEDICINE

A. Diagnostics: their role in future healthcare

Diagnostics is the flagship of personalized medicine, because it addresses the main factor behind any given therapy having different efficacy and toxicity when administered to different individuals: genetic variation[14]. Humans are known to share much of their DNA, though the consistently accepted statement that it is 99.9% identical could be contradicted by a recent study focusing on the functional role played by the copy number variation (CNV) of DNA sequences [15,16]. In any event, understanding biological diversity –which encompasses not only genetic but also biochemical and molecular characteristics of an individual, collectively known as biological markers or "biomarkers"[17]– has become fundamental to turn to a preventative and individualized approach to healthcare, and diagnostics play a key role in studying this variation among humans.

Although molecular diagnostic methods have been broadly referred to in patent law as any method that establishes a correlation between the detection and/or analysis of a biomarker and a medical outcome[18], the latest literature is drawing a distinction based on all the possible different outcomes. Narrowly defined, biomarker-based diagnostics only relate to methods which correlate a given biomarker with a diagnosis or severity of a disease[19]. Where the correlation is made between a biomarker and the likeliness of "developing a disease" or "attaining a clinical endpoint[20]", the method is prognostic. Finally, where the outcome of the correlation is the "treatment response in terms of efficacy and/or safety[21]", the method is predictive. Throughout this paper, we are going to use diagnostic methods in its broadest meaning, to also include prognostic and predictive biomarker-based methods.

Contrary to what may seem, identifying biomarkers to make clinical conclusions is not a trivial issue. As it has been noted, this sort of methods can be used for diagnostic, prognostic and predictive purposes. And it is far from being a straightforward idea, because "identifying and validating clinically significant molecular biomarkers" involves complex research[22]. Diagnostic researchers have to isolate significant genetic variations from other genetic and non-genetic environmental factors in order to come up with a correlation[23].

B. Securing intellectual property on diagnostics: challenges

Patent protection of diagnostic methods is thus of utmost importance for innovators and for public health. Testing for the clinically significant variations among humans to face disease is a time and resource consuming endeavor. Hence the necessity to provide this incentive for innovators. To protect molecular diagnostics, the most effective strategy is to claim the method itself in the patent application, though claiming the isolated biomarker identified in the method has become another pathway to indirectly protect the latter.

As will be explained below, patents on molecular diagnostics have been challenged as protecting methods that are cheap to develop, discovered by academic researchers with government funding and not clearly novel[24]. Challenges have ignored that new diagnostic

tests are not limited to finding a gene associated with a disease –as we see in the first wave of molecular diagnostics, with Myriad's discovery of BRCA genes– but they add a much more innovative step which lies in understanding the clinical significance of the variation of a gene or another biomarker[25].

When the value of this research is underrated and exclusive rights are denied, innovators and venture capitalists lose their incentive to invest in research, so their funds are withdrawn from a very promising field of medicine because the expectation to get any return from research vanishes.

But patient access is also impaired. Those who oppose diagnostic method patents on the basis that they are broad enough to claim a "scientific observation" rather than an actual "innovation", contend that they end up raising costs and preventing patient care because physicians refrain from doing their work to avoid involuntary infringement[26]. However, patient access can be harmed another way: without a patent at the end of the road, researchers and companies will protect methods as trade secrets so this knowledge will not be disclosed to the public[27].

II. PATENTABILITY OF DIAGNOSTIC METHODS

A. Subject matter requirement: diagnostics as medical processes

Utility patents are the most relevant category to the biotechnology industry in general and to medical diagnostics in particular[28]. For a utility patent to be granted, an invention must observe a set of requirements: it must be novel, non-obvious and useful, but it also has to qualify as a patent-eligible subject matter under 35 U.S.C. Section 101: the scope of the statute encompasses any "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof[29]. This last requirement has been the most contentious when it comes to medical diagnostics.

Innovations in this realm are unique in that they are seen by many as the "raw materials for future biomedical innovation", basic research that should not be eligible for patent protection because if patented further research would be impeded[30]. Likewise, they are unique in that they don't quite fit the traditional regime of patent-eligibility: personalized medicine claims do not describe a "tangible invention" but rather a "hierarchy of steps involving known methods of genetic testing and the administration of existing medication based upon the results of those tests.[31]"

Diagnostic method patents have found protection as medical processes. That makes much sense, for diagnostics consist of looking at specific biomarkers to make a diagnosis, a prognosis or a prediction. Processes have been a patentable subject matter for so long. However, prior to the irruption of biotechnology and software in the 1980s, patents were mainly limited to "inventions arising out of conventional technologies, such as mechanics, electronics and chemistry"[32]. After an era of expansion of the scope of patentability, there was a retreat starting in 2005, motivated by the concern that the USPTO could be patenting methods that should not be patented according to the long-held exclusions of "laws of nature, natural phenomena, and abstract ideas". With a case law swinging all the time and no clear rule in place regarding the subject-matter requirement, diagnostic method claims face the risk of being rendered a non-patentable "natural process"[33]. In the following subsection, we address in depth how the evolution of the definition of patentable subject matter in case law has affected the status of diagnostics.

To slightly introduce the conundrum of patentability of diagnostic methods, we can start pointing out that innovation in diagnostics is not self-evident, since discoveries in that area are built upon various judicial exceptions. On one hand, the biomarkers and correlations observed by researchers are judicially classified both as laws of nature and as natural phenomena, non-patentable because they naturally occur in the human body. On the other hand, the critical thinking and determination of results is considered an abstract idea that is non-patentable either.

B. Case law and USPTO guidance review

1. Overview of recent decisions with direct impact on patenting of diagnostic methods

Over the past twenty years, the patentability of inventions pertaining to life sciences and computer or business methods has been decided on the basis of the subject matter requirement in 35 U.S.C. Section 101[34]. A number of decisions at the Supreme Court and the Federal Circuit levels have invalidated claims for failing to qualify as eligible subject matter. This has reversed the product of nature doctrine, dating back to the 1980s and set out in *Diamond v. Chakrabarty*, which fueled the growth of the biotechnology sector because the standard used for assessing subject matter eligibility was human intervention[35].

Starting in 2005, the bar for patentability of biotechnological processes was raised and subject matter became a hot issue. Although it was not decided, the dissenting opinion by Supreme Court Justice Breyer in *Labcorp v. Metabolite* caused concern among innovators. The Supreme Court laid down the ground for a new, narrower scope of patentability. Faced with a diagnostic method claim relating to a correlation between total homocysteine and vitamin D deficiency, judges disagreeing with the refusal to hear the case warned against the policy implications of allowing patents over fundamental principles such as the correlation at issue (a natural phenomenon, according to them)[36].

Labcorp led many patent attorneys to challenge the validity of similar patents, and patent examiners to be stricter[37]. Despite not being upheld in *Ariad v. Eli Lilly*, the natural phenomenon doctrine was closely observed. In 2008, the Federal Circuit reformulated it in *Bilski v. Kappos*, a case concerning a business method patent that the Board of the USPTO had rejected on appeal38. The court affirmed unanimously the decision, and the majority established the "machine or transformation" test to evaluate all process claims[39]. To prevent the ownership on fundamental principles and ensure that only the application of such fundamental principles was protected, the Federal Circuit asked applicants to show that a machine or transformation was central to the claimed invention and not an "insignificant extra solution activity", namely data gathering[40]. As one of the dissenting judges to the test warned, *Bilski* brought much uncertainty, especially for personalized medicine and the field of in vitro diagnostics.

But the big blow for diagnostics innovators arrived with the Supreme Court decision in *Mayo*. In 2011, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* (*Mayo*) reached the Supreme Court, the issue in question being the subject matter eligibility of a method of measuring a thiopurine drug metabolite to adjust drug dosage[41]. The Supreme Court came up with a two-step test –otherwise known as the "*Alice/Mayo*" test for its subsequent use in *Alice Corp. v. CLS Bank Intl.*, concerning a software patent– which dismissed any patent application claiming: a (1) law or product of nature; with (2) no additional inventive step[42]. The two steps were intended to evaluate patent applications as a whole and to accept claims covering a judicial exception provided that a practical application was added[43]. But, no matter how well-intentioned it was, it threatened the patentability of many discoveries of personalized medicine that are based on the detection or correlation of naturally occurring phenomena, though using new and useful methods[44].

Following *Mayo*, the Supreme Court decided another subject matter eligibility case in 2013: *Association for Molecular Pathology v. Myriad Genetics, Inc.* (*Myriad*). *Myriad* revolved around diagnostic genetic medicine: "claims to DNA associated with breast cancer (BRCA1 and BRCA2) that had merely been isolated (genomic DNA or gDNA)[45]" were rejected, whereas "claims to DNA that codes for full proteins (cDNA)[46]" were protected, arguably because granting exclusive rights over whole-genome sequencing would have hindered innovation out of fear of infringement[47]. In a similar vein to *Mayo*, *Myriad* required the subject matter to be "markedly different" from product of nature[48]. Although the court stated that method claims were not implicated by its decision, it impacted claims covering "methods of "analyzing" or "comparing" gene sequences and other biomarkers[49]". Impliedly, this case consolidated a narrow interpretation of 35 U.S.C. Section 101, by restricting patentability to "novel method claims, applications of knowledge about genes or altered DNA[50]".

2. Current state of affairs after *Mayo*: uncertainty

Broad as the *Alice/Mayo* test is, it left patent examiners and lower courts with no clue as to how it should be applied[51].

Since *Mayo* was decided, the USPTO has released some guidelines which seek to introduce some clarity in the topic of subject matter eligibility.

Since Mayo was decided, the USPTO has released some guidelines which seek to introduce some clarity in the topic of subject matter eligibility. Prior USPTO guidance (*2014 Interim Guidance on Subject Matter Eligibility*) took the Mayo test and tried to elucidate the meaning of the "additional inventive step". First, it stressed that "[w]hile abstract ideas, natural phenomena, and laws of nature are not eligible for patenting by themselves, claims that integrate these exceptions into an inventive concept are thereby transformed into patent-eligible inventions[52]". Second, it went on to say which limitations to the scope of the method claims added "significantly more[53]" to a judicial exception and which were not enough, where the "insignificant extra-solution activity" standard in *Bilski* and other standards in case law served as proxies to interpret this test.

To hold that a diagnostic method, despite being directed to a judicial exception (Step 1 in the *Mayo* test, 2A in the USPTO guidance), amounted to "significantly more" (Step 2 in the *Mayo* test, 2B in the USPTO guidance), the patent office had outlined which were not valid limitations of the scope of the claims: (i) adding the words "apply it" (or an equivalent) with the judicial exception, or mere instructions to implement an abstract idea; (ii) simply appending well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial

exception; (iii) adding insignificant extra-solution activity to the judicial exception; or (iv) generally linking the use of the judicial exception to a particular technological environment or field of use[54].

This guidance analyzed the concept of "well-understood, routine, conventional activity" introduced in *Mayo* as an additional step that was unable to turn a judicial exception into patentable subject matter. Interestingly, the USPTO listed some examples of conventional activities specific to the diagnostics field that did not add any inventive step, such as "[d]etermining the level of a biomarker in blood by any means", "[d] etecting DNA or enzymes in a sample" or "[i]mmunizing a patient against a disease", among others[55].

There were two possible outcomes according to the USPTO:

"a) The claim as a whole does not amount to significantly more than the exception itself (there is no inventive concept in the claim) (Step 2B: NO) and thus is not eligible, warranting a rejection for lack of subject matter eligibility and concluding the eligibility analysis; or

b) The claim as a whole does amount to significantly more than the exception (there is an inventive concept in the claim) (Step 2B: YES), and thus is eligible at Pathway C, thereby concluding the eligibility analysis.[56]"

This revised guidance was to be completed with a guidance document issued in May 2016, on the subject matter requirement as applied to life sciences innovations[57]. In the Example 29, called "Diagnosing and Treating Julitis", the USPTO held patent-eligible the claims that incorporate an activity different from the diagnosis, be the detection of a new protein marker or the treatment of a disease.

Therefore, drawing on the 2014 guidance and the related examples, a purely diagnostic method claim would likely fall for its failure to add "significantly more" to a judicial exception: namely, the natural law that in their view is the correlation between a biomarker and a health outcome, or the mental process represented by the observation and evaluation of that correlation.

However, in January this year, the USPTO released new guidance (*2019 Revised Patent Subject Matter Eligibility Guidance*) intended "to improve the clarity, consistency, and predictability of actions across the USPTO[58]". Revised guidance elaborates on Step 1 of the Mayo test or Step 2A of the USPTO guidance, which is described as a two-prong analysis. Patent examiners will assess in Prong One whether the patent claim "recites" a judicial exception, and if it does, Prong Two will be about resolving whether it is actually "directed to" the relevant judicial exception.

As for the first prong, reciting a judicial exception, the hitherto vague "abstract ideas" exception is defined as those claims falling within one of the following groupings: "mathematical concepts", "certain methods of organizing human activity" or "mental processes". The USPTO notes there are no changes regarding the "laws of nature" and "natural phenomena" exceptions, so a diagnostic claim can be considered to recite those exceptions without further justification[59]. Therefore, diagnostic claims will generally go straight to the next prong, because they will involve a natural law represented by the correlation between a biological material and a disease, and a mental process represented by the observation and evaluation of that correlation.

As for the second prong, the USPTO wants to see the integration of the judicial exception into a practical application to get the claim patent eligible. Examiners will look for additional elements beyond the judicial exceptions which amount to a practical application. In other words, an application that "imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception". This is different from prior guidance in that analysis of "a well-understood, routine, conventional activity" is left for Step 2B and the USPTO is supposed to take all the additional elements of a claim as a whole[60]. Hence a claim can be patent eligible despite having non-inventive elements, if altogether there is a practical application. However, the 2019 guidance leans on the judicial interpretation of those limitations that make an exception applicable in practice. Therefore, regarding diagnostics, it only echoes recent holdings which are not-so-favorable for diagnostics as it will be explained below[61].

Nothing has changed, though, when it comes to Step 2 of the *Mayo* test or Step 2B of the USPTO guidance. This is where the question whether the claim adds "significantly more" to the judicial exception should be dealt with[62]. When a diagnostic method has not been declared patent eligible in Step 2A, it is unlikely to have a better fate here because in practice there is an overlapping with Prong Two of Step 2A[63]. Also, because the old guidance applies with its already mentioned examples which basically ruled out mere diagnostic claims as not inventive enough to limit the natural law exception in a significant manner.

For their part, lower courts have been quite restrictive in their application of the Supreme Court's doctrine in *Mayo*, deviating from the will of Justice Kennedy in *Bilski* to leave Section 101 open to interpretation to avoid unwanted effects, mainly a disincentive for further research on personalized medicine. As of 2016, the

Federal Circuit had consistently used the two-step test to invalidate claims on grounds of Section 101 in eighteen of the nineteen cases addressing this issue, and district courts had ruled similarly in 70% of the 155 cases concerning Section 101 that had been heard after *Alice*[64]. The few post-*Alice* cases that decided over diagnostic method claims invalidated them[65].

Among the latter, *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, in 2015, was a major decision that deepened the uncertainty reigning in patent jurisprudence. After a few favorable decisions for the biotechnological industry regarding software patents[60], the Federal Circuit ruled that a method of prenatal diagnosis of fetal DNA was not patentable subject matter, after considering the detection of fetal DNA a natural law and rendering the preparation and amplification of cell-free fetal DNA a conventional, non-inventive, activity. Such a decision prompted concern among patent lawyers, who stated the court had invalidated an improved diagnostic method, while upholding an improved Mickey Mouse (an improved animation method) in *McRO Inc. v. Bandai Namco Games America Inc.*[67].

After *Ariosa*, the prevailing feeling of uncertainty was well reflected in the concurring opinion of Judge Richard Linn: "This case represents the consequence — perhaps unintended — of that broad language in excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain[68,69]". Various other diagnostic method cases ensued, leading to the same outcome. For instance, *Genetic Technologies Ltd. v. Merial LLC*, concerning a patent on methods for DNA sequences, held the claims unpatentable because they merely covered natural phenomena. Patent lawyers on the side of innovators disagreed, warning against an excessively broad interpretation of the inventive step in *Mayo* and what seemed a raised bar for patentability[70]. Claims in *Genetic* showed for many "a significant improvement over previous diagnosis methods", but the court disregarded the analysis of amplified DNA as the additional step that the *Mayo* test demands[71].

III. HOW TO NAVIGATE UNCERTAINTY

A. Proof of "something more" to escape the judicial exceptions

Despite the uncertain patent landscape shaped by *Mayo*, there are grounds to be hopeful about the future of patentability of personalized medicine claims, in the absence of a legislative reform. A 2018 decision by the Federal Circuit in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.* (*Vanda*) upheld a patent on a diagnostic method. Yet in that case, the applicants did not claim solely an in-vitro determination of a biomarker, but they added a second step of dosage determination and treatment administration[72]. This different holding in *Vanda* raised the question about the patentability bar. Was the message sent to applicants that a diagnostic method could not be patented unless there was an administration step? If so, what will be the fate of sheer diagnostic methods and prognostic methods, where the inventiveness lies in establishing a correlation between an identified biomarker and a disease or the likeliness of developing a disease?

Such a narrow scope of subject matter eligibility crowds out much of the ongoing ground-breaking research on personalized medicine, covering only one kind of diagnostics, those specifically directed at an active treatment.

1. Attention to the novelty of the method itself

Part of the devastating blow for diagnostics innovation was due to the requirement of a new and innovative method to turn a non-patentable natural phenomenon, such as a correlation between a biomarker and a medical judgment, into "something more".

The vague "something more" requirement was introduced in *Roche v. Cepheid*, a case concerning a purely diagnostic discovery, with no linked treatment, of a test to detect the bacteria that causes tuberculosis and to determine its drug resistance[73]. Claims addressing the polynucleotides used as primers in the test were dismissed because these were identically found in nature, and claims covering the polymerase chain reaction (PCR) method to amplify the sample were also disregarded because PCR was considered a conventional technique[74]. The Federal Circuit thus stated that Roche's discovery lacked the "something more" element, even though PCR was being used for the first time to detect that bacteria[75].

To clarify that the "something more" requirement was being consistently applied at the federal level, the court compared the facts in *Roche* to those in the recently decided *Vanda* case, concluding that claims in the latter pointed to "a novel way of using an existing drug[76]".

Rulings immediately after *Mayo* could suggest there is little margin for improvement because personalized medicine is mainly about critically thinking about the relevant biomarker and correlation, and then determining the results using a procedure that is often known. For many patent lawyers, unless the Congress amends Section 101 to recognize the innovative nature of diagnostics *per se*, it is even fruitless to argue that there is

innovation in looking at a specific indicator, because the courts will stress that the studied phenomenon exists in nature and the method to detect it exists in prior art.

Nevertheless, the latest case law shows there is some margin to prove that a diagnostic method claim adds "something more" to a judicial exception. In 2018 case *Exergen Corporation v. Kaz USA, Inc.*, an improved method of detecting human body temperature and an improved detector were granted protection by the Federal Circuit. Although the patent owner did not challenge the fact that claims covered a law of nature –human body temperature as a function of ambient and skin temperature–, they managed to establish "an inventive concept sufficient to transform the claims into a patent-eligible application[77]". The court held that the patent had "incorporated an inventive concept" because "following years and mil-lions of dollars of testing and development, the inventor determined for the first time the coefficient representing the relationship between temporal-arterial temperature and core body temperature and incorporated that discovery into an unconventional method of temperature measurement[78]". This opened the door to a judicial recognition of the innovative added value of diagnostic methods. However, it is not clear whether the holding would have been different had the patent owner claimed only the coefficient, without its application through an electronic detector.

Anyhow, patent applicants should closely monitor the favorable interpretation in *Exergen* of what is a "well-understood, routine, and conventional" method. *Exergen* rules that "[t]he question of whether a claim element is well-understood, routine, and conventional to a skilled artisan in the relevant field is a question of fact and deference must be given to the determination made by the fact finder on this issue [the district court][79]". The district court had found the detector was non-conventional because despite its existence in prior art, it had never been used for temperature measurement, and the federal court assumed this as a proven fact, in conflict with the interpretation given in *Roche*.

Pending a Supreme Court ruling, this precedent –identically found in *Berkheimer v. HP Inc.*– allows patent lawyers to argue that methods in prior art are used innovatively to discover a patent-eligible diagnostic, prognostic or predictive method. Diagnostics innovators are thus encouraged to incorporate the coefficients they discover into unconventional methods of measurement to be granted patent protection[80]. However, latest diagnostics case decided in April, *Cleveland Clinic Foundation v. True Health Diagnostics (Cleveland Clinic II)*, discourages that idea because presented with a conventional immunoassay of blood samples innovately used for the correlation between myeloperoxidase levels and risk of artherosclerotic cardiovascular disease, the Court of Appeals for the Federal Circuit invalidated the prognostic claim and regarded the innovative use of an old method as a "superficial distinction"[81].

Based on the Federal Circuit case law, assurance of non-routine, non-conventional nature of the claimed method when drafting the patent application is critical[82]. Hence patenting a method of detecting a newly identified biomarker could be a pathway to get patent protection of medical diagnostics. Reagents are components used in diagnostic testing assays to produce a reaction that, when measured and compared against known values, renders a diagnostic, prognostic or predictive test result[83]. There is some evidence showing that diagnostics are more favorably examined by the USPTO when claiming a method of detecting a biomarker that uses a novel or non-conventional agent[84]. For instance, PCR was not upheld by the Federal Circuit as a patentable method of detection in *Roche* because it was routine among researchers, but this would change were the agent a novel antibody.

Regarding patentability of specific biomarkers, it is not an option even if they are isolated according to the *Myriad* decision. But what *Myriad* did not challenge was the patentability of artificial methods of using natural DNA[85]. This would include diagnostic claims focusing on a novel combination of various biomarkers, which has been upheld by patent examiners[86].

For patent application purposes, revised guidance by the USPTO clearly states that "a claim that includes conventional elements may still integrate an exception into a practical application, thereby satisfying the subject matter eligibility requirement of Section 101[87]". Thus, novelty of the method will not be examined insofar as there is a practical application of a judicial exception. But this is not precisely good news for the diagnostics industry because the idea that the USPTO has of what constitutes a practical application of a diagnostic claim seems to be overly influenced by decisions of the Federal Circuit such as *Vanda*[88]. That is, a diagnostic innovation claim "applying or using a judicial exception to effect a particular treatment or prophylaxis for a disease or medical condition[89]". This idea is reproduced with regard to novelty, since it has been stated that the practical application step and the inventiveness step kind of overlap. Even though there is not a closed list and any "meaningful" limitation to a judicial exception "beyond generally linking the use of the judicial exception to a particular technological environment" should be considered, reference to Vanda suggests they might not be eager to admit a practical and innovative, yet purely diagnostic combination of steps[90].

So far, the policy choice showcased by the USPTO and courts seems clear: mere diagnostic method claims will not survive a patent law exam without an attached treatment or prophylaxis step.

2. Attention to the end result of the method: key role of an administration step

In some cases, the reason why the claims in *Roche* and similar cases were not upheld is the absence of a treatment step: the mental determination of a result is not translated into any physical step, thus for courts and patent examiners there is not really an additional inventive step as mandated in *Mayo*.

Indeed, the Federal Circuit argued in *Roche* that the claims had failed because they related to a diagnostic method instead of a method of treatment[91]. Therefore, the right analysis of *Vanda* as a favorable outcome for a diagnostic method patent as opposed to outcomes in *Mayo* and post-*Mayo* cases is rather about the necessity to show an end result that is not the diagnosis itself but a treatment.

This reasoning was already applied in *Classen Immunotherapies, Inc. v. Biogen Idec*, where claims covered a method of data gathering and analysis, a non-patentable abstract mental process by itself, and an administration step –in that case, the immunization of mammals–. For the PTO, the administration step was "meaningful because it integrated the results of the analysis into a specific and tangible method that resulted in the method "moving from abstract scientific principle to specific application."[72]".

Another post-*Mayo* case, *Cleveland Clinic Found v. True Health Diagnostics*, made this judicial requirement overtly necessary. Among the claims, the one involving a treatment method was not challenged under Section 101 whereas the other claim involving a prognostic method to assess the risk of developing a medical complication from a determined biomarker raised some concerns[93]. By virtue of this combination of a diagnostic and a treatment method, the patent application as a whole went ahead.

Finally, *Vanda* tries to explain why claims in *Mayo* failed, in an attempt to clarify the all too unclear *Mayo* test. The court finds that the claims at issue are directed to a method to treat a disease, whereas in *Mayo* the claim as a whole was directed to a diagnostic method because it "did not go beyond recognizing (i.e., "indicates") a need to increase or decrease a dose[94]". This tells diagnostics innovators that even if they develop a predictive method, tied to the determination of the efficacy and safety of a drug regimen for an individual or a subpopulation, they will not be able to patent it unless they incorporate an actual treatment or prevention step. Otherwise, it will be regarded as a non-patentable natural law if we think of the correlation or a mental process if we think of the diagnosis, prognosis or prediction.

In fact, this is what happened with the *Mayo* claim. The majority reminds us that "[a]lthough the representative claim in *Mayo* recited administering a thiopurine drug to a patient, the claim as a whole was not directed to the application of a drug to treat a particular disease[95]". Therefore, a proper method of treatment claim directed to determine a specific dosage rather than the general need to increase or decrease it was missing in *Mayo*.

Some comments on *Vanda* have stated that predictive method claims and by extension personalized medicine claims are strengthened after this ruling[96]. However, this seems only true of predictive claims accompanied by an active treatment or prevention claim. Indeed, we could say that *Vanda* only reaffirms what was already the rule of patentability for diagnostics in some post-*Mayo* cases, so the optimism surrounding its holding is not really justified. Also, we could make the point that the main standard used to assess *Vanda* against *Mayo* was the existence of a specific treatment claim, relegating the analysis of step 2 of the Mayo test –addition of "something more"– to a second place.

Such reading is confirmed by *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC (Athena)*, a case decided last February at the Federal Circuit level where the majority rejected patentability of a multistep method of diagnosis –correlating antibodies to a protein with neurological disorders– for being directed to the natural law exception represented by a biological correlation and for not adding "an inventive application beyond the discovery of the natural law itself[97]". On behalf of the majority, Judge Lourie drew a difference between the mere diagnostic method at issue and the diagnostic method with a therapeutic step in Vanda. To conclude that only the second was patent eligible because any application other than a strict administration step is not really a practical application of the natural law exception, thus not deserving patent protection[98]. However, dissenting Judge Newman thinks that the claim should not even be related to the natural law exception because it is not directed to the antibodies but to a multistep method of diagnosis[99].

Altogether, these decisions leave patent protection out of reach for most of innovation in the diagnostics sector, which is not directed to active treatment yet it still has a clear and innovative end result in the diagnostic method itself. As Judge Newman regrets, "for procedures that require extensive development and federal approval, unpredictability of patent support is a disincentive to development of new diagnostic methods. The loser is the afflicted public, for diagnostic methods that are not developed benefit no one[100]".

On the other hand, it drives some innovators to shift to concrete treatment applications for their diagnostic inventions to gain protection from Section 101. For these innovators there is remarkable certainty, especially after the Federal Circuit amended the divided infringement loophole in *Limelight III*[101].

As a final note, even though purely diagnostic claims seem doomed to fail, it could be worth trying to claim for instance a method for detecting whether a patient has an (increased) risk for a particular disease by looking for a particular abnormality of a particular biomarker[102]. Even though *Vanda* seems to envision a necessary additional treatment claim, the specific drafting technique therein –"a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome[103]" – can be applied to a prognosis claim to give the patent examiner or the court a better sense of a specific method for a specific end result. In the end, a treatment step is not mandated by the law and some specificity should increase the chances of prognostic and predictive claims being patent-eligible.

B. Mitigating the risk of statutory language: comparative view of diagnostic methods patents in Europe v. the United States

Despite the relative settlement of a judicial doctrine regarding diagnostics, the *Mayo* test is still too vague, decisions by the Federal Circuit are inconsistent and generally the subject matter eligibility of diagnostic methods is too narrowly interpreted. On top of that, the Supreme Court denied certiorari to Sequenom, therefore *Mayo* could not be clarified[104].

Considering the adverse landscape created in the United States after *Mayo*, and while innovators in the field of diagnostic methods have been encouraged to file patents in Europe, where diagnostics methods involving laws of nature are more welcome[105, 106]. Remarkably, the *Prometheus* patent succeeded there[107]. There is data showing that diagnostic method claims have a much better chance of success before the European Patent Office than before the USPTO. As a matter of fact, two researchers tracked the fate of 31 international patent applications – pursued under the umbrella of the Patent Cooperation Treaty (PCT)– and found out that in Europe, "30 of the 31 diagnostic PCTs either had successfully matured into patents with diagnostic or prognostic claims or were still pending at the EPO with objections on the basis of novelty, inventiveness or clarity but without objections corresponding to a US '*Mayo* rejection', which in Europe could be considered a lack of 'industrial applicability'[108]", whereas in the United States "29 of the 31 diagnostic PCTs were either abandoned after receiving a *Mayo* rejection (and often others as well, such as lack of novelty and non-obviousness) or still pending at the USPTO but with a *Mayo* rejection in place[109]".

Filing a patent application in Europe is therefore a strong alternative to U.S. market, since a European patent can result in national patents in the chosen countries[110]. To understand the radically different outcomes in the two patent systems, we must go to the substance of the issue: case law-based exceptions to patent eligibility in the United States, as opposed to the statutory exclusions and exceptions in Europe. Article 52(1) European Patent Convention (EPC) sets the patentability requirements – it expressly requires inventions to be new, inventive and susceptible of industrial application, and implicitly to be of "technical character"[111]–, whereas Article 52(2) EPC lists some exclusions from patentability that are pretty much coincident with U.S. judicial exceptions –broadly grouped in "claims that are abstract in nature (discoveries) or non-technical in nature (scientific theories or methods for performing mental acts)[112]"–.

For the purposes of patenting diagnostic methods, Article 53(c) EPC includes a specific exception regarding "[m]ethods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body [underlining added]". This shows in turn two-fold difference with the U.S. patent system. First, treatment methods are non-patentable. Second, diagnostic methods are exempt from patentability only when they are practiced on the human body and they meet four consecutive steps: "an examination, a comparison, a finding of any significant deviation and a decision[113]". Thus, in vitro diagnostics –on a sample– are not problematic as for their subject matter eligibility provided that they don't limit themselves to a deductive decision amounting to a diagnosis, a prognosis or a prediction –excluded as mental acts–[114].

This does not mean that diagnostic method claims are not challenged in Europe, simply the grounds on which they are challenged are different. Since the subject matter eligibility is not an issue, challenges are focused on the novelty and inventiveness of diagnostics[115]. In this regard, the discussion on those other issues is much more nurturing and positive for the patent system because the baseline is clear –in vitro diagnostics are patentable in principle– and patent applicants can move on to argue the really boundary questions of personalized medicine claims that matter to innovators and to the public. For instance, whether there is novelty in a patient group selection of a subpopulation group sharing an identified feature or biomarker[116].

The patent eligibility deadlock in the U.S. has led to petitions for a legislative change that brings certainty to application of Section 101 and prevents judges from twisting the exceptions to patentability. In this regard, it is noteworthy that U.S. Senators and Representatives are working on a joint reform of the Patent Act, driven

by a will to strengthen the patent rights of innovators[117]. In the draft outline of their Section 101 reform released last April, they commit, among other things, to "[c]reate a "practical application" test to ensure that the statutorily ineligible subject matter is construed narrowly"; to "[s]tatutorily abrogate judicially created exceptions to patent eligible subject matter in favor of exclusive statutory categories of ineligible subject matter"; and to "[m]ake clear that eligibility is determined by considering each and every element of the claim as a whole and without regard to considerations properly addressed by 102, 103 and 112"[118]. This framework document has already been criticized by some on the innovators side, who consider codifying ineligible categories and the "practical application" test would deepen the current situation because it could be used to validate the narrow doctrine created by courts. Courts retain too much discretion and could create new exceptions based on the ineligible categories or the practical application test[119].

CONCLUSION

Over the past ten years, personalized medicine has experienced high pressure on many grounds. Patent law has been a critical front, especially since the *Mayo* case was decided and a too broad two-step test was instituted[120]. During this time, the Federal Circuit has hampered efforts to interpret *Mayo* with a handful of inconsistent rulings. Previously, the USPTO had complicated rather than clarified the case law by issuing some guidance that, in order to approach judicial concepts such as *Mayo*'s "significant more", combined subject matter with novelty or non-obviousness to the point that patentability requirements were no longer distinguishable from each other to patent applicants. Although new guidelines shed some light on Section 101, courts do not necessarily abide by them. Indeed, many diagnostic methods have been judicially struck down for claiming a –broadly interpreted– judicial exception and not adding a truly inventive activity. Thus, the innovative value of diagnostics research, based on finding among other things the relevant biomarker and the relevant correlation, is neglected.

Faced with so many challenges at the level of subject matter eligibility, it is foreseeable that diagnostic innovators move to other ways of protecting their inventions. Without a patent incentive, trade secrecy emerges as an alternative for the innovators most impacted by the *Mayo* test and the judicial narrowing of Section 101, probably diagnostic testing companies[121]. However, these are not the only ones left out of the patentability scheme, since as researcher Rebecca Eisenberg once noted, "most important advances in [diagnostic testing] lie outside the boundaries of patent-eligible subject matter"[122]. Against this backdrop, not only innovation is jeopardized but also access to new health care solutions is compromised as a result of the non-disclosure of game-changing medical diagnostics.

The Supreme Court has denied requests to review its doctrine by Sequenom and other innovators like Novartis[123]. In parallel, some actors have previously advocated for a legislative reform of the subject matter requirement set in 35 U.S.C. Section 101 to redress this situation, in a similar manner to how the EPC has set the exceptions and exclusions from patentability in a statute. Two patent lawyers recently made it clear in a blog post: [a]s the Supreme Court, the driver of these decisions, is unlikely to overrule its relatively recent recent § 101 decisions in the near future, change, if any, will likely need to come from Congress[124]". But as of today, there are no clear proposals in the pipeline apart from the above mentioned framework on Section 101 reform, still at an embryonic stage. While we await legislative change, patent applicants and patent owners in the field of diagnostics have to try to navigate this uncertainty and ensure that the drafting of their patent applications emphasize and conform to the evolving doctrine that courts and the USPTO shape together.

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Article

How Should Start-Up Biotechnology Companies Manage Learning and Generate the Necessary Knowledge to Achieve an Alliance-Based Stage of Growth?

Christopher C Lamb
Weatherhead School of Management, Case Western Reserve University, Cleveland OH, USA

ABSTRACT

Ethical drugs can take hundreds of millions of dollars and over 10 years to bring to market. Start-up biotechnology companies are recognized for their unique exploration and then exploitation in the development of future drugs. However, these potential new drugs are highly unpredictable and require a broad scope of inquiry. Significant and complex knowledge along with openness to learning is required because of the unusually high risk and uncertainty of biotechnology. After initial start-up, biotechnology companies often form a strategic partnership with an established pharmaceutical company to get additional funding and incorporate needed later stage development knowledge.

To conclude an alliance, a company needs to develop learning processes that transition the organization to the next stage of growth. These processes advance the technology sufficiently to conclude a strategic deal. Effective learning enhances exploitation of knowledge needed to generate unique insights and understandings related to the development of a new drug.

This paper examines seven biotechnology companies and identifies key processes that should optimize "effective learning" to enhance the probability of creating the necessary new knowledge needed for a start-up to achieve an alliance stage of growth. Despite a majority of the companies successfully reaching the scaling-up stage of growth, some ultimately fail due to a lack of one or more the explored factors.

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INTRODUCTION

While research been conducted on how start-up companies in general use open innovation networks to generate knowledge, much less is known with respect to biotechnology start-ups.[1,2] Some of these publications have highlighted the need for strong teams but there is limited data on how this is accomplished in practice.[3] Within the pharmaceutical sector the chance of any newly identified drug making it all the way through clinical trials and regulatory approval—at an average price of $2.6 billion—has been estimated to be about 5,000 to 1.[4] Likewise, of the many hundreds of biotech companies that have ever existed less than 1% have succeeded in terms of profitability and those successful few have been notably successful for investors.[4-9] Given these odds, what drives investors and managers to participate in start-up opportunities that almost always result in financial loss? What is the most effective corporate strategy to lead a start-up to success?

Adam Smith noted the following: (1) the tendency of human nature is to exaggerate the value of a small chance of large winnings; (2) most founders and entrepreneurs have an irrationally high confidence in their own good fortune; and (3) most may be timid and critical on first embarking in new ventures but hold on to the end once committed.[10] Biotechnology illustrates all three of Adam

Smith's observations: first there is a very small chance of a profitable return even if the eventual profit could be very large, leading to a distorted sense of the economic value of the enterprise. Biotechnology illustrates all three of Adam Smith's observations: first there is a very small chance of a profitable return even if the eventual profit could be very large, leading to a distorted sense of the economic value of the enterprise;[11,12] second, entrepreneurs and founders have an exaggerated confidence that their technology will be the winning one;[13,14] and third, once players become exceptionally committed, once they do reach this stage.[15] These conclusions are supported by interview-based surveys of biotechnology executives.[4,16-20]

Pharmaceutical companies do not usually have the resources to get involved in early stage research—the endeavor is too risky for them and would involve an intense focus on research questions and creating knowledge in excess of their capability to make use of it.[20-24] Instead, pharmaceutical companies are willing under the right circumstances, to enter into strategic partnerships with biotechnology start-ups and gain potentially valuable data from the start-up companies' research.[11,18,25]

Given the odds of failure, what is the best strategy? A biotechnology start-up should use its limited resources to gain enough knowledge to achieve a strategic deal with a pharmaceutical company. An alliance stage of growth will give the company sufficient resources and expertise to survive and grow to the next level (commercialization). Knowledge generation is a start-up's primary objective since a deal and strategic partnership is highly unlikely without this. It is the unique knowledge from the founding team composition that is sought by pharmaceutical companies.[26,27] The more knowledge acquired—usually that associated with the regulatory stage of drug development—the more valuable the deal becomes.[11,18]

This report focuses the ways in which biotechnology start-ups should best transform themselves to achieve an alliance with a partner pharmaceutical company, including the ways they on implement business practices that encourage a learning environment. By doing so, the likelihood of adding significant value from the strategic deal will be enhanced. Investors and executives should assess the capabilities of start-ups and the likely success of implementing learning processes before investing in early stage technology that typifies a biotechnology start-up.

General Proposition for Exploration: Strategic Partnerships are a Critical Requirement

Biotechnology requires the application of extensive scientific knowledge to explore new, unpredictable technology and market developments and start-up companies provide this knowledge from their broad scope of research and greater openness to new scientific inquiry and learning.[28,29] In no other fledgling industry have scientists played such an extensive role as they have in biotechnology.[24,30-32] After initial formation, a start-up usually has some combination of the following assets: technology with significant commercial potential, protected intellectual property (most likely a patent), Orphan Drug Designation, proof of concept preclinical (animal) data, only limited competition, credible founders, and venture capital financing.[33-35]

The next stage of growth for a biotechnology company is a strategic partnership with a pharmaceutical company, an altogether larger organization—this alliance typically includes additional financing, a significant step up in valuation and sometimes a whole or partial exit for the financial investors.[36-40] Alliances are a key factor in the survival and the growth of new biotechnology firms.[11,18,26,41,42] For a biotechnology company, a strategic partnership conveys the resources and credibility to get established, obtain additional funding, and to gain later stage development knowledge from the pharmaceutical company.

Technology is not enough

Good technology is not enough: in order to conclude an alliance, a start-up needs to establish processes to generate the necessary knowledge and transform the company—structures, culture, internal control systems and values—to drive the new organization and transition to a next stage of growth.[43-45] These additions can dramatically change the company by support new initiatives, learning, competence, and skill development that will advance its technology.

The start-up biotech company seeking a strategic partnership must demonstrate to a pharmaceutical company that they have an adequate knowledge of the target drug regulatory environment, and marketplace. The knowledge of the drug must include how to manufacture it, why it works as well as evidence that it is safe and effective in humans.[46-48] The regulatory knowledge must be sufficient to meet the requirements of markets with the most commercial opportunity, usually an IND (Investigational New Drug) for the US FDA (Food and Drug Administration) and CTA (Clinical Trial Application) for the EMA (European Medicines Agency). The marketplace demands New Value in the form of solutions to unmet medical needs, namely, significant improvements over existing therapies as well as solutions to ensure patient access to new drugs.[49] Given the uncertainty surrounding knowledge generation, biotechnology companies need to have a high degree of

flexibility and decentralization to create science while maintaining the right mix of structure and process.[5,50,51]

Conceptual framework: managing learning to achieve an alliance-based stage of growth

This paper explores the proposition that in order to reach an alliance-based stage, start-up biotechnology companies must successfully implement three processes: (1) build excellent knowledge networks to enhance learning, (2) create high performing teams with sufficient diversity to generate knowledge that will advance drug development through the regulatory process, and (3) improve deal-making capability through the involvement of experienced financial investors who can package the knowledge into a story that a pharmaceutical company will buy.[52] The start-up operates within a larger macroeconomic system that encompasses an existing industry, regulatory framework, market, products and perceived unmet needs.

Below is a conceptual framework that will be used in this paper (Figure 1). A "bins" approach is used whereby the framework is a visual catalogue of the interrelationships between the environment, the required adaptive behavior. This framework highlights the interactions among multiple variables. It assumes, and individuals involved with the company, including financial investors, CEOs, and the executive management team. The approach draws on social science research methodology.[53,54] In this particular instance it is assumed that the underlying product works, and that the start-up is able to cope with the fundamental challenges created by science and its extreme uncertainty.[4,5,24,55,56]

Given the above framework, Argyris' Theory of Action is an appropriate starting point for how start-up biotechnology companies should.be effectively organized.[55] Effective Action is about learning that produces knowledge, insights and understandings related to the development of a new drug. In the context of biotechnology this is about "effective learning" and the output is "new knowledge". "Action Science" is the way organizations can design processes that internally promote effective learning and the creation of new knowledge: "how we design action and how we might create better organizations".[57,58]

As a result of its complexity, biotechnology requires that the Actors, namely the financial investors, CEOs, and executive management team, question the status quo and encourage rare events. Organizations must explicitly design management practices that avoid competitive infighting, unilateral control and defensive routines. The key outputs are valid documented information and the effectiveness of implemented actions. Given the uncertainties and lack of routine in the industry, personal characteristics needed in effective Actors include all of the following: a willingness to challenge ideas, assumptions, and bias; a high capacity for reflection and examination; advocacy by encouraging inquiry; and creating an environment permitting members of the organization to express fears and doubt.

The question explored in this paper is how to best implement learning processes with a particular focus on knowledge creation needed to conclude a strategic deal. Firstly, a descriptive review of the literature examines the state of current knowledge and to help understand issues around implementation. Secondly, there is a report of the authors own research in which seven start-up companies were surveyed through interviews with Actors. These included five companies that have successfully concluded an alliance, as well as one in the process and one company that ultimately failed. Yet only two of the companies have successfully gotten a product to market, which is consistent with the low success rate of biotechnology companies reported in the literature.[59]

LITERATURE REVIEW

What is Special About Biotechnology?

The biotechnology industry is based on biological techniques founded in the 1970s and 1980s and have resulted in new commercial applications over the past 40 years. Investors and managers invest time and money into biotechnology because of the belief that cutting-edge science will result in future blockbuster drugs.[60-62] Pharmaceutical companies increasingly demand new products to come onstream to compensate for the trends toward lower research and development productivity and more intense generic competition once patents expire.[63-65] With its extensive reliance on macromolecules, biotechnology is less at risk of generic competition because, unlike chemically synthesized drugs, macromolecules such as human based proteins are produced from living cells and any competing biosimilar generic equivalents needs to undergo extensive development, including time consuming safety and efficacy testing in the same way the innovator drug did. Biotechnology products therefore have a form of "data exclusivity".[66-68] As a consequence, macromolecule biotechnology drugs that come off patent often continue to show strong long-term profitable sales for many years and continue to reward investors and executives.[5,68]

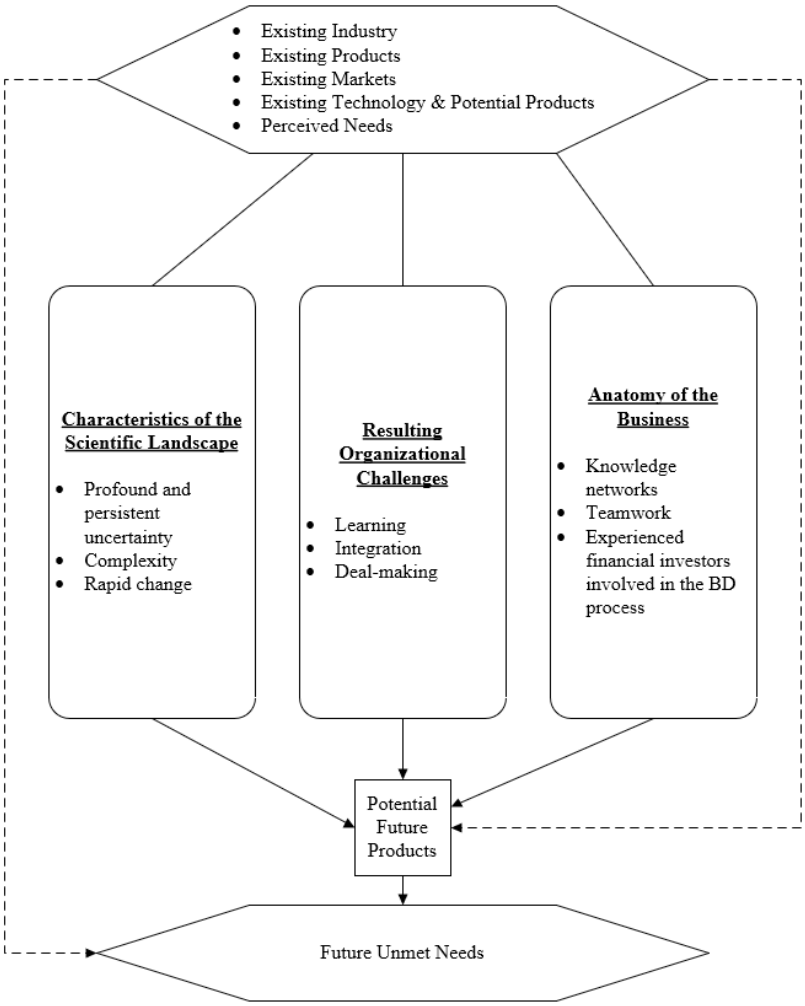

Figure 1: Conceptual framework for a study of start-up biotechnology companies and the necessary conditions for a strategic partnership.
Conceptual model adapted from Argyris[54]

Life-Cycle Stages of Biotechnology

The literature stresses the importance of the starting conditions of new biotechnology firms.[40,69,70] These conditions include the founding team's quality and size in both scientific and business expertise,[71-73] the main strategic decisions regarding product markets,[74,75] and the competitive environment.[40,76-78] These factors are critical to attract an investor and get the start-up going. Once the initial conditions are set, they are difficult to change.[34,35,79,80] Attractiveness, therefore, depends on the initial starting niches the founders have chosen for the firm.

The development of a biotechnology start-up can be considered as four successive stages (Figure 2) as originally described by Arnold and colleagues.[11]

Discovery Stage: A biotech company is formed by scientific entrepreneurs who have identified a target drug, licensed or generated intellectual property (IP) and have in vitro data that show that the drug has commercial potential.[82] These entrepreneurs typically come from universities or other academic institutions or from previous biotechnology start-ups; they are inventors and entrepreneurs.[24,83]

The initial success factors at this first stage include targeting high-growth product niches[24,61,84] and targeting major markets to maximize returns;[85] improving the quality of the founding team to establish credibility[41,86,87] and patenting of innovative research and development (R&D). The latter is especially important for securing a profitable return on investment and for ensuring credibility.[88,89] Orphan drug designation, when appropriate, can also maximize the period of commercial exclusivity and thereby enhance valuation.[90]

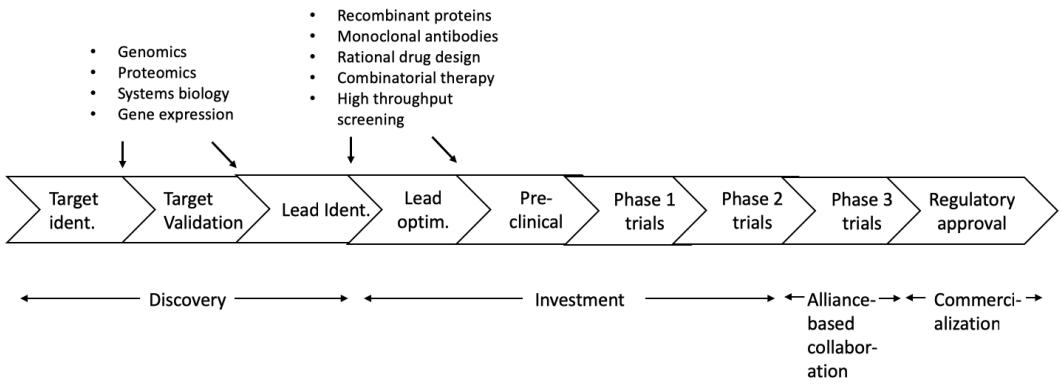

Figure 2: Phases of the drug R&D process.
Adapted from Ng et al 2014 [81]

Investment Stage. The second stage begins when a professional financial investor is attracted into the new company and the "start-up" process begins. A start-up company is usually founded after lead identification, some optimization, and some preclinical development.[91] Success factors include efficient R&D management and venture capital support. Efficient R&D management is needed to produce new general publishable knowledge and create new or better products and processes in competition with other business enterprises, when these are defended by patents.[92-94] Venture capital support involves initial funding, often reinforced by non-dilutive government innovation funds. This early funding is, nevertheless, much smaller than the multi-million-dollar funding possible in the third stage of development when alliance-based collaboration with pharmaceutical firms is ongoing.[84,95] A successful investment stage concludes with an IND/CTA filing. Usually by this time data from the earliest clinical studies (in humans) will have become available.

Alliance-based Collaboration Stage. The third stage occurs once a company has concluded an alliance/collaboration with a strategic partner, usually a pharmaceutical company. This phase usually begins after Phase II clinical studies when FDA/EMA has approved the pivotal study for licensure/approval.

Commercialization Stage. The fourth stage begins when a company's product has regulatory (FDA and EMA approval) and begins to be profitable. Oftentimes the pharmaceutical company will acquire its strategic partner only after this stage.

Alliances are critical for biotechnology start-ups

Biotechnology start-up firms serve as intermediaries in a value chain that links basic science to commercial application. Stuart and Sorensen analyzed 429 U.S. headquartered firms that went public between 1972 and 2002 and found that biotechnology companies with more in-licensing relations with universities engaged in more frequent revenue-generating deals with large partners.[42] This suggests that biotechnology companies have a "technology brokerage" role in the process.[97]

Timing of an alliance

Pharmaceutical companies have increasingly sought to place their bets on companies that are further advanced toward producing marketable products. In the early 1990s, the highest market valuations went to companies with technology platforms that could potentially lead to biologic targets, Human Genome Sciences with its genomics platform being one such example. In contrast the more recent tendency has been that of a value chain of successive steps, beginning with identifying novel drug targets of value, then to focusing on product leads, then to acquiring development candidates in clinical trials, and finally to paying for revenues for approved products.[98] There currently exists a break point in the biotechnology industry value chain between front end discovery and late-stage development[99] with alliances most likely to be entered into at the time of this breakpoint. While historically most deals were done at an early stage, deals are nowadays most frequently made after completion of the initial efficacy clinical trials in patients (Phase II).[100] There is a high rate of failure of clinical trials (to show efficacy or safety) at this stage so there is less attendant risk to potential partners once clinical development is past this phase but before the high cost Phase III studies that necessitate a partnership with a pharmaceutical company.

Value of an alliance

As products advance through successive stages of drug development, there are a number of variables that affect the value of a deal with a strategic partner: type of therapy, novelty, type of molecule or protein, type of license

(marketing vs. non-marketing), and scope (global vs. U.S.). In general, however, knowledge increases, and the risk of product failure decreases with each successive stage. In one sample of companies, a 22% increase in deal value was shown with each clinical phase from 1 to 4.[11] Thus, a strategic partner/pharmaceutical company is willing to pay incrementally more for a start-up the more it has advanced through preclinical and clinical trials.

Environment for Start-Up Biotechnology Firms

Biotechnology is a science-based business, that is, biotechnology companies seek to both create science and capture value from it.[5,101] Firms must engage in research where the science is still "raw", the data are mixed, and the basic technical feasibility remains in doubt. The unique operating challenges include a profound and persistent uncertainty of the underlying science that requires mechanisms for managing and rewarding risk, a highly complex and heterogeneous scientific body of knowledge that requires integration across disciplines and areas of expertise, and rapid advances in the underlying science that require mechanisms for cumulative learning. Funding, regulatory, and legal challenges must also be addressed at various stages (Figure 3). These, just as much as the science, impact the sustainability of start-ups.[5,102]

The complexity and wide importance of the knowledge base underlying biotechnology requires companies to develop technological capabilities in a wide range of scientific disciplines, to use of old and new technologies, and to integrate these effectively.[56] Knowledge sources are located in a multiplicity of agents, institutions, and companies. Firms have to develop networks in order to acquire the components of knowledge necessary to start innovative activities—linkages among different firms and institutions, which, individually, possess only fragments of relevant knowledge.[103]

Uncertainty

Profound and persistent uncertainty requires specialized mechanisms for managing learning and innovation. Biotechnology R&D confronts fundamental questions about technical feasibility. For example, is it possible to combine two proteins into a sterile spray powder formulation while preserving their biological properties? How does a liposomal formulation improve the clinical efficacy of the Factor VIII protein? Not only are such questions difficult to answer but attempts to answer these questions lead to more questions and unexpected results. For these reasons, the uncertainty faced by biotechnology is of a different type from that faced by most other industries.

Fredrick Knight distinguished between primary and secondary uncertainty. Secondary uncertainties can be characterized by probability distributions (the chance that it will rain tomorrow) and are referred to as "known unknowns". Primary uncertainty refers to "unknown unknowns"—what you did not even know you did not know.[104]

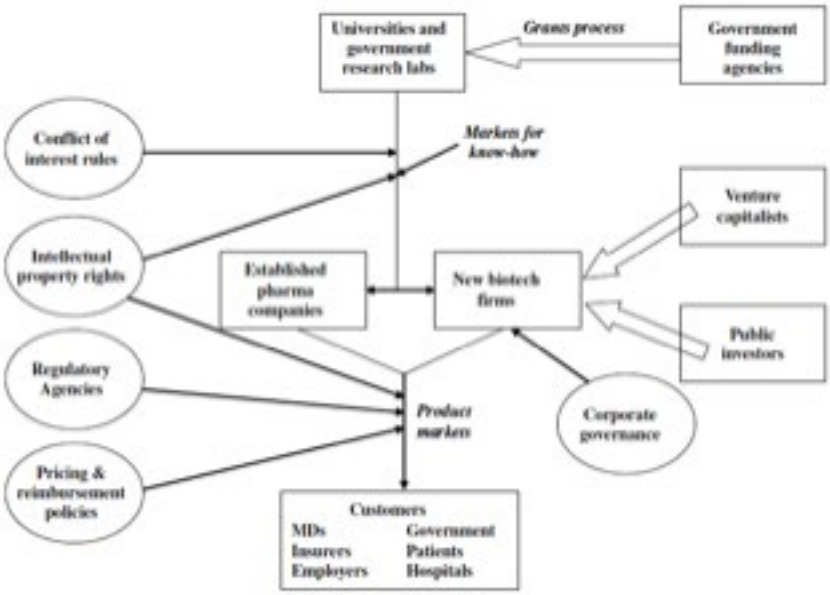

Figure 3: Biotechnology industry architecture
Ahn (2008)[98] (reproduced with permission)

This profound uncertainty relates to knowledge or what may be designated by the term "invention" taken in a broad sense. Biotechnology is about the discovery of new facts or new knowledge, which are the result of deliberate thought, investigation, and experiment. The timing and likelihood of serendipitous discoveries cannot be predicted. Consequently, it is extremely difficult to predict the investment of resources needed to secure the acquisition of this new knowledge.

The challenges of high risk and primary uncertainty are further magnified by the long-time horizons over which these risks and uncertainties are resolved. Biotechnology start-ups are specialized mechanisms for managing risks under conditions including: a) reliance on venture capital, which is attracted to high risk/high return b) contractual licensing relationships, which are needed to allocate rights to inventors, and c) the involvement of a much larger pharmaceutical company after a Phase II clinical study when more advanced drug development processes can be applied.

Integration of complex and heterogeneous knowledge

Integration across disparate scientific fields, approaches and functional skill sets is perhaps the most important aspect of drug development. The integration problem is not limited to biotechnology: building fighter jets or skyscrapers or conducting military operations all require integration of this kind. However, whereas many complex systems can be isolated into modular parts with well-defined interfaces enabling specialists to focus on separate components, biology cannot yet be modularized. Start-ups need mechanisms to bring specialists together and to facilitate the flow of information across organizational boundaries and across different disciplines—all in the face of primary uncertainty and long lead times. The biotechnology industry in particular has been built around a plethora of important alliances.[105,106] Henry Chesbrough has referred to this as the "open innovation" model (see Table 1) in which the pathways to market cannot necessarily be restricted to using a company's internal knowledge and suggests a very different organizing principle for research and innovation.[107,108]

For biotechnology companies operating in a rapidly changing environment, no matter how well planned the organization or project, something from outside will likely change unexpectedly and the company must be organized to expect and deal with this uncertainty. The company's most valuable asset, its people and its network or "entrepreneurial ecosystem", must be prepared and expect this uncertainty—teamwork and integration are critical and people must be well informed, ready to respond to change, and be prepared to lead or step back.[109] Therefore, integration within a start-up not only involves incorporating various specialties but involves recognizing that the importance of any one component at any given time may vary depending on the problem to be solved.

Table 1: Contrasting principles of closed and open innovation

Closed Innovation Principles	Open Innovation Principles
The smart people in our field work for us	Not all the smart people work for us. We need to work with smart people inside and outside our company
If we discover it ourselves, we will get it to market first	We don't have to originate the research to profit from it
The company that gets an innovation to market first will win	Building a better business model is better than getting to market first
If we create the most and the best ideas in the industry, we will win	If we make the best use of internal and external ideas, we will win
We should control our IP, so that our competitors don't profit from our ideas	We should profit from others' use of our IP, and we should buy others' IP when it advances our own business model

(Chesbrough, 2006)[108] (reproduced with permission)

Need for cumulative learning

Biotechnology enterprises must have a high capacity for learning in their team members because the pace of technology development is rapid and specialized networks are needed.[110] Indeed, most organizations need entrepreneurial learning when in a complex environment[111] and must "unleash the power of learning" and use knowledge more effectively to "learn how to do something better";[93,112] however, the necessity for learning is especially great in the biotechnology sector. It often less a matter of learning to do something better than learning to do something for the first time. Mistakes are common, not from incompetence, but because decision makers are "dancing on the edge of knowledge". When failure is more common than success, learning from failure is a key to making progress. Indeed, the learning can even take a start-up in an altogether new direction. To some extent this learning is connected to Complexity Theory in that it deals with the uniqueness of events and the indeterminacy of future scientific discovery.[113] Predictable pattern learning in such circumstances may not be possible.

Pascale alternatively describes learning as descending into the unknown, disregarding the proven cause-and-effect formulas, and defying the odds. "Discontinuous leaps, by their very nature, arise from unforeseen combinations, and are impossible to reverse engineer." Discontinuities do not lend themselves to logical explanation and do not respond predictably to direction beforehand.[114]

Learning can be at the individual, group, or organizational level and will likely spill over into members of the larger scientific and biotechnology community. However, organizational learning is what matters with biotechnology. Firms play a critical role as keepers of intellectual property (IP, patents and know-how), which will later be monetized through a deal with a strategic partner. The start-up is essentially a container for knowledge that will become the critical selling point for any future pharmaceutical partner. The core of this container is IP.

Requirements for a Biotechnology Start-up

As described in the previous section, biotechnology start-up companies succeed in part by the ability of their founders to assimilate complex knowledge and cope with the uncertainty in inherent in scientific discovery. Figure 1 shows a conceptual framework of the conditions for the success of a biotechnology start-up. Figure 4 summarizes the critical practices needed in this framework.

The learning organization and building a knowledge network

Several aspects of the learning organization need to be considered in a biotechnology start-up. Has a company put in place the right knowledge network? How do companies build an adaptive learning environment that integrates both internal and external expertise? What managerial practices encourage inquiry and probing questions to ensure that the knowledge base of the technology is being shared, expanding and proceeding along the development path? How do senior managers create a constructive network within which it is okay to make mistakes (encourage trial and error), particularly when complex or ambiguous situations arise?[115] How does the organization create an open environment that encourages key staff to seek out and invite testing of assumptions that underlie the core innovation idea?

The challenge of getting a start-up to an alliance stage is to create the requisite learning organization. To make this happen, consideration should be given both to the design of the organization and the mental models of the individual knowledge workers. Organizations should ideally be designed around knowledge networks (the Open Innovation model as described by Chesbrough), and individuals (mental models) and operate consistent with the values described by Argyris in Theory of Action.[115] To this end managerial practices should ideally encourage inquiry and use probing questions to ensure that the knowledge base of the technology is being shared and advanced along the development path. They also should facilitate a constructive network in that making mistakes is acceptable because of the need for trial and error when coping with complex or ambiguous situations. Key staff need to be encouraged seek out and invite testing of assumptions that underlie the core innovation idea.

Management in biotechnology start-ups requires an "absorptive capacity" to recognize, assimilate and apply external knowledge to achieve innovative and financial performance.[116] Management cannot allow a "core competence" to become a "core rigidity" whereby a "not invented here" syndrome gets reinforced and there is a refusal to learn from the external environment.[117] Integration of highly technical scientific knowledge across boundaries is crucial for adaptation and survival. Both the requisite organizational design or network and the requisite individual behavior of team members should be in place in order for a start-up to have some chance of success.[118]

Knowledge networks are the basic infrastructure for a start-up to establish a learning environment. Moreover, a pharmaceutical company will be more willing to invest significant amounts to advance a drug to the next stage if the science was built within a credible knowledge network that has also been validated by regulatory

Knowledge Network	**Integrated High Performing Team to Effectively Learn and build New Knowledge**	**Monetizing New Knowledge using Investor Experience**
CEO Executive Management Team 3rd parties	Exploration Exploitation Effective Learning	New Knowledge + Experienced Investors = Favorable Alliance

Figure 4: Anatomy of a biotechnology business: critical practices conceptual framework.
Adapted from Argyris, 2004[55]

Knowledge Network 1. CEO 2. Executive Management Team 3. Directors and Advisors 4. Third Parties	↔	Effective Action • Exploration • Confronting • Reflection examination • Encourage inquiry • Express fears and doubts • Exploitation • Valid information • Monitoring effectiveness	↔	New Knowledge 1. Formulation 2. Method 3. Proof 4. Efficacy in humans

Figure 5: Developing a knowledge network.
Source: Adapted from (Argyris 2004[55]; Cook et al., 2008[122]; Zucker et al., 1994[73])

authorities.[56,119] Biotechnology requires significant learning that builds on innovation and scientific knowledge in areas of immunology and molecular biology, and which differs from the rest of the pharmaceutical industry with its greater reliance on organic chemistry. The output of the knowledge network is new knowledge—know-how, patents, licenses, agreements— related to the new drug. They include the final formulation (properties of the drug), method of manufacture (how the drug is made), proof of concept (how the drug works), and safety and efficacy (is the drug safe and does it work in humans?).

In order for innovation (exploration) to proceed to commercialization (exploitation), learning must be successful on two dimensions: inter-organizational networks and individual information exchange within the start-up. Developing a knowledge network (Figure 5) and creating new knowledge must be approached at the time a biotechnology company is founded. First, the CEO must hire an executive management team (EMT) with the right mix of experienced team members that exhibit expertise related to the product manufacturing, clinical, regulatory, and marketing. Then the CEO and EMT build external networks to encourage individual exploration and integrate knowledge into the organization. The start-up must establish inter-organizational collaborations to help drive innovation and scientific knowledge. The use of boundary-spanning networks increases both learning and flexibility.[120] Building networks through alliances (contract research organization [CRO], external consultants, contract manufacturing organization [CMO]) is vital at the early stage of growth when learning is associated with exploration—failure to do so will likely result in "organizational death".[121]

Learning must be accompanied by an environment where individual exploration is encouraged — search, variation, risk taking, experimentation, play, flexibility, discovery, innovation — but not to the exclusion of exploiting or capitalizing on existing technology and techniques. Companies must employ processes that allow experts to constantly recalibrate their hypotheses (confronting ideas, assumptions, and bias) from the beginning of a project, and always be willing to jettison ideas that aren't living up to the initial thesis.

Biotechnology operates within a larger system in which three significant variables can have a positive or negative influence on the drug development process. As represented in Figure 6, these include emerging technology, which can influence the drug development process; the regulatory environment which can force changes the development path; and the marketplace into which the drug is to be launched.[5] The knowledge network must be designed in such a way that developments related to these variables are constantly monitored and incorporated into the network when necessary.

Weaknesses in knowledge networks can appear at any time, from early stage to maturity. Figure 7 summarizes the potential limitations in performance according to network size and network density. Norms are hard to establish in the early stages because roles and relationships between Actors are not clearly defined. This situation is similar to the hazard of the "liability of newness" in which a disproportionately large number of start-ups fail. With time, a full complement of EMT members, and frequent exchanges with external third-party experts, a team's performance will improve. Between the early start-up and an alliance-based stage, the EMT has the opportunity to build a frame of reference, trust, and reciprocity leading to smooth cooperation. Ties between team members and third parties become more reliable and denser, thereby facilitating transfer of knowledge. At this stage the greatest level of knowledge flow takes place, resulting in diffusion of innovations across multiple functions.[104]

A threat to the effectiveness of such learning is the possibility that individuals within the EMT will adjust to the organization before the organization can learn

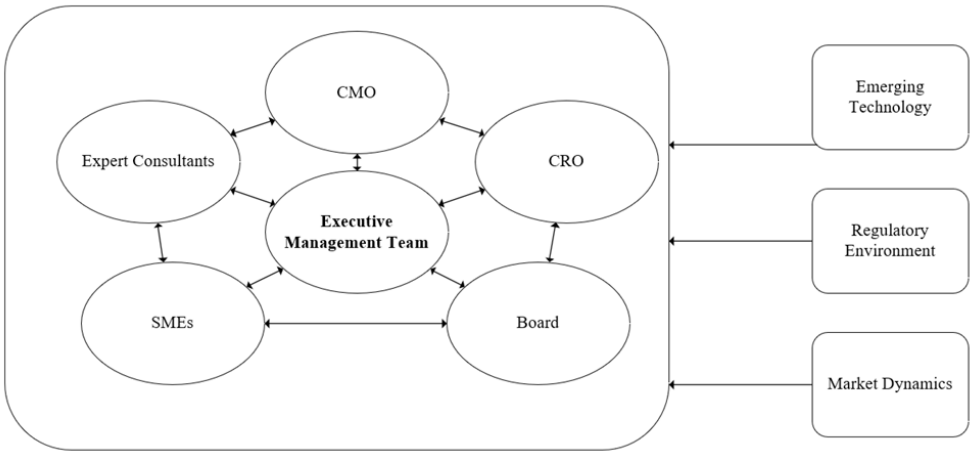

Figure 6: Knowledge networks within a larger system.
CMO = Contract Manufacturing Organization; CRO = Contract Research Organization

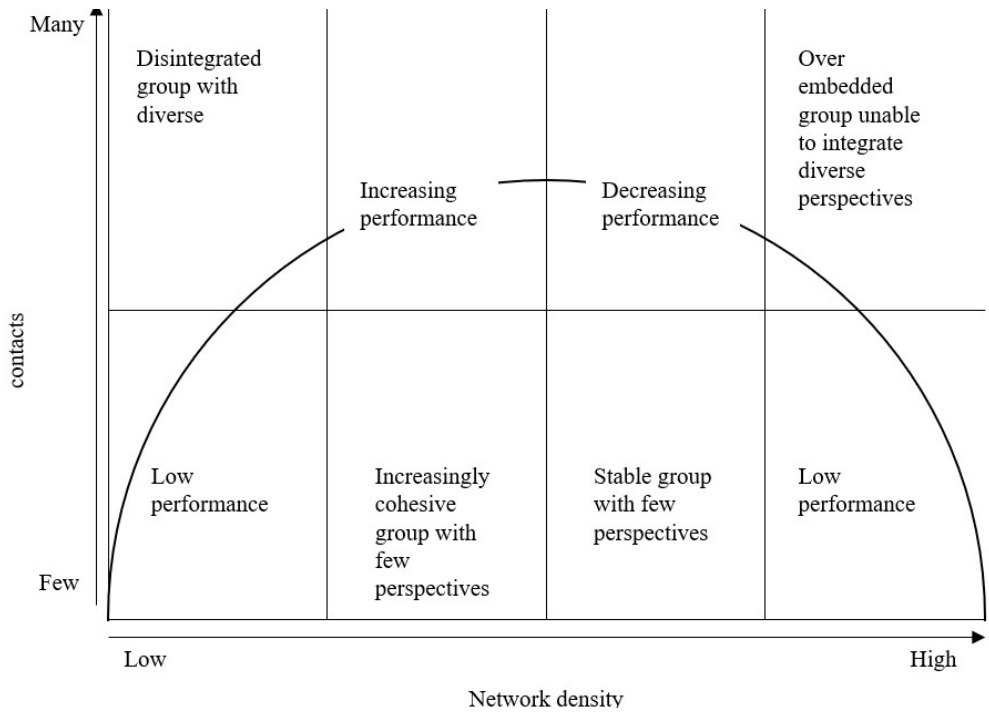

Figure 7: The inverted U-curve relationship between network density and performance.
Burt (1992)[123] Reproduced with permission

from them—Therefore, more prolonged socialization of new organizational members and limited turnover may be desirable to improve organizational and individual knowledge.[124] This has implications in early stage start-up biotechnology companies where members of the EMT are new to the organization. New staff and experts must be allowed to continuously challenge the drug development process and bring new perspectives that will move the product forward. Thus, knowledge networks must be complemented by a questioning environment with an acceptance of the unique contributions made by new team members.

Individuals can bridge roles to innovation by connecting networks: in the drug development context, they link the EMT, third parties and organizational stakeholders and are beneficial to innovation by brokering the flow of information and bringing together the wider network.[125] An individual who brokers the flow of

Table 2: Seeing cultures from different points of view

Perspective	Integration	Differentiation	Fragmentation
Orientation to consensus	Organization-wide consensus	Subcultural consensus	Multiplicity of views (no consensus)
Relation among manifestations	Consistency	Inconsistency	Complexity (not clearly consistent or inconsistent)
Orientation to ambiguity	Exclude it	Channel it outside subcultures	Force on it
Metaphors	Clearing in jungle, monolith, hologram	Islands of clarity in sea of ambiguity	Web, jungle

Martin (1992)[128] Reproduced with permission

information between others in a network has access to more information sources and can bridge across functions. For an EMT, a greater number of external contacts by individuals in bridging roles will likely increase the knowledge base. These contacts will allow the EMT to more readily acquire new information from outside the team. A large number of external contacts increases a team's intellectual capital and has a positive effect on its performance.[104]

Integrated cross-functional teams

Biotechnology requires a high degree of integration between science (process, development, preclinical and clinical), governmental regulatory bodies such as the US FDA and EMA, and commercial opportunity (physician acceptance and 3rd party reimbursement). Companies that set up practices to integrate these three elements into high performing cross-functional project teams will be better equipped to drive the drug development process forward and build new knowledge. Firms that establish practices that can get specialists to work collaboratively together in cross-functional project teams will more likely advance their products through the drug development process to improve and accelerate effective learning.

Teams include everyone in the knowledge network.[126,127] The team operates within a culture (repeated pattern or configurations of organizational behavior and span of accountability & authority).[128] The effective "action science" is the integration of the various functional areas (preclinical, clinical, regulatory and commercial) to create better solutions.[57,129]

There are many perspectives on organizational culture and this paper is not intended to go too deep into this topic (see Table 2). Martin has characterized three social scientific perspectives on organizational culture as follows: integration, differentiation and fragmentation.[128] Of these, the fragmentation perspective seems to best describe the start-up biotechnology with its focus on ambiguity and its reliance on connecting individuals in temporary, issue-specific coalitions. Patterns of connections vary according to the issue to be addressed. Whenever a new issue becomes important to researchers, a new pattern of connections within the knowledge network becomes important. The fragmentation perspective "reconceptualizes consensus" which acknowledges that members of the team sometimes change their view from moment to moment as new issues come into focus. Multiplicity of meanings is common and can have important practical consequences—this is particularly true when trying to interpret data.[128]

A fragmentation perspective requires a high capacity for reflection and examination in the way the team operates. First, knowledge is context-specific and needs a situated action for it to be created.[130,131] Individuals need to empathize the specific context of their knowledge to create and share new knowledge and to transcend their own limited perspectives.[105] There must also be a permeable boundary so that alternative actions can be accepted. Participants' diverse viewpoints and backgrounds can introduce multiple contexts, which are shared through dialogues and practices.

Knowledge assets are the result of the knowledge-creating process and are not limited to IP (know-how and patents) but also include the organizational capability to innovate ("knowledge to create knowledge") and social capital (the economic value of interactions among knowledge workers). One of the most important knowledge assets for a firm is the pattern of dialogues and practices—creative routines which make knowledge creation possible by fostering creativity—for exampling incorporating a feedback function that sharpens senses and helps to identify and modify the differences between predicted outcomes and reality.

To encourage creation of new knowledge (better solutions linking exploration to exploitation) management practices should delegate responsibilities to cross-functional teams and hold them accountable for the creation of new knowledge. While it is imperative for a technology to be understood, it also must be demonstrated to work. There are practical issues in getting a

drug manufactured, conducting preclinical testing in animals to show safety (no toxicity) and to show some evidence of efficacy, and then preparing a formal dossier (IND) to submit to regulatory authorities in order to be able to initiate human clinical studies. Getting this document filed reflects the nuts and bolts (exploitation) of the drug development process. Cross-functional teams are needed to integrate all the necessary technical areas (preclinical, clinical, research, regulatory, manufacturing and tech ops) to successfully complete this milestone event. Moreover, the IND should ideally be constructed in a way that clinical outcomes will demonstrate "New Value" by solving unmet needs, creating much better alternatives to existing therapies, and ensuring that patients have access to inventions. Unless all these aspects are integrated the project is at risk of failure.

Monetizing new knowledge and obtaining financial investors

Innovation may be defined as the creation of New Value that the marketplace understands and recognizes. The benchmarks for performance include whether drug companies are solving unmet medical needs by creating demonstrably better alternatives to existing treatments and by ensuring patient access to the benefits from using the new treatments. Start-up biotechnology firms need a creative deal-making capability to conclude a successful alliance. The alliance is the final link between exploration and exploitation at this stage of growth.

Start-up biotechnology companies are usually too small to justify a full-time business development executive. Typically, the expertise for business development in a small biotechnology company resides with the financial investors due to their wide network of contacts within the specific therapeutic area and a successful track record that will attract pharmaceutical companies. Furthermore, biotechnology deals can often be highly complex and involve sophisticated financial structures. In contrast the lead manager (CEO) and the surrounding management team are more likely to be scientists who can develop the technology but who lack sufficient commercial and financial engineering experience. Experienced investors typically will take a very active role in the business development process and are highly motivated to do so since a deal often leads to their exit and monetization of their investment.

Management practices ideally need to integrate expertise from financial investors into the organization to enhance the deal-making capability. The quality of the investor matters. Biotechnology start-ups backed by financial investors with a previous history of successful transactions in the specific targeted therapy will more likely achieve an alliance and get the best deal. Biotechnology financial investors have become more sophisticated because aside from a few giant scale ventures—like the sequencing of the genome—biotechnology has not been able to capture the imagination of generalist investors. Deal structures have become more complicated between a strategic partner and its collaborator's shareholders.

At the stage when company has successfully brought the drug through a Phase II clinical study, companies are more likely to conclude its best strategic deal if experienced financial investors take the lead in negotiating with the pharmaceutical company. The value of biotechnology products is not a precise calculation and, therefore, savvy negotiating skills combined with quantitative data play a role in getting the deal done.

In summary, this literature review points to the importance of integrating knowledge networks, diverse competent teams and deal-making investors for the success of biotechnology start-ups.

METHODS AND RESULTS

To explore current perspectives on integrating knowledge networks and how it relates to the success of a biotechnology start-up company, the author conducted a qualitative study using semi-structured interviews of two or three key Actors (total of 32) across seven companies. This sample size was sufficient to reach a saturation point at which no new themes or concepts were emerging.[132] The Actors were asked about their perspective related to how knowledge networks were built, the key factors needed for successful teamwork, and how or whether the financial investors contributed to a strategic deal. The Actors were from a variety of biotechnology fields, all of which were developing new and potentially blockbuster drugs—all with commercial values potentially exceeding $1 billion. Participants included at least one financial investor, the CEO and one member of the EMT.

The transcripts were coded to extract factors and themes.[133] The coding focused on "identifying, analyzing and reporting patterns (themes) within data" where the "a theme captures something important about the data in relation to the research question and represents some level of patterned response or meaning within the dataset".[134] Codes were derived from participants' words and added or modified as necessary when new meanings or categories emerged. All participants were guaranteed anonymity for themselves and their companies. Each interview was conducted using an interview guide (see Appendix) and lasted between 30 to 90 minutes.

The interviews provided informed expert views to better understand how each person viewed the

importance of establishing strong processes early on in the formation of the start-up and what contributed to getting these processes implemented. Themes emerging from the codes are shown in Table 3:

Result of Building Knowledge Networks

> "It is critical that people know what they don't know." – Participant #05

> "Start-up to [strategic partnership]: most biotech companies follow this model. Good technology is essential but not sufficient. How a big pharmaceutical company perceives the small biotech company is critical. Yes, a company can have interesting technology but what gets them over the hump is a feeling that the company is for real, there is real data and a team that can execute—this makes them feel more comfortable." – Participant #03

Table 3: Emergent themes from intervews with biotechnology company Actors

Theme	
Team Integration	Integration of each team member to share and coordinate effort.
Team Self-confidence	Confidence of team member to accomplish goals.
Teams Credibility	Credibility of the team to execute.
Knowledge Networks	Understanding knowledge and gaps.
Business Development	Ability to tell a story that the product/ technology will solve an important unmet need ("deal making").

For many companies, the "thrill" of the initial investment was like a shot of adrenaline. Most Actors had plans but had not deeply thought through what was needed for success. Most seemed to adapt over time, usually at the cost of a lot of money and time. Table 4 summarizes the Actors' qualifications in according to company. While several companies achieved success, most of these appeared to have done so through a process of trial and error.

Company #1 lacked manufacturing knowledge (EMT and CMO), which delayed the project. Specifically, there were issues related an automated filling process and whether the product could meet FDA standards if it was not filled aseptically—lack of this specific knowledge prevented the product from being tested in human trials under an FDA approved IND or meet the quality (robustness) standards expected by an established pharmaceutical company. While the Board and management recognized this deficiency, no initial action was taken in order to preserve cash until the next round of financing. Company #1 acknowledged that manufacturing expertise was needed but postponed the addition of this needed expertise. Company #1 assumed that the sterilization technique they had decided on was not technically difficult to achieve. Acquiring the necessary manufacturing insights was impeded due to a gap in their knowledge network.

Company #7 lacked clinical expertise. The various reason given by respondents were cost, ignorance, or hubris yet the company spent millions of dollars on failed clinical studies. Company #7 could manufacture a product that met all regulatory requirements but was not able to negotiate a simple clinical design with the

Table 4: Summary table of team completeness of biotechnology companies

Name of the Company	Qualified CEO	Balanced EMT	Knowledge Network	Extended Network
Company #7	√	*	√	√
Company #4	√	√	√	√
Company #2	√	√	√	√
Company #5	√	**	√	√
Company #1	√		√	
Company #6	√			
Company #3	√			

* Company #7 lacked a medical director but added later.

** Company #5 lacked a quality regulatory but added later.

CEO = chief executive officer; EMT = executive management team

regulatory authorities. While the company lost significant time and money on this failed effort, it did recover and learn from its mistake and was successful with a subsequent clinical study. The manufacturing and scale-up learning was successful; "scale-up" occurs in Stage 3 of development, where alliances are formed. There was an interesting interplay between an expert and the EMT. Each version of the product could then be tested in a timely manner using a standardized treatment protocol. This allowed for a rapid understanding of whether the formulation worked. There was also a very successful collaboration with a third party on the development of a delivery device. There was a 3-way interaction between one EMT member, the third party, and a panel of surgeons from the U.S., Europe and Japan. The result was a combination product that was far superior to anything else on the market. Company #7 however had assumed that its product worked so well that clinical design and target clinical indications were not such important considerations. Its clinical knowledge network was deficient.

Company #5 had problems with quality because it lacked expertise with good current Good Manufacturing Practice (cGMP) and its director of quality lacked credibility. Company #5 assumed that Israeli GMP alone could suffice. This caused considerable difficulty establishing credibility with a potential strategic partner. Additionally, company #5 failed to heed the warning of many potential strategic partners. A number of external auditors were brought in to assess their compliance with FDA standards and remedies to some of the deficiencies were proposed. However, funding concerns, and a lack of expertise within the internal staff resulted in the inability to internalize the knowledge generated from third-party consulting experts and resolution of the cGMP problems took too long to achieve. The delay cost the company 2-3 years in lost sales.

Company #6 lacked good preclinical expertise needed to understand its active ingredient. This was eventually remedied but at too late in process to be effective. Their failure to develop an assay for FDA required preclinical studies meant that the financial community did not have sufficient confidence in the company being able to achieve this learning and solve the problem and declined to provide further funding. Although they were able to manufacture the product and complete 99% of an FDA IND application the lack of a release assay meant that they could not complete the filing and were therefore unable to move on to clinical studies of their product.

Company #2 withdrew their product from the market despite gathering a necessary mix of expertise to reach the next stage of growth. Its network was built around solving one problem, but it was not flexible enough to solve a second. The Company #2 team solved their key learning problem, which was how to enhance the safety of a plasma-based product; this learning was accomplished by setting up a collaboration between the FDA and the company. It was informative for the team to learn how a government body and private company could work together to solve a problem. However, there was a second safety issue for which Company #2 assumed it had a solution, yet the assumption was never tested or challenged by internal or outside experts despite the availability of validated data.

Company #4, in the same way as Company #2, had a good mix of expertise but did not invest in knowledge related to drug mechanism of action. However, the company was able to recover, solve the problem and continue its strategic partnership. A good mix of experts was assembled, which was particularly strong in the area of preclinical and clinical development. However, less attention was devoted to manufacturing and transferring the manufacturing technology required a lot of rework due to lack of robustness and reproducibility. However, this problem was successfully overcome through a positive interaction between the CMO and an expert consultant. After the deal was complete, further work on understanding the mechanism of action was stopped. This deficiency turned out to be a mistake because it substantially delayed execution of the Phase 3 clinical study.

Company #3 lacked both the technical manufacturing expertise and an experienced Board. Transferring of the technology to the CMO's facility failed because of this lack of manufacturing expertise in the therapeutic category, resulting in major delays. There also remains a real lack of commercial and deal-making experience within the EMT and Board. None of the Board had a background in the product related industry. Company #3 had assumed that simple bench top prototypes could be easily transferred into a large-scale manufacturing facility. Company #3 was able to implement its technology at the bench level but has still not learned how to scale up.

In summary, the interviewees identified a number of knowledge deficiencies and that, in retrospect they could have accelerated solutions or minimized risks if they had had in place the right network of expertise. Some of the companies were ultimately able to reach the alliance stage of growth, however a more effective establishment of knowledge networks to recognize and reduce knowledge deficits could have accelerated learning and minimized the loss of time and sales opportunities.

Result of Team Performance

Team integration and credibility

Drug development teams must have a high degree of integration and utilize the right social values (mental models) to challenge and contest ideas. As Participant #28 stated, they must be "like a team of soccer players advancing the ball horizontally toward the goal".

No one person in the network can possibly solve all the questions. Flexibility, permeability and critical thinking are all necessary to get knowledge into the organization. Company #6's inability to develop and validate an assay of antitumor activity was a team failure between an outside laboratory and select executives within the company.

> "… Good technology is essential but not sufficient. How a big pharmaceutical company perceives the small biotech company is critical. Yes, a company can have interesting technology but what gets them over the hump is a feeling that the company is for real, there is real data and a team that can execute—this makes them feel more comfortable." – Participant #04

When considering the required knowledge that each company had to obtain there was certainly a "struggle" within most companies. Usually there were funding constraints that required a trade off with required expertise—this however turned out to be a false trade off since ultimately it cost the company much more in lost time and money. Usually this ambiguity was not addressed at all during budget discussions. In six of the seven companies, there appeared to be a good mix of empowerments. In general start-ups are usually understaffed and there is a willingness to both share and delegate responsibility. This survey did not find sharing or delegation to be an issue. In most cases alignment was achieved through high enough compensation to attract staff. Key Actors typically were compensated with generous stock options and large bonuses tied to milestones.

Company #7 decided not to hire a medical director due to budget constraints and instead relied on someone with extensive industry experience, although this did not include conducting clinical studies. All of the interviewed Actors readily admitted to this mistake but could not address why such a critical component was missing. Company #7 did not make full use of its research capabilities to learn how its product would likely work in a clinical setting before they filed the IND. The result was a failed clinical study. In this example, the CEO had given the Actors a lot of autonomy to experiment, but the team executed poorly.

Company #4 had a good mix of exploration and exploitation around demonstrating that its product worked in humans. However, it did not take the same approach with understanding the mechanism of action. From the beginning, Participant #15 had a clear vision of the product and the commercial application. The vision was rooted in Participant #15's deep understanding of one orphan disease, the community of affected patients and the unmet therapeutic needs for convenience in drug delivery. The team was given a lot of freedom to innovate and execute. Each member has a strong sense of what was needed and took responsibility to make it happen. However, there was a lot of infighting and complaining about too much rigidity. Innovation seemed to be stifled after completion of the Phase I study.

Company #1 had delayed adding manufacturing expertise the reason given being "to reduce overhead spending". The need was stated but the risk of avoiding action was not discussed. With some aspects such as device design there was very open and direct discussion which led to a lot of hypothesis testing and challenges. With other aspects of the drug such as the commercial value of a recombinant protein there this willingness for open discussion was not evident. While having the appearance of a high performing team, Company #1 neglected to discuss issues around structure, roles, and responsibilities. Indeed, one respondent had previously experienced the same problem in a previous company but was not able to talk about it with the CEO. New Actors joined the team at Company #1, bringing extensive expertise developing similar drugs; however, there was some friction between older and newer members ("I thought that was my responsibility") and possibly preventing the transfer of new knowledge from new members into the organization. There was limited commercial (marketing and sales) input into their drug development process—better feedback, specifically from the surgical community, was lacking. (This was the opposite of Company #7 where success was achieved from a formal trial and error process with surgeons and the device manufacturer.) This weakness was cited in the interviews, but it had never been openly discussed at the time. Considerable effort was devoted to a 2nd generation product which seemed to be diluting the earlier efforts devoted to the 1st generation product. There remained considerable uncertainty around the 2nd generation product since no assessment of this commercial value was ever made.

Company #5 delayed hiring of quality and manufacturing expertise in part due to its reliance on one individual who had a strong history with the company and with its CEO but whose background was in R&D. The CEO did not perceive the R&D director's weaknesses in this respect. The problem was noted within the company at the time but never discussed. Successful

implementation of an organizational design and a "way of working" require open communication. Oftentimes there was an unwillingness to discuss issues that could have significant impact on the budget. In the end company #5 filed an IND without doing the necessary work in process characterization and good manufacturing processes and resulted a rejection of the IND by the FDA.

At Company #2 the financial investor had a clear vision of the product and the commercial application from the beginning. The company had a variety of other products in the pipeline which they dropped to focus on FDA approval of its lead product. This decision emphasized the need to focus on exploitation of the lead product and eliminate all other "so-called" distractions. The management team culture lacked the good practice of challenging key assumptions. There was a lack of consensus around how to operate as a company. The R&D and medical director believed that the company had to do everything possible to improve safety and there was a feeling that the CEO and Board were willing to sacrifice research efforts for short term financial gain. R&D wanted far less structure so as to be able to explore solutions for potential problems; management wanted a focused effort with clear milestones and financial returns.

Company #6's team experienced a lot of friction. The animosity was palpable and at times prevented all relevant work. The CEO was "very controlling" and the EMT members chafed at the lack of freedom and flexibility. The medical director was "furious" about the lack of freedom to operate and would discuss it openly with an outside consultant but never with the CEO despite having ample opportunity to do so. The team had decided that the company could file an IND without developing a release assay, but the approach was subsequently rejected by the FDA. Company #6 had an excellent concept aimed at meeting a significant unmet treatment need in an advanced cancer indication. The atmosphere was described by several Actors as "top down" and not open to experimentation and exploration. The overall environment was plagued by a "poisonous acrimony" with a lot of infighting and animosity.

The Company #5 team was very focused on the goal and had a high degree of collaboration. Delegation of responsibility was effective, and the right level of structure was achieved. However, Company #5's application of values was inconsistent: there was a deep denial about problems in manufacturing quality and there was a lot of open experimentation surrounding clinical exploration and development. The head of quality complained about the R&D person's role in manufacturing but did not discuss the issue with the CEO for fear of being alienated.

Team self-confidence

All Actors were willing to place bets on future performance of their biotechnology start-up. In the seven companies analyzed there was no lack of confidence, and also a willingness to make investments in time and money. When asked about the likelihood of financial success through an alliance with a pharmaceutical company, almost half (15 out of 32) had a very high confidence of success. All but three had at least a medium level of confidence (Table 5). High was defined as greater than 50%, medium was defined as around 50% and low was defined as less than 50%. This level of confidence may seem extraordinary given that less than 1% of drugs are successful. This data must be viewed with some skepticism—it is natural that among the successful companies, the Actors looked back with a sense of optimism and confidence. However, the interviewees' opinions are likely consistent with others in the industry.

Table 5: Confidence level among Actors interviewed

	Level of confidence		
	High	Medium	Low
Company #6	1	1	2
Company #7	5		
Company #4		4	
Company #2	1	2	1
Company #5	3	2	
Company #1	5	1	

Confidence level was based on response to questionnaire item on Actors' impression of likelihood of success at the time they joined the company (High, >50%; Medium, 50%; Low <50%)

But perhaps this confidence is what is necessary to get started. A common quote from many of the Actors was along the lines of "if at the beginning, I knew what I needed to do, I never would have started".

Result of Business Development with Financial Investor

> "You have to have a product; you are selling hope for a product; hope for something that is clinically relevant; really has clinical meaning. If an idea is weak, it doesn't matter if the product is good; you have to understand the need for the product; marginal improvement is not going to fly; the idea has to be strong—some medical problem solved or some benefit, but the benefit has to be clear." – OR#03

> "Big Pharma and Biotech need each other. Biotech will be killed if they do it all themselves—you need more experience than you think. Big Pharma simply doesn't have

the organizational innovation, creativity and flexibility for new drugs." – Participant #01

Biotechnology is usually considered too technical for generalist financial investors and this study seems to confirm the role of the highly specialized financial investor. Participant #07 of Company #2 says that "biotechnology is too tough and uncertain" and his firm has since stopped investing in biotechnology. Participant #07 was able to use the expertise of a world-renowned scientist to minimize the risk to a potential partner. The potential strategic partner was identified early and there were close linkages with the potential partner. The partner already had a product in the market and an extensive network. Negotiations with the partner were successfully concluded by Participant #07, a highly experienced financial investor in the related industry.

Company #7 had a strong multidisciplinary team that supported the financial investor who was able to direct the negotiations "like a conductor". The CEO and lead investor were very experienced in the field and were successful in getting an alliance partnership deal with a large pharma company who have subsequently acquired Company #7.

Company #1 required specific preclinical and clinical expertise in the field, and at present still lacks this expertise. Company #1 was slow to identify and target a partner and clearly define what a strategic partnership should look like. There was also limited marketing and commercial expertise among the EMT and Financial Investors. This gave a distorted view of the value of the company—the initial funding was at a half or a third of the level that investors were seeking, whether as value or as funding by an additional investor. Their lack of deep industry experience resulted in a failure to reach the alliance stage.

Company #4's medical director built a financial model which detailed the value to the company of a long acting formulation. This enabled Participant #16 to credibly use the model to negotiate a deal with a large pharma company that had been identified early on and had the advantage of existing collaborations. Two other significant players in the same therapeutic area were also potential partners; one was approached early on and collaboration was established. The CEO of Company #4 had a keen understanding of the patient population needs and the value of the knowledge and was able to get a $200m + deal from the pharma partner.

Company #3 had a potential strategic partner identified at an early stage which they already had close linkages with. However, the lack of deal-making experience within Board and management prevented any creative framework for an agreement with the partner.

Company #5 lacked expertise on the Board and EMT with specific deal-making experience in its target indication and getting to an alliance stage took longer.

Company #6 lacked expertise on the Board. None of the financial investors had biotechnology experience, much less specific product expertise and the company subsequently went bankrupt.

DISCUSSION AND CONCLUSIONS

Biotechnology offers the hope to significantly improve healthcare in the 21st century. Enormous scientific efforts have been expended to achieve this potential. If the past is an indicator the future, society will be investing tens of billions of dollars every year in biotechnology. However, most biotechnology companies are unprofitable, cannot sustain themselves, and are too early in product development for a partnership with a pharmaceutical company. Drug development has become longer and costlier, in part because of the greater demands from regulatory authorities. Furthermore, there is more pressure from government and third-party insurance companies to cut drug prices and thereby reduce the value of a potential drug. Despite the clear risks to future return, there remains a willingness to invest. The purpose of this review and survey is to help in thinking through how to make biotechnology in the start-up context more successful or, conversely, how to diagnose potential problems.

The journey from ideation and patent application to commercialization is a decade long process that must be managed in stages. This review and survey investigated for elements that may improve successful initial stages of biotech start-ups. Although most of the companies surveyed were ultimately able to reach the scale-up stages of development, some ultimately failed due in part to themes that were revealed in the survey. These themes included the successful implementation of good business processes that create a learning environment, which in turn enhances exploration and exploitation.

FUTURE RESEARCH

Additional research is needed to confirm if any factors uncovered in this paper provide significant improvements to start-up biotech companies. A theoretical model fitting the factors and relationships believed to represent key components to a successful start-up is shown in Figure 8.

The right mix of experienced senior executives would appear to be critical in the formation of a biotechnology start-up. A team of diverse drug development experts connect establish the foundation to strong Team Credibility, Team Integration, Team Self-Confidence, Knowledge Network, and business development. The team must have specific expertise related to the product

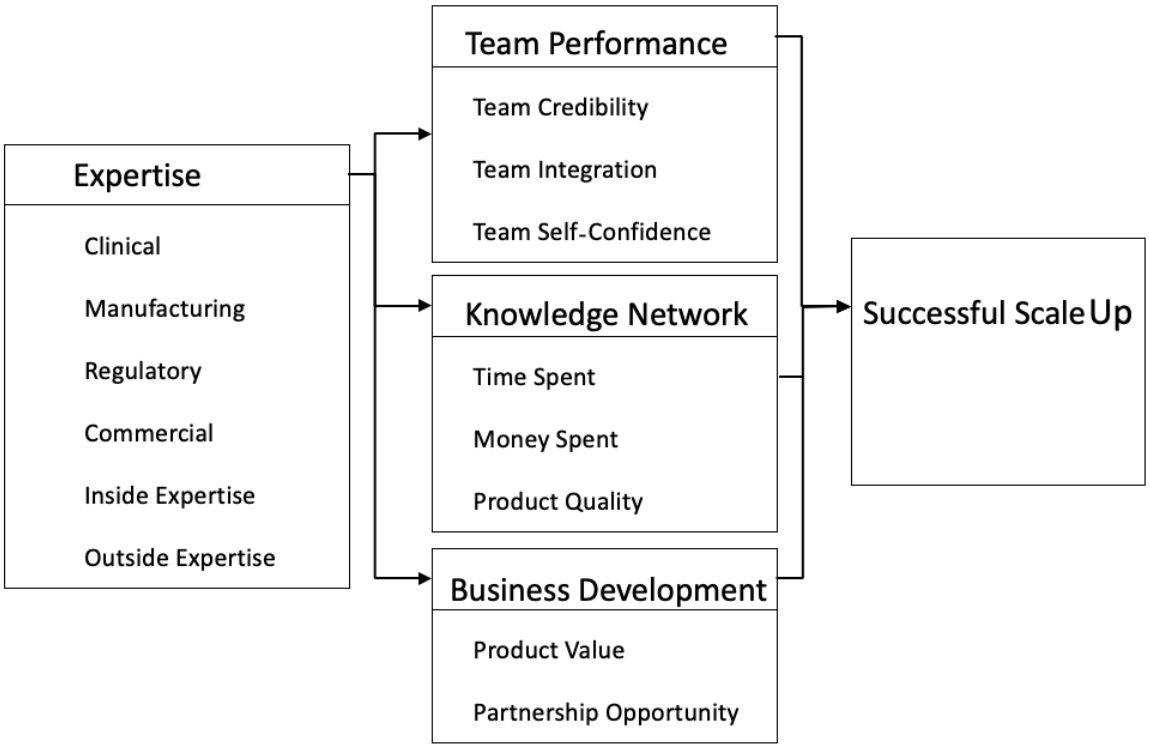

Figure 8: Components of sucesssful start-up biotechnology companies.

under development including manufacturing, clinical, regulatory and commercial. Furthermore, the expertise must include inside and outside perspectives. Third-party networks are the basic action design for expanding the knowledge base within an organization. Start-ups do not have all the capabilities internally and an "open innovation model" is required to secure needed expertise. Getting all elements in place is necessary; indeed, missing any one can be a fatal misstep, with a high probability that the company and all the Actors will lose 100% of their investment in money, time and options.

CONCLUSION

Society must look critically at how to foster innovation and achieve biotechnology's promise of innovative therapies and improved quality of life. While there are certainly many examples these are more the exception when one considers the industry as a whole. It is time to step back and better understand the factors of success and how they can be modeled to improve outcomes.

The relationship between achievements in science, technology and economic success has been long established, but the path is not always predictable and the process by which intellectual concepts move toward commercialization for the benefit of society is not well understood. Many factors can contribute to innovation: these include fluidity of capital, flexibility of the labor pool, government receptivity to business, information communication technologies, private sector development infrastructure, legal systems to protect IP rights, available scientific and human capital, marketing skills, and cultural propensity to encourage creativity.

But, perhaps an underlying question: can the science of biotechnology be translated into a business? It would appear that the answer, based on the experience to date, is no. Biotechnology has not yet been profitable, nor has it been particularly productive in terms of turning scientific advances into drugs. This answer is correct only if we take existing organizational arrangements and existing management technologies as a given. What this paper proposes is that biotechnology requires novel business structures as a means to encourage innovation and new knowledge. At nearly 40 years from the inception of biotechnology, we are still learning what such science-based enterprises might look like, how they can work, and what kind of management skills are needed to lead them. Much has been learned, but so much more needs to be learned. The challenge for scholars and practitioners is to better understand the business of science and the management of knowledge.

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APPENDIX

Interview Guide

Learning culture

1. Tell the story of the venture and why it was successful. Did the company have the necessary pre-conditions for success? Was anything missing?
    a) Technology with clear commercial potential
    b) Protected intellectual property
    c) Orphan Drug Designation (ODD)
    d) Preclinical data was needed for success? How was this process managed?
    e) Limited competition for the therapeutic area
    f) Experienced Scientific team
    g) Adequate initial financing
    h) License agreement with the University
2) Describe the learning environment. What kinds of networks were used to expand learning? What were the key alliances, both external (CMO, CRO, etc.) and internal (project teams); how did the two interact?
3) How was learning enhanced? How were skills developed? Were academic researchers brought into the company during the spin out?
4) Was there a process to integrate or transition university researchers into the company? Are there any special challenges to do so?
5) How were public doubts raised? How are technical questions vetted within the scientific community? How are outsider experts used to question assumptions and data?

Teamwork

1) Did the company integrate various functions into a project team? Were processes put in place to ensure successful team performance to drive development?
2) How were delays, uncertainties and ambiguities handled in the cross-functional teams?
3) How was the identity of the scientific team aligned with New Product Development cross-functional teams? How were the needs of the scientists supported?

Leadership

1) Describe the leadership style of the CEO regarding the project teams: delegation vs. centralized. How were teams supported and monitored?

Business development

1) Describe the business development function? What (if any) was the relationship between the function (processes and practice) and the financial investors? Did the financial investors have a role in the strategic deals?
2) How experienced was the initial investor in the field or in biotechnology in general? Was it a venture capital or angel investor?
    a) Describe the events surrounding the first successful alliance.

Other

1) (thinking back to when you joined the company) Your impression at the time of the likelihood of success of drug (>50%, 50%, or <50%)

Company History

Summary of each company's status:

- Company #1: developed product and concluded a deal with a larger pharmaceutical company
- Company #2: successfully developed a product and concluded a deal with a larger pharmaceutical company
- Company #3: Currently developing a product for transfusion therapy
- Company #4: successfully developed product and concluded a deal with a larger pharmaceutical company
- Company #5: developed a product and concluded a deal with a larger pharmaceutical company
- Company #6: Went after failed development of an antitumor antibody
- Company #7: successfully developed a surgical product and concluded a deal with a larger pharmaceutical company

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Business correspondence and inquiries should be addressed to *editor@CommercialBiotechnology.com* or to thinkBiotech LLC, 1133 15th Street NW, 12th Floor Washington, DC 20005.

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