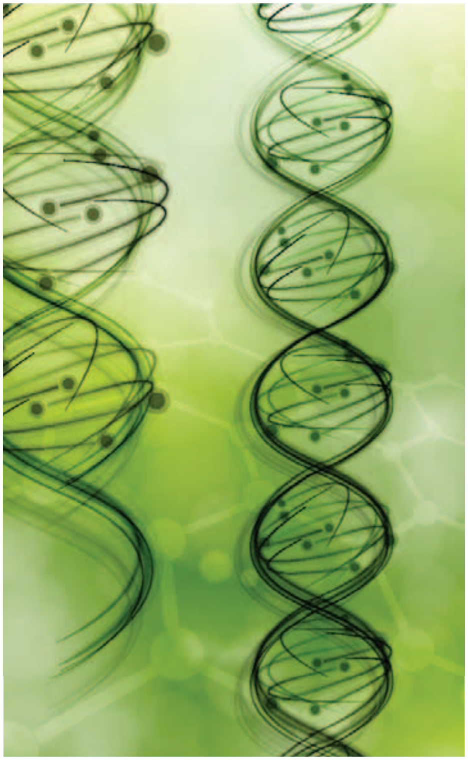

Bioscience at a Crossroads

Access and Benefit Sharing in a Time of Scientific, Technological and Industry Change:

Industrial Biotechnology

CBD

Bioscience at a Crossroads:
Access and Benefit Sharing in a Time of Scientific, Technological and Industry Change: Industrial Biotechnology

Sarah A. Laird

About the Author and Acknowledgements:

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The author would like to thank all of those who offered their time, assistance and thoughts to the research process that produced this document. Particular thanks are due to Anthony Arundel, Valerie Normand, Sam Johnston, Marjo Vierros, Geoff Burton, Paul Oldham, Kathryn Garforth, Olivier Rukundo, Beatriz Gomez, Eric Hoffman, Jay Short, Robert Friedman, and Michele Garfinkel for assistance with research and helpful comments on drafts of this document. We would also like to thank the Northern Territory Government of Australia for their support of earlier research and this process.

Published by:
Secretariat of the Convention on Biological Diversity 2013

ISBN Print: 92-9225-489-8

Photos:
Shutterstock

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Note that separate policy briefs review ABS issues pertaining to the pharmaceutical, agriculture, botanicals, cosmetics, and food and beverage sectors. The reader is also referred to the overview brief in this series: Laird, S. and Wynberg, R. 2012. Bioscience at a crossroads: Implementing the Nagoya Protocol on access and benefit sharing in a time of scientific, technological and industry change. Secretariat of the Convention on Biological Diversity, Montreal. The overview and other industry briefs are available at http://www.cbd.int/abs.

INTRODUCTION

Industrial biotechnology has come of age in the last five years. Advances in science and technology, combined with concerns over climate change, energy security, and an interest in more efficient, cost-effective and green manufacturing processes and products, have led to rapid growth in this sector. With increased and significant government support, particularly for biofuels, industrial biotech is "now mature enough to be scaled up from a laboratory of curiosities to full commercialization."[1]

Biotechnology is defined by Article 2 of the Convention on Biological Diversity (CBD) as "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use". This definition is also included in the Nagoya Protocol on Access and Benefit-sharing (Article 2). Biotechnology includes a wide range of constantly evolving technologies and activities that are applied in a range of sectors. These include:

- *Healthcare or red biotechnology*, the largest and most profitable sector, refers to a medicinal or diagnostic product or a vaccine that consists of, or has been produced in, living organisms and may be manufactured by recombinant technology;
- *Agricultural or green biotechnology* encompasses a range of modern plant breeding techniques including genetic modification; and
- *Industrial or white biotechnology* uses "the extraordinary capabilities of micro-organisms and enzymes, their diversity, efficiency, and specificity"[2] to make bio-based products from agricultural feedstocks and other biomass. Industrial biotech is employed in a wide range of industries, including chemicals, plastics, food and feed, detergents, pulp and paper, electronics, automotive, textiles, bioprocessing catalysts, and biofuels.[3]

In recent years, increasing numbers of large companies have jumped into industrial biotechnology and an extraordinary number of partnerships have been formed in an array of industries, and around the world. From snack foods, sneakers, cosmetics and jeans to biofuels, cars, agriculture, and the active ingredients in drugs – virtually every manufacturing sector incorporates an industrial biotech element today.

Research and development (R&D) in the sector of industrial biotechnology is, however, difficult to track. Industrial biotech processes and products are often neither sold nor patented, and are instead developed and used within the same company, and are protected through secrecy; many companies are privately-owned and so do not disclose their practices to shareholders; and industrial biotechnology is very lightly regulated by most governments. Few governments collect data on this sector, and most are struggling to come to terms with the novelty and implications of its technologies. As a result, it is difficult

"It is possible to do this research in a way that helps countries, and takes care of the three key pieces – that it is sustainable, is done with prior informed consent, and shares benefits. At Diversa we signed many agreements, in many countries, and none of our products made billions of dollars, but some made money, and we were able to share some benefits."

– Eric Mathur, Vice President and Chief Technologist, SG Biofuels

to fully grasp the scope, size and approach of much industrial biotechnology research and development, including demand for access to genetic resources.

It is evident, however, that companies retain an interest in novel microorganisms. Most companies source these from existing internal and external collections, from their own backyards, and a few from field collections overseas. Industry's main interest is enzymes that can withstand industrial process conditions like extremes of temperature, pH, and pressure, which means that companies bioprospect in extreme environments, as well as areas of high species diversity and unique ecological niches. With synthetic biology, nanotechnology, and other advances, researchers can improve upon the enzymes they already have, but nature continues to lead them to genetic novelty and diversity they would otherwise not find. Companies also often access genetic material digitally today, rather than through a transfer of physical material, as gene sequences are published at exponentially increasing rates and decreasing cost.

Industrial biotechnology can have mixed effects in the areas of conservation and sustainable use. It can contribute to biodiversity conservation by reducing consumption of fossil fuels, and so emissions of greenhouse gases, by relying on biological processes that use renewable raw materials. New technologies have also produced cleaner, more efficient manufacturing processes that pollute less and reduce waste.[4] Other possible applications might include heat-tolerant coral reefs, pollution-sensing soil microbes, treatments for diseases affecting wild animal populations, and the controversial concept of "de-extinction", in which extinct species are recreated using the tools of synthetic biology.[5]

It should come as no surprise that as the sector solves one set of problems, new and different ones arise. For example, the way biomass is currently sourced for biofuels is considered unlikely to reduce greenhouse gas emissions, and in some regions high biodiversity forests and 'marginal' or 'degraded' lands, for which there is no agreed-upon definition, are cleared for biomass production.[6] The basic model is one in which large quantities of low value biomass are converted into high value products, so the pressure on finite land and resources has become significant.[7] In some regions, food crops are supplanted by feedstocks, and indigenous and local communities and traditional livelihoods are displaced through land grabs.[8] The industry also runs the risk of releasing genetically modified, or synthetic, organisms into the environment in ways that damage natural genetic diversity or create invasive species.

Within this sector, awareness of the Nagoya Protocol and the Convention on Biological Diversity is extremely inconsistent, with some companies and researchers actively involved in signing ABS agreements and attending CBD meetings, and others entirely unaware of the CBD. The timely arrival of the Nagoya Protocol could not only help raise awareness of the CBD and promote the equitable sharing of benefits arising from the use of genetic resources. In conjunction with other policy measures, implementation of the Protocol could also strengthen the potential links between industrial biotechnology, conservation, and the sustainable use of biodiversity.

MARKET AND BUSINESS TRENDS

There is hardly an area of industrial activity today that does not involve some form of industrial biotechnology, and yet most of this is invisible to the average consumer (Table 1). In the food industry, for example, industrial biotech produces flavours and colours, new vitamins, improved enzymes and emulsifiers, as well as ways to assess food safety and treat waste, but few are aware of its role.[9]

Most industrial biotech products take two to five years to reach the market,[10] which is a significantly shorter time than pharmaceuticals. They also cost a great deal less to develop, in part because of less stringent safety and efficacy testing, but they tend to generate significantly smaller revenues than pharmaceuticals, usually between $10 - $200 million. Companies may market hundreds of products, so the industrial biotech business model is dependent upon a larger number of products of lower value than pharmaceuticals, rather than a few blockbusters.

Following is a quick review of three areas of recent growth in the industrial biotechnology sector: biofuels, bio-based chemicals, and bioplastics.

Biofuels

Biorefineries convert sugars, oils and proteins derived from renewable biomass into biofuels, chemicals and materials like plastics and polymers, much as a petroleum refinery converts crude oil into fuels and chemicals, with multiple products and revenue streams. The main biofuels in use today are ethanol, made from crops like sugar cane and corn, and biodiesel, which can be obtained from oil crops like oil palm, jatropha and soybeans. Conventional or 'first generation' biofuels like these are relatively low tech and are well-established in commercial markets. Advanced or "second or third generation" biofuels are still in development, are more high tech and efficient, and are the portion of the industry that involves biotech through the use of genetically modified organisms. Advanced biofuels include cellulosic biofuels, algae-based biofuels, and bio-synthetic gas derived from woody biomass, grasses, agricultural by-products, algae and seaweed.[11]

Researchers have shown increasing interest in biomass from oceans and aquatic ecosystems, in particular algal oils. These are still under development but are considered to have uniquely high yields, are fast growing, and their use as biomass might remove pressure from land, although it could instead shift pressure to other biomes and raise a suite of different problems.[12] A great deal of recent R&D has also focused on enzymatic conversion of cellulose, which is the cheapest and most abundant source of renewable sugars,[13] but with potential environmental and social

"We did a preliminary calculation on what a company in Michigan producing ethanol from wood biomass would need to produce 40 million gallons of ethanol. The mid-range of their calculation came to 71,000 acres of timber annually, an area the size of Washington, D.C. This is just one company making one product in one facility. DuPont is making a bioplastic through synthetic biology, turning corn into plastic used in clothing and fibers. Its single plant in Tennessee consumed 6.4 million bushels of corn from 40,000 acres of farmland, just to make one product. The idea that we can produce all of our stuff through engineered microbes and biomass is very questionable. Even if they increase the efficiency of these processes, they still need a lot of land to produce enough feedstock to replace oil. It's unclear if enough land actually exists to create this 'bioeconomy' and to feed the world's population that is currently using much of that arable land for food production"

– Eric Hoffman, Friends of the Earth

problems of its own. These include the loss of biodiversity and forests, conflicts over land, and a lack of local control over this new land use practice.[14]

In response to these concerns, a number of companies are focusing R&D efforts on increasing yields from feedstocks, and diversifying raw material sources. Consumers in some regions are also demanding certified sustainable feedstock, and voluntary certification schemes and national regulatory frameworks increasingly include sustainability criteria and standards.[15] These standards could also apply to bio-based chemicals, bioplastics, and other products of biorefineries.

Bio-based Chemicals

Recent advances in science and technology make it possible to manufacture traditional chemicals from renewable biomass instead of petroleum.[16] Industrial biotech production of chemicals uses enzyme-based processes that operate at lower temperatures, produce less toxic waste and fewer emissions than conventional chemical processes, and often require less purified raw material.[17] The main end uses of bio-based chemicals are as active pharmaceutical ingredients, organic chemicals, cosmetics, polymers and fibres, agrochemicals, food additives, detergents, and paints and coatings.[18]

In 2010, bio-based chemicals made up 3.5% of base chemical sales, 9.1% of specialty chemicals, 11.7% of consumer chemicals, and 33.7% of active pharmaceutical ingredients, and these percentages are steadily increasing. Sales of bio-based chemicals are estimated to rise to 15.4% of all chemical sales in the European Union (EU) by 2017.[19] An analysis by the US Department of Agriculture (USDA) broke down the potential markets for bio-based chemicals in the US in 2025 as: 6-10% of commodity chemicals, 10% of polymers, and 45-50% of specialty and fine chemicals.[20]

The chemical giant DuPont's industrial-biotech sales went from $50 million in 2007 to $200 million in 2009, and are projected to grow to $1 billion by 2015.[21] Among other partnerships, DuPont has developed a joint venture with Tate & Lyle that combines DuPont's polymer manufacturing expertise with Tate & Lyle's experience in milling and fermentation. The joint venture, DuPont Tate & Lyle BioProducts, is focused on production of propanediol from corn and other feedstocks. Propanediol is a chemical used in cosmetics, laundry and cleaning products, as well as engine coolants, de-icing fluids and other applications.[22]

Many biofuel companies have realized that they can use existing production processes to enter bio-based chemical markets that have lower costs and potentially higher returns than biofuels. Integrated refineries merge chemical and fuel production into a single operation, converting a broad range of biomass feedstocks into biofuels, biochemicals and biomaterials. By doing this, high value, low volume chemical products (e.g. $10-1000/litre) that provide higher margins can supplement earnings from lower value fuel (e.g. $1/litre). Many of the top biotech companies working in biofuels are also those working in bio-chemicals and related areas (Table 2). This is similar to the economics of traditional petrochemical refineries, which dedicate 7-8% of crude oil to chemical production that results in 25-35% of profits.[23]

Bioplastics

Plastic consumption is expected to grow steadily in the coming decades, leading to increased use of crude oil to make plastics and the dangerous accumulation of plastics in the environment. Bioplastics or biopolymers are an alternative to these products. They are biodegradable and/or have bio-based content produced from renewable raw material.[24] Bioplastics from renewable sources were a niche market in 2001, but their use has exploded over the last decade, with annual growth of 19%. Bio-based versions of the main types of plastic are emerging and are used not only in packaging, but also automobile manufacturing and consumer electronics, with companies like Fujitsu, Mitsubishi, Philips, Siemens, NEC, and Sony actively working in this area.[25] Frito-Lay, controlled by Pepsi-Co, is adopting compostable potato chip packets, and Walmart is also expanding its use of bioplastics.[26]

GLOBAL MARKETS

Global revenues for goods produced using industrial biotechnology in 2010 were estimated at between $65-78 billion annually, with the 2020 market estimated at $95 billion, and the 2030 market at $390 billion.[27] In 2010, the ethanol and biodiesel industries reached a combined wholesale value of $56.4 billion, and one estimate of growth, assuming a continued supportive policy environment, predicts sales of $112.8 billion by 2020. By 2020, around a fifth of biofuel sales are estimated to be advanced biofuels that are not currently on the market.[28]

The global market for industrial enzymes was $3.3 billion in 2010, and 6.6% growth rates are anticipated to produce

Geyser Sol de Manana, Bolivia

2015 revenues of $4.4 billion. The use of industrial enzymes is spread across several industries, including food (which accounts for 45% of industrial enzyme use), detergents (34%), textiles (11%), leather (3%), and pulp and paper (1.2%).[29] The emergence on the market of bio-based chemicals and bioplastics from companies like Solazyme, Gevo and Amyris, are contributing to overall growth.[30]

LEGAL AND REGULATORY CONTEXT

Policy measures and incentives introduced in the last decade to promote the biofuels industry have resulted in an explosion of biorefineries. More than 25 countries currently have mandates and supportive regulatory environments for biofuel production, including the EU (The Renewable Energy Directive, 2009), the US (The Renewable Fuel Standard, 2005), and China (which aims to replace 15% of conventional energy with renewable energy by 2020, partly by investing around $800 billion in this sector).[31] Brazil, one of the top three largest producers in the world (along with the EU and the US), put incentives for ethanol production from sugarcane in place in 1975, and has a National Program on Biodiesel Production and Usage.[32]

In Europe, government support has also focused on maintaining a competitive chemicals industry. Once the world's

TABLE 1. Consumer Products Made with Industrial Biotechnology

CONSUMER PRODUCT	OLD MANUFACTURING PROCESS	NEW INDUSTRIAL BIOTECH PROCESS
Bread	Potassium bromate used as preservative and dough strengthening agent	Genetically enhanced microorganisms produce baking enzymes to enhance rising, strengthen dough and prolong freshness
Vitamin B2	Aniline and other toxic chemicals used in nine step chemical synthesis that produces hazardous waste	Genetically enhanced microbe developed for one step fermentation process, using vegetable oil as a feedstock and sugar as a nutrient, and using 33% less energy
Personal care	Chemical ingredients such as propylene glycol and butylenes glycol from petroleum are used as solvents to mix ingredients	Genetically enhanced microbe produces 1,3 propanediol from renewable feedstocks, used as solvent, humectant and emollient
Cosmetics	Mineral oil and petroleum jelly from fossil fuels	Metathesis chemistry applied to convert renewable vegetable oils to higher quality ingredients to replace petrochemicals
Detergent	Phosphates added as a brightening and cleaning agent, but cause water pollution	Microbes or genetically enhanced fungi produce enzymes; protease enzymes remove protein stains; lipases remove grease; amylases remove starch
Textiles	New cotton textiles prepared with chlorine or chemical peroxide bleach	Use of biotech cellulose enzymes to produce peroxides, allowing bleaching at lower temperatures and neutral pH range, with higher quality product.
Paper	Wood chips are boiled in a harsh chemical solution to yield pulp for paper-making	Wood bleaching enzymes produced by genetically enhanced microbes selectively degrade lignin and break down wood cell walls during pulping, reducing use of chlorine bleach and release of dioxins in the environment
Furniture	Polyurethane foam produced from petroleum	Polyols (such as Cargill's BiOH or Dow's Renuva) derived from soy and other feedstocks, mixed with other ingredients to create a flexible foam using much less energy
Polyesters	Polyester, a synthetic polymer fibre, is produced from petroleum	Bacillus microbe ferments corn sugar to lactic acid, which is heated to create a biodegradable polymer (e.g. Nature-Works' Ingeo)
Stone washed jeans	Open pit mining of pumice, fabric washed with crushed pumice and/or acid	Fabric washed with biotech enzyme (cellulases) to fade and soften fabric, less mining and energy
Biofuels	Petroleum is cracked and distilled into gasoline and by products	Novel enzymes convert starches and cellulose in biomass into sugars. Genetically enhanced microbes convert sugars to a growing range of alcohols and esters.
Beverage and food packaging	Polyester, a synthetic polymer fiber, produced chemically from petroleum; Polypropylene also made from petroleum	Bacillus microbe ferments corn sugar to lactic acid, which is heated to create a biodegradable polymer
Plastic containers	Plastics (olefins and styrenics) used for eating utensils, beverage and food containers, and personal care products – all made from petroleum	Naturally-occurring microbial process is genetically enhanced to produce polyhydroxyalkanoates (PHAs, such as Telles' Mirel). PHAs can also be grown in genetically engineered switchgrass plants.

Source: Adapted from table on www.bio.org, Biotechnology Industry Organization, 2013

"...research and development continues to be both privately and publicly funded, but the work has emphatically moved out of the laboratory and into the marketplace. Major corporations are putting new intellectual properties to work in new factories in the US and abroad. The players on this new field include new companies that come directly out of university research riding large holdings of intellectual property and established multinational giants that have the networks necessary to distribute and market the new materials. Between these two ends of the spectrum, companies are emerging that can intermediately supply the substances and services that bridge the gaps. The result is intricate patterns of interconnection between layers of the new supply chains. Acquisitions up and down these supply chains are frequent..."[41]

leader, Europe now faces strong competition from Asia, primarily China, but also India, Japan, Malaysia and others.[33] In addition to promoting biofuels, the Chinese government also supports a range of industrial biotechnology R&D and commercial projects on bioplastics and biobased chemicals.[34]

Governments around the world are actively supporting industrial biotech, but most are still grappling with regulatory oversight of its products and processes, and the social, health and environmental implications of their use.[35] In addition to causing public unease, the absence of regulatory guidance creates uncertainty for industry.[36] In most countries, a patchwork of laws and authorities regulate these activities, and significant differences exist across regions and countries.[37] The pace of change in this sector is outstripping the ability of governments to keep up, and as we will discuss below this includes developments with relevance to ABS and implementation of the Nagoya Protocol.

COMPANIES

The US has the largest number of biotech companies (including all forms of biotech), followed by Japan, Germany, Canada and France. The EU in total has similar company numbers to the US.[38] Biotechnology companies vary significantly in size, scope, and approaches to R&D and intellectual property. Companies may undertake early stage discovery, provide "services" and know-how to other companies that will own the intellectual property and develop products, establish production facilities with significant capital investment, or they may combine some or all of these and other activities. Clustering, or collaboration between groups with complementary skills, is increasingly common in this sector.[39] As the world's largest energy, chemical, food, pharmaceutical and other companies have come to embrace industrial biotechnology, a surge of partnerships, joint ventures, mergers and acquisitions, and other collaborations have resulted, spanning and further breaking down divisions between sectors.[40]

TABLE 2. Biofuel Digest's "Hottest Companies" 2012-2013[42]

Renewable Chemicals and Biomaterials	Bioenergy
Genomatica	Solazyme
Solazyme	KiOR
Myriant	LanzaTech
Elevance renewable Sciences	Novozymes
LS9	POET
DuPont Industrial Biosciences (Genencor)	DuPont
LanzaTech	Gevo
Amyris	Sapphire Energy
ZeaChem	Joule Unlimited
Gevo	ZeaChem
Virent	Honeywell's UOP
OPX Biotechnologies	BP Biofuels
DSM	LS9
BioAmber	Beta Renewables
Novozymes	Amyris

RESEARCH AND DEVELOPMENT TRENDS

INVESTMENTS IN R&D

Biotech R&D can be high-risk and costly, and very high levels of investment are required to sustain companies through the pre-revenue, intensive R&D phase, particularly in pharmaceutical biotech. Most biotech companies run on venture capital, grants, initial public offerings and collaborative agreements.[43] During the economic crisis these sources of funding dried up in the US and Europe, and they have not fully come back.[44] Within the biopharmaceutical area, small and medium sized companies, which generally partner with larger companies to market and distribute products, were particularly affected by the economic crisis and have struggled to reduce cash burn rates by cutting early stage capital-intensive R&D.[45] Government, academic and private non-profit research institutions that partner with the private sector to commercialize research results and new technologies have also been hurt by the economic crisis.[46]

In general, however, industrial biotech R&D has weathered the storm better than other areas of biotech. It is significantly less costly and less risky than biopharmaceutical R&D, and recent advances in science and technology mean the commercial potential of this sector is finally being realized. While direct government support for R&D has contracted in many countries, government mandates and incentives, particularly for biofuels, but also for biochemicals and bioplastics, have resulted in dramatic growth in the industrial biotech component of the biotechnology sector. In the private sector, venture capital funds have contracted but large companies with available cash appear to have expanded their investments in industrial biotech R&D.[47] Through partnerships with smaller industrial biotech companies, and their own internal research programs, these groups are fueling a new wave of R&D.

ADVANCES IN SCIENCE AND TECHNOLOGY

Industrial biotechnology R&D seeks to maximize the effectiveness and efficiency of biocatalysts that can withstand industrial process conditions. These biocatalysts, usually enzymes that have evolved to act as the 'tools of nature' for cutting and pasting products and facilitating and speeding up complex biological processes in cells, are used in the production of raw materials, intermediates and consumer products. Although in use for more than 60 years in the textile, detergent, food, feed and other industries, advances in science and technology[48] in recent years have allowed researchers to expand the engineering and

"In my view, the most promising ABS activity results from bubbling up from projects on the academic research side, rather than a company walking in and saying - let's cut a deal, and I'll give you 5% royalties... There just isn't much money in royalties from this industry, thus it is not a particularly productive place to focus. Building up their own science should be at least of equal importance to countries as benefit-sharing through royalties, and this is more likely to result from research collaborations with academic researchers... This is particularly important today when even countries without a lot of research money can do biology. Biological research is ever more affordable, and it is easier for countries with biodiversity to participate. If countries strengthen their scientific talent pool, opportunities will follow."

– Robert Friedman, J. Craig Venter Institute

application of microbes and enzymes to a broader range of industrial processes. These new applications are often faster, cheaper, and use fewer resources and less energy, than processes dependent upon petroleum.[49]

As a first step in the R&D process, microorganisms are collected from soil, water or other natural environments, or *ex situ* collections. The last decade has seen dramatic advances in researchers' ability to access the genome sequences contained in these samples. "Genome-mining", or metagenomic approaches, allow researchers to search directly within a sample for genes that produce enzymes with specific biocatalytic capabilities, rather than growing organisms in the laboratory as was previously necessary.[50] Enzymes are then identified and characterized for their ability to function in specific industrial processes, and might be modified or improved through gene shuffling, gene transfer, directed evolution or metabolic engineering. Nanotechnology – the interdisciplinary study of the functional system at atomic or molecular (nanometer) scales – is used to improve stability, activity, efficiency, and other qualities required of enzymes in industry's large-scale fermenters.[51]

In the last decade, sequencing of whole genomes has become 'commonplace, rapid, and relatively inexpensive', with the number of whole bacterial genomes entering the public literature in the thousands, and increasing exponentially.[52] DNA sequences are widely available in the form of electronic data from which DNA can be reconstructed in the laboratory. Genetic material might be transferred in a matter of hours from one country to another through the internet. As gene synthesis becomes cheaper and faster, it may be easier to synthesize a gene or genetic pathway than to find it in nature or collections, and companies may soon receive their genetic sequences digitally, making field collections, taxonomic identification and storage of environmental samples a thing of the past.[53]

DEMAND FOR ACCESS TO GENETIC RESOURCES

Industrial biotechnology companies have a strong interest in novel enzymes found in nature, and there remains "a lack of well-characterized, diverse biological switches and widgets" as one researcher described one of the challenges for synthetic biology.[65] Most companies access material through internal or external collections, while a few collect genetic resources outside their countries. The use of traditional knowledge in this sector is limited or non-existent.

Companies primarily look for novel enzymes in microorganisms, considered the most abundant and least understood organisms on the planet, with enormous metabolic capability and diversity, most still untapped.[66] It is estimated that more than 500 commercial products are made using microbial enzymes (Table 3).[67] Markets for microbes, microbial products and enzymes used in all sectors are expected to increase to more than $259 billion in 2016, with a compound annual growth rate of 10.7%.[68]

BOX 1. SYNTHETIC BIOLOGY

Synthetic biology broadly refers to the use of computer-assisted, biological engineering to design and construct new synthetic biological parts, devices, and systems that do not exist in nature, and to redesign existing biological organisms.[54] It draws upon the advances described above, and moves science from "reading the genetic code to writing it."[55]

Synthetic biology integrates disciplines like molecular biology, engineering, computer modeling, information technology, control theory, chemistry and nanotechnology and is a set of tools that is integrated into the work of many industrial sectors.[56] While genetic engineering usually involves the transfer of individual genes from one microbe or cell to another, synthetic biology assembles novel genetic pathways from standardized genetic parts that are then inserted into a microbe or cell. Industrial biotechnology researchers and companies have been using synthetic biology tools for years, including gene splicing, metabolic engineering, and directed evolution.[57] Synthetic biology is not limited to the modification of natural organisms, but also has the potential to construct new life forms with no natural counterparts.[58]

Applications of synthetic biology include turning microbes into 'living chemical factories' to produce fuel, industrial chemicals, or pharmaceuticals. Natural product substitutes are also a focus of research today, including the production of synthetic 'natural' rubber, 'natural' food flavors like vanilla and saffron, essential oils like vetiver, and palm oil. Amyris, based in California, has coaxed yeast to produce industrial-scale artemesinin, the antimalarial drug that now comes from *Artemisia annua* production in China and elsewhere.[59] Civil society and other groups have expressed concerns that farmers will lose their livelihoods if bulk raw plant materials are replaced with synthetic biology versions of products like artemesinin, vanilla and rubber.[60]

Since 2004, at least $1.84 billion has been invested in synthetic biology start-ups from private investors, and governments have spent millions more, but "most of those companies have made grinding progress, not breakthroughs." Although synthetic biology has enormous potential, realizing this in practice has not been as easy as some had hoped, and many feel the hype of the last ten years has hurt the research.[61]

As Voosen put it: "The tools have outpaced the knowledge. The cost of genetic sequencing and synthesis continues to plunge, but the functions of many genes in even the simplest forms of life, like bacteria and yeast, stubbornly hold on to their secrets. Genetic networks interact in complex, mysterious ways. Engineered parts take wild, unexpected turns when inserted into genomes. And then evolution, a system that would drive any electrical engineer mad, tiptoes in."[62]

The global market in 2011 for synthetic biology was $1.6 billion, and this is expected to rise to $10.8 billion by 2016. Products already on the market include maize-sourced bioplastics sold by DuPont and Archer Daniels Midland, biodiesel sold in Brazil by Amyris Inc., and biosynthesized 'natural' grapefruit flavour sold by Allylix. More than 20 synthetic biology products are on the market. [63] Synthetic biology is moving more slowly than promised, but it has hit the marketplace and its role in industry will continue to grow.

In 2012, 113 civil society and environmental organizations from around the world endorsed a call for proper oversight and regulation of synthetic biology, requesting that the precautionary principle be applied to governance of these new and poorly understood activities, and that a moratorium be placed on the environmental release and commercial use of synthetic organisms until national and international laws are improved and in place to ensure their safety.[64]

"Nature provides an incredible array of novel parts, and scientists then assemble those parts to have speed and efficiency to create novel things. But without those basic parts, we would never be able to do that. Eventually, we will learn nature's rules, but we are still dependent upon nature. Even synthetic biology – all of the inspiration is coming from nature. You absolutely have to have it, it is not going away."

– Jay M. Short, CEO of BioAtla

In recent years, metagenomics and other approaches have made it possible for researchers to study the 99% of microorganisms found in soil, water and other environmental samples which were previously inaccessible because they could not be cultured in the laboratory. A one gram sample might yield tens of thousands of microorganisms, which could represent more than a million 'open reading frames encoding putative enzymes'.[69] This means novel chemical and biological diversity has become available to researchers from sources they thought exhausted, as well as from the organisms found in their backyards.

Industrial biotech companies that continue to seek novel enzymes by collecting in nature tend to focus on areas with high species diversity, extreme environments, or unique ecological niches.[70] A number of companies look for microbial diversity associated with endemic flora (e.g. epiphytes, endophytes, and pathogens) and fauna (e.g. insects, pathogens and endosymbionts, organisms that live within the body of another). Others collect extremophiles, microorganisms found in extreme environments like hydrothermal vents, deserts, caves, cold seeps in the deep sea, salt lakes, and subglacial environments in Antarctica. These environments resemble industrial processing conditions.[71] For example, starch and baking require high temperatures and low pH; textiles, pulp and paper, and detergents a high temperature and high pH; and dairy and food production a low temperature and low pH.[72] Metagenomics allows researchers to access the genetic material in these extreme organisms, which cannot be grown in laboratories, enabling rapid discovery of new enzymes.[73]

Examples of companies undertaking research in extreme environments include Verenium, a US-based industrial biotech company with 2012 revenues of $57 million. Verenium Corporation (formerly Diversa, before it merged with Cellunol and then sold part of the company to British Petroleum) markets at least seven products that resulted from bioprospecting. These include starting enzymes that were further enhanced by directed evolution, as well as final products. Collections that led to commercial products include those from thermal hot springs (Xylathin and Luminase), warm volcanic mud (Cottonase), and geothermal vents (Fuelzyme and Pyrolase). The company describes Fuelzyme, for example, as having "superior thermostability, broader pH range, and more specific mode of action"

Jatropha curcas, used to produce biofuel.

TABLE 3. Selected products of industrial importance obtained from environmental microbes

Industrial products	Examples	Microbial source
Industrial enzymes	Amylase, lipase, protease	Bacteria/fungi
Organic acids	Citric acid, lactic acid	Fungi
Fine chemical	Active ingredients of medicine	Bacteria
Antibiotics	Streptomycin	Bacteria/Fungi
Microbial insecticide	Bacillus thuringiensis protein	Bacteria
Anti-parasite agents	Avermectins	Bacteria
Vitamins	Cyanocobalamin, riboflavin	Bacteria
Amino acids	Glutamate, lysine	Bacteria

Source: Singh, 2010

than comparable products and being "differentiated from the competition by nature itself."[74]

Luminase PB-100 Xylanase , which enhances the reactivity of pulp fiber to bleaching agents, was developed from a microbe discovered in a thermal feature in Kamchatka as part of a research partnership with the Center for Ecological Research and BioResources Development (CERBRD) in Russia. Cottonase, another marketed enzyme used in textile scouring, resulted from a collaboration with the National Institute of Biodiversity in Costa Rica (InBio). As Jay M. Short, former CEO of Diversa, describes: "With the exception of one product, Verenium's current revenue comes from biodiversity based deals which were forged early in the company's founding." These partnerships have also yielded benefits for partners and provider countries.

IMPLICATIONS OF MARKET AND RESEARCH TRENDS FOR ABS AND IMPLEMENTATION OF THE NAGOYA PROTOCOL

In the last decade, researchers' ability to manipulate microbial genomes has revolutionized industrial biotechnology. With the massive jump in production of liquid biofuels since 2005, and smaller but significant growth in bio-based chemicals and bio-plastics, the field of industrial biotechnology has come of age, and is increasingly part of the products and manufacturing processes around us.[75] It is difficult to fully grasp the diverse size and scope of companies, revenues, R&D, business practices, and the 'web of partnerships' that characterize the sector today. Most governments lack a mechanism to collect basic data on this sector, a significant impediment to effective regulation of these new commercial and scientific activities. As a first step towards implementation of the Nagoya Protocol (as well as other policies on bioenergy, biosafety, the environment, health, rural development, etc.), governments should build capacity and understanding of the advances in science and technology that underpin this industry, how these advances are applied and commercialized, and the structure, scale and scope of the industry as a whole.

The likelihood of commercial product development in this sector is higher than some others, and there is real potential for this industry to generate benefits for provider countries.[76] Governments must be aware, however, that any single industrial biotech product is likely to generate revenues far smaller than a pharmaceutical, on average between $10-$200 million, and many products will generate much less than this. Expectations for benefit-sharing must be in line with business realities. Unlike pharmaceuticals, the price of industrial biotech products reflects those of competing products, so a biofuel must be competitive with petrochemicals, and biochemicals and bioplastics comparable in price to synthetic and petrochemical alternatives. Niche markets exist for more expensive 'green' biotech products, but they are dramatically smaller than mainstream markets.

As we have seen, the ability to isolate microbial DNA directly from soil and water samples, without resorting to culturing, has meant that the vast genetic diversity of microorganisms found in a company's backyard and existing collections is now accessible, and many companies do not seek access to genetic resources in other countries. However, some companies continue to seek access, as interest in new enzymes and metabolites persists, in particular those from areas with high species diversity, unusual ecological niches, and extreme environments. For example, in July 2013 the US comapny Ciris Energy signed a multi-year biodiversity access agreement with INBio in Costa Rica in order to access novel microbes useful for conversion of coal into natural gas and chemicals. Also of significance for implementation of the Nagoya Protocol are the thousands of microbial genomes already sequenced and available digitally[77], and the potential to

"If people start engineering microbes with genes inserted from many different microbes, who owns it? Do the scientists need to obtain permission from all of the many countries of origin for genetic material? How would ownership be shared? This question applies equally well to both the more familiar rDNA and newer synthesized DNA. And if the genes are synthesized from sequence downloaded from a public database, how do you even identify the countries of origin? DNA sequence data do not always identify the geographic origin of the sequence. Complicating this even further is that very similar sequences can often be found in samples from different countries. And sometimes slight variations in sequence intentionally introduced by the scientist (i.e., not identical to the sequence found in nature) might function as well or better."

– Robert Friedman, J. Craig Venter Institute

Oil palm plantation

transmit the sequence of genetic material over the internet from a field site to a laboratory within days. Once digital material arrives, perhaps in another country, genes can be synthesized. Countries should consider these aspects when establishing checkpoints and implementing Article 17 of the Nagoya Protocol on monitoring the utilization of genetic resources.

In addition, it is increasingly understood that microorganisms found in different parts of the world share some of the same genes, so companies can look in alternative locations for sources of an interesting enzyme. At the same time, it is difficult to trace genetic material back to a provider country unless sequences were entered into databases and published. Another issue with implications for implementation of the Nagoya Protocol is the way genetic material from a number of different organisms is commonly combined into a new, synthetic organism, and what this entails for the negotiation of ABS agreements and modalities for benefit sharing.

Magnifying the effect of these complexities is the fact that the industrial biotechnology sector is largely unaware of the Nagoya Protocol and the CBD. As a manager at a biofuels company put it: "Genomics is unstoppable, people can take samples out so easily, and most people in industrial biotech don't know about the CBD. In the plant world people know better, but in the microbial world it is a free for all." Another company executive said: "Most big companies are ethical in terms of ABS, it makes sense.

"The ABS policy approach that has been taken to date is inefficient at best. In my view, an international set of standards will likely need to be created that incentivize both basic research and industrial commercialization, while building capacity. Without these things, biodiversity will continue to be challenged to attract the capital and stewardship it needs for protection."

– Jay M. Short, CEO of BioAtla

But when it comes to small companies it is hard to know. Who is policing all of this stuff? Big companies have more to lose, so they police themselves."

Implementation of the Nagoya Protocol in relation to the industrial biotech sector will necessarily be linked to other policy arenas, as groups raise concerns about the safety of synthetic biology (e.g. the Cartagena Protocol on Biosafety), and the need for a precautionary approach, and seek sustainable and equitable biomass production (e.g. forestry, environment, and agricultural policy, as well as land tenure and customary law).[78] In addition, ABS regimes must reflect the unique scientific, technological and business realities of the sectors they regulate, and retain flexibility in order to adapt to the rapid and unpredictable scientific and technological changes that characterize these industries today.[79]

"If regulations under the CBD are too tight, no one in this industry will want to do the research. One idea we talked about was having on the customs forms, when you come back into the US, a few lines after they ask if you have guns, alcohol, etc ... that ask if you have any genetic material from another country. This way a paper trail is created to where the collections were made. Things like cyclosporine, developed from a soil sample from Norway, or basmati rice – they would not have been commercialized without a tie to the source country... Another idea is to develop an international standard ABS agreement, maybe learning from places like Costa Rica and Queensland that have good, mature ABS laws."

– Eric Mathur, Vice President and Chief Technologist, SG Biofuels

THE NAGOYA PROTOCOL: RESPONDING TO SCIENTIFIC, TECHNOLOGICAL, POLICY AND MARKET CHANGE

Although much of the industrial biotechnology industry is unaware of the Convention on Biological Diversity and the Nagoya Protocol, those companies with awareness of the CBD have voiced concerns similar to those in other sectors: a need for clarity and streamlined procedures for accessing genetic resources, ideally coordinated across regions, and a need for government departments in charge of ABS to better understand the scientific, technological and business realities of their sector. The Nagoya Protocol responds to these and other concerns as follows:

Helping researchers and companies follow ABS laws – In addition to supporting information-sharing mechanisms and tools at the international level like the ABS Clearing-House (Article 14), the Nagoya Protocol encourages governments to establish information dissemination and outreach programs, and to help researchers identify and follow what will be streamlined ABS procedures.

Legal certainty and clear, workable regulations – Difficult, time-consuming and bureaucratic regulations and permitting procedures, and an absence of legal certainty when acquiring genetic resources from some countries is of concern to some industrial biotech companies seeking access. The Nagoya Protocol requires Parties to designate one or more competent national authority responsible for granting access to genetic resources, and thereby reduce uncertainty, and establish ABS national focal points responsible for making information available on procedures for obtaining prior informed consent and reaching mutually agreed terms (Article 13).

Building the capacity of governments – Article 22 of the Protocol also calls for building the capacity of governments to effectively implement the Protocol, including the development and implementation of ABS legislation, negotiation of mutually agreed terms, and improved research capacity to undertake research on their genetic resources. Article 21 also provides that Parties are to take measures to raise awareness of the importance of genetic resources, traditional knowledge associated with genetic resources and related ABS issues.

Defining the scope and activities covered by ABS measures – The Protocol applies only to genetic resources within the scope of Article 15 of the CBD (Article 3). In addition, as further clarified by the Protocol (Article 2(c)), "utilization of genetic resources" means to conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology as defined in Article 2 of the Convention". Governments may also wish to consider, when developing ABS agreements and national ABS measures, particularly in relation to monitoring the utilization of genetic resources, that information on genetic resources is often transferred digitally.

Responding to scientific and technological advances – The process through which the Nagoya Protocol is implemented provides governments with an opportunity to update and modify previous ABS strategies in order to accommodate dramatic new scientific, technological and business realities. Awareness and understanding of the industrial biotech industry is particularly low, and existing legal and policy frameworks that impact this sector and overlap with ABS are often a patchwork, and have not kept pace with recent rapid advances.

ENDNOTES

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24 Not all bioplastics from renewable materials are biodegradable or compostable, however, and some petroleum-based plastics are formulated to be compostable. Most biodegradable and compostable biopolymers are of microbial or plant origin.

25 OECD, 2011; van der Valk, 2010. The Japanese government legislated in its 2002 Biomass Nippon Strategy that 20% of all plastics must be sourced renewably by 2020, prompting numerous Japanese companies to accelerate research into bioplastics (OECD, 2011).

26 The Economist, 2010.

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36 For a discussion of US public perceptions of synthetic biology see: Pauwels, E., 2013. Public Understanding of Synthetic Biology. *Bioscience,* vol 63, no 2, February 2013.

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38 Van Beuzekom, B and Arundel, A. 2009. *OECD Biotechnology Statistics 2009*. OECD. The majority of biotech companies in the 2009 OECD survey had fewer than 50 employees, although there are significant variations by country, with the US and France, which spend the most on biotech R&D, having a larger portion of middle range (50-249 employees) and large (250+) companies.

39 Festel, G., 2010. Industrial Biotechnology: Market size, company types, business models and growth strategies. *Industrial Biotechnology*, April 2010. OECD, 2011

40 The Economist, 2010.For example, the chemical company DuPont and the oil company BP have a joint venture, Butamax, to commercialize fuels derived from seaweed. DuPont bought Danisco, an enzyme and specialty food ingredient company, and DuPont is already the world's second largest seed company and sixth largest pesticide company. Solazyme, the synthetic biology company which works in biofuels, chemicals, nutrition and health sciences, has partnerships with Dow Chemical, Unilever, Chevron, Bunge Ltd., the US Navy, Roquette Freres, and San-Ei-Gen. Amyris is another example of a company with a 'web of partnerships', including in this case with Procter & Gamble, Chevron, Total Shell, Mercedes Benz do Brasil, Michelin Tire, Gruppo M&G, Bunge Ltd. and Guarani (ETC Group, 2011. *Who will control the Green Economy?* November, 2001, www.etc.org). See, too, the overlap in top biotech companies working in biofuels, renewable chemicals, and other areas (Table 2).

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42 "The rankings, which recognize innovation and achievement in [renewable chemicals and] bioenergy development, are based 45 percent on votes from invited international selectors, 45 percent on votes from subscribers of Biofuels Digest and Biobased Digest, and 10 percent on votes via Twitter. More than 300,000 individual company ratings were

logged by selectors, subscribers and Twitter voters, in total, in the 2012-13 Hot 30 and Hot 50 rankings." www.biofuelsdigest.com.

43 An OECD workshop in 2010 found that financial sources for industrial biotechnology small and medium sized companies and start ups, ranging from most common sources to least common, included: operational income, private investors, government, debt funding, equity investors, and mezzanine financing (OECD, 2011).

44 Ernst and Young, 2012. *Beyond Borders: Global Biotechnology Report*; EuropaBio, 2009. *Time for Action: The Financial Crisis and Biotech SMEs.* September, 2009, www. europabio.org.

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47 As noted, however, we lack good data to estimate the level of investment in industrial biotech R&D.

48 Advances in science and technology include those in genomics, metabolomics, proteomics, nanotechnology, metabolic engineering, systems biology, as well as information technology that enables faster and cheaper gene sequencing (van der Valk, 2010; Singh, 2009; Scott, 2009; Erikson et al, 2012; BIO, 2013; OECD, 2011). These advances not only help researchers understand the basic biology of the processes they want to control or modify, they also allow them to manage vast quantities of data, and have changed the research questions scientists ask and the methods, processes, research tools and instruments employed in this sector (OECD, 2011; BIO, 2013).

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54 The International Civil Society Working Group on Synthetic Biology, 2011. *A Submission to the CBD's SBSTTA on the Potential Impacts of Synthetic Biology on the Conservation and Sustainable Use of Biodiversity*, October 15, 2011.

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66 Singh, 2009; Friedman, 2007; Mathur et al, 2004.

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68 BCC Research, 2011. *Microbial products: Technologies, Applications and Global Markets*. April 2011; Erikson et al, 2012.

69 Singh, 2009.

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71 Marine and aquatic organisms are of growing interest to the industrial biotechnology industry, and not only those from extreme environments. The global market in 2009 for marine biotechnology products was estimated at $2.4 billion, with industrial biotechnology products including antifoulants, biofilm inhibitors, bioremediation, enzymes, and cosmetics. Bulk products – with potential applications as feedstock – include microalgae for large-scale production of polyunsaturated fatty acids (PUFAs) for food and feed additives, and biofuels. Allen, M.J. and Jaspers, M., 2009, Realizing the potential of marine biotechnology. *Industrial Biotechnology* 5(2), pp 77-83; Li, Y., Horsman, M., Wu, N., Lan, C.Q., and Dubois-Calero, N., 2008. Biofuels from microalgae. *Biotechnology Progress* 24, pp 815-820.

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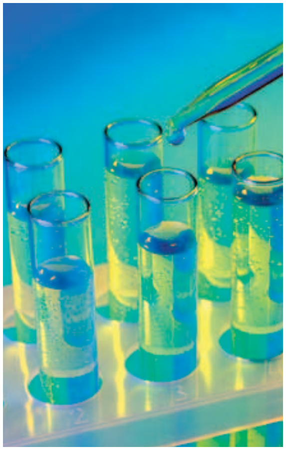
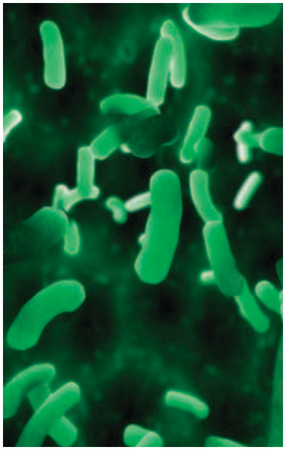
79 ETC Group, 2012. *Synthetic Biology: 10 Key Points for Delegates to COP 11*; Hoffman, E., 2012. *Synthetic Biology – Big promises backed by bad theory.* Friends of the Earth. www.foe.org. As an article in *Nature* put it: "…no one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data." Dana, G.V., Kuiken, T., Rejeski, D. and A.A. Snow, 2012. Four Steps to Avoid a Synthetic-biology Disaster. *Nature* 483, p 29; Woodrow Wilson International Center, 2010. *Trends in Synthetic Biology Research Funding in the United States and Europe.* Research Brief 1, June 2010; Schei, P. and M. Tvedt. 2010. *The Concept of 'Genetic Resources' in the CBD and how it relates to functional International Regime on Access and Benefit-Sharing*. The Fridtjof Nansen Institute. CBD/UNEP/CBD/WG-ABS/9/INF/1; Friends of the Earth, CTA, ETC Group, 2012. *Principles for the Oversight of Synthetic Biology,* March 2012. International Civil Society Working Group on Synthetic Biology; Ho, Mae-Wan, 2010. *Synthetic Life? Not By a Long Shot.* ISIS Report 24/5/10.





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