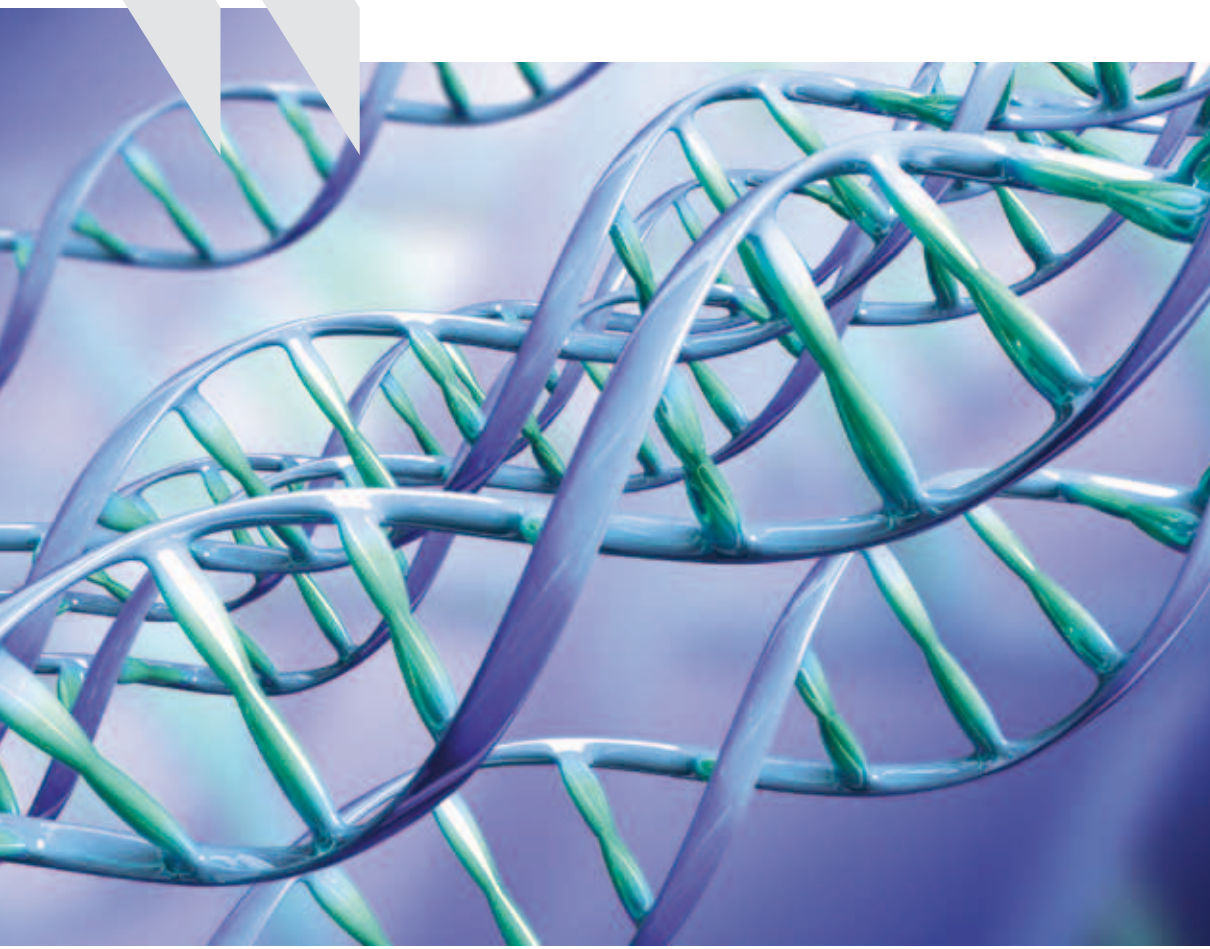
The Bioeconomy to 2030

DESIGNING A POLICY AGENDA



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The Bioeconomy to 2030

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Foreword

The concept of a "bioeconomy" invites the reader to think about the global challenges of the future and how the biological sciences may contribute to solving these complex problems.

There is a growing strategic interest in the concept of the bioeconomy in the OECD and non-OECD countries, not least because it addresses the potential for significant global economic, social and environmental benefits in an integrated framework. But for the bioeconomy to succeed, considerable uncertainties facing both public and private actors in our economies will need to be addressed.

A large part of the task of addressing global challenges will involve the biological sciences, from the contributions of industrial biotechnology through environmental applications to climate change issues, improved health outcomes, and feeding global populations with better yielding crops and better delivery of nutrients and vitamins in foods. Changing population demographics will mean more creative healthcare solutions for every generation of citizens. With the evolving consumer appetite for individualised medical care and medicines, biotechnology can make significant contributions to economic productivity and wellbeing in the health sector. Agricultural biotechnology can contribute to a more sustainable and productive agriculture sector.

In short, the bioeconomy holds at least some of the cards to ensure long term economic and environmental sustainability. But that potential will not become reality without attentive and active support from governments and the public at large. Innovative policy frameworks are needed to move forward to meet these global challenges, and these need strategic thinking by governments and citizen support.

The present report is the outcome of an interdisciplinary, strategic foresight project on the Bioeconomy to 2030. It provides a broad-based, forward-looking, policy-oriented review of future developments in the three sectors examined: primary production, health and industry. It also explores the implications of developments in these sectors for the economy and society in the 21st century.

The Bioeconomy project was carried out by an OECD secretariat team in the International Futures Programme (IFP). The IFP, which reports directly to the OECD Secretary-General, was created in 1990 to examine long-term futures. Past work has covered such themes as long-term prospects for the world economy, the future of international air transport, emerging risk in the 21st century, and infrastructure investment needs in the 21st century.

Conceived and designed in 2007-08, the 18-month project on the bioeconomy was completed at the end of 2008. The IFP's long experience in forward-looking, multidisciplinary activities helped to lay the groundwork for this project by organising the participation of governments, businesses and academic experts.

The work was overseen by a Steering Group whose membership (see Annex A) consisted of high-level representatives from governmental departments and agencies, corporations, and international organisations. The Secretariat's work benefited considerably from substantive contributions provided by members of the Steering Group throughout the project.

This report was written by Anthony Arundel and David Sawaya.

Michael Oborne, the IFP Director, initiated and directed the project as well as chaired the meetings of the Steering Group. Barrie Stevens and Pierre-Alain Schieb provided oversight and guidance to the project. Ioana Valeanu provided research assistance. Anita Gibson assisted in promoting the project. Lucy Krawczyk, Concetta Miano, Jane Leger and Rosella Iannizzotto provided secretarial and logistical support. Randall Holden edited the final text.

The project also benefited from the input of leading experts in the field of the biosciences (see Annex B) and from the knowledge and advice of colleagues in various OECD Directorates and Agencies, notably the Directorate for Science, Technology and Industry (Iain Gillespie, Benedicte Callan, Alexandre Bartsev, and Christina Sampogna), the Directorate for Trade and Agriculture (Ken Ash, Wilfrid Legg, Ron Steenblik, and Martin Von Lampe), the Directorate for Employment, Labour and Social Affairs (Elettra Ronchi), and the Environment Directorate (Peter Kearns).

This publication brings together the analytical work of the project and focuses on the findings arising out of that work. It is conceived as a forward-looking, evidence-based thought piece to stimulate thinking about a policy agenda to ensure that the biosciences are able to make good on the promise of a significant contribution to tomorrow's world through productivity gains, welfare gains and environmental sustainability.

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Abbreviations and Acronyms

ADR	adverse drug reaction
AG	agronomic trait
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukaemia
APHIS	Animal and Plant Health Inspection Service
BP	British Petroleum
BRIC	Brazil, Russia, India and China
BSE	bovine spongiform encephalopathy
CDER	Center for Drug Evaluation and Research
CGAP	Cancer Genome Anatomy Project
CGIAR	Consultative Group on International Agricultural Research
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DBF	dedicated biotechnology firm
DDT	dichlorodiphenyltrichloroethane
DHA	Department of Health and Aging (Australia)
DHHS	Department of Health and Human Services (United States)
DNA	deoxyribonucleic acid
DNDi	Drugs for Neglected Diseases Initiative
DOE	Department of Energy (United States)
EEC	European Economic Community
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
EU KLEMS	European Union Capital (K) Labour (L) Energy (E) Materials (M) Service Inputs (S) Database
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (United States)
FFN	functional foods and nutraceuticals
GAO	Government Accountability Office (United States)
GBOARD	government budget outlays and appropriations for research and development

GDP	gross domestic product
GHG	greenhouse gas
GM	genetically modified *or* genetic modification
GVA	gross value added
HAS	*Haute Autorité de Santé*
HIV	human immunodeficiency virus
HR	human resources
HT	herbicide tolerance
HT-IR	combined herbicide tolerance and insect resistance
IAVI	International AIDS Vaccine Initiative
IB	industrial biotechnology
ICH	International Conference on Harmonisation
ICT	information and communication technology
IEA	International Energy Agency
IMSR	improvement of medical service rendered
IPCC	Intergovernmental Panel on Climate Change
IPO	initial public offering
ISAAA	International Service for the Acquisition of Agri-biotech Applications
ISO	International Organization for Standardization
IT	information technology
IVD	*in vitro* diagnostic
IVF	*in vitro* fertilisation
LCA	life cycle analysis
M&A	mergers and acquisitions
mAb	monoclonal antibody
MAS	market-assisted selection
MEOR	microbial enhanced oil recovery
MSR	medical service rendered
Mtoe	million tons of oil equivalent
NAFTA	North American Free Trade Agreement
NCE	new chemical entity
NGO	non-governmental organisation
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health (United States)
NMA	*Noordwijk* Medicines Agenda
NME	new molecular entity
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
PCR	polymerase chain reaction
PCT	Patent Cooperation Treaty
PDO	polydioxanone

PGD	preimplementation genetic diagnosis
PHA	polyhydroxyalkanoates
PHB	polyhydroxybutyrate
PPP	purchasing power parity
PQ	product quality
PVC	polyvinyl chloride
QALY	quality adjusted life years
R&D	research and development
RFA	Renewable Fuels Association
RNA	ribonucleic acid
RNAi	RNA interference
SARS	severe acute respiratory syndrome
SM	small molecule
SME	small- and medium-sized enterprise
SNP	single nucleotide polymorphisms
Synbio	synthetic biology
TB	tuberculosis
TRIPS	Trade-Related Aspects of Intellectual Property Rights (WTO)
UN	United Nations
UNU-MERIT	United Nations University Maastricht Economic and Social Research and Training Centre on Innovation and Technology
USDA	United States Department of Agriculture
USITC	United States International Trade Commission
USPTO	United States Patent and Trademark Office
VC	venture capital
WHO	World Health Organization
WTO	World Trade Organization

Preface

Over the past two decades, the biological sciences have provided a motor for innovation and sustainability in our economies, by developing new processes and products. We have called this development a bioeconomy. Yet none of the progress these innovations represent will come automatically. Much more lies ahead. A fundamental necessity is a policy framework to capture and to enhance the benefits of the bioeconomy. Both the public sector and the private sector must be involved in designing this policy agenda, with as open and inclusive a dialogue as possible. The full engagement with citizens is essential to ensure a smooth transition to an economy that is driven by the second great technology revolution of the late 20th century, the bio-revolution.

The task we put before ourselves in developing this project on *The Bioeconomy to 2030* was clear from the outset: examine the claims for a new wave of innovation, driven by the contributions of the biosciences to new and better products affecting every aspect of human existence. Some of these products and processes are already in the market place; many more are moving along the pipelines of research and development, and yet others remain tantalising out of current technological reach. Our goal in this study is to gather the disparate evidence for a bioeconomy, analyse it and refine it into both a series of policy options and a vision of the possible future of the bioeconomy. Possible, but not certain. We will need to understand how the bioeconomy can better serve the goals of a sustainable economy and improve the well being of citizens through better food, better health, better use of our industrial processes and a better productivity in our societies. In this way, we hope to open a vista on that future, and encourage those readers with interests and responsibilities in developing strategic policy on emerging issues to look themselves into the evidence from the multidisciplinary approach we have taken here.

Michael W. Oborne
Director, OECD International Futures Programme

Executive Summary

Biotechnology offers technological solutions for many of the health and resource-based problems facing the world. The application of biotechnology to primary production, health and industry could result in an emerging "bioeconomy" where biotechnology contributes to a significant share of economic output. The bioeconomy in 2030 is likely to involve three elements: advanced knowledge of genes and complex cell processes, renewable biomass, and the integration of biotechnology applications across sectors. This book evaluates existing evidence and the characteristics of biotechnology innovation in order to estimate where the bioeconomy is today, where it could be in 2015, and more speculatively, what it might look like in 2030. It develops a policy agenda to help guide the use of biotechnology to address current and future challenges.

Several factors will drive the emerging bioeconomy by creating opportunities for investment. In addition to the use of biotechnology to meet the challenge of environmentally sustainable production, a major driver is increasing population and per capita income, particularly in developing countries. The latter trends, combined with rapid increases in educational achievement in China and India, indicate not only that the bioeconomy will be global, but that the main markets for biotechnology in primary production (agriculture, forestry and fishing) and industry could be in developing countries. Increases in energy demand, if combined with measures to reduce greenhouse gases, could create large markets for biofuels.

The emerging bioeconomy will be influenced by public research support, regulations, intellectual property rights, and social attitudes. Regulations to ensure the safety and efficacy of biotechnology products influence the types of research that are commercially viable and research costs. Pure regulatory costs are highest for genetically modified plant varieties (ranging from USD 0.4 million to USD 13.5 million per variety) and for the open release of genetically modified micro-organisms (approximately USD 3 million per release), such as for bioremediation to clean up polluted soils. In health, the future of regulation is not clear, with economic pressures and technical opportunities pushing the system in different directions. Intellectual property rights could be increasingly used to

encourage knowledge sharing through collaborative mechanisms such as patent pools or research consortia. Social attitudes to biotechnology will continue to influence market opportunities, but public opinion can change, for instance when biotechnology products provide significant benefits for consumers or the environment.

The report identifies two new business models for biotechnology that could emerge in the future: collaborative models for sharing knowledge and reducing research costs and integrator models to create and maintain markets. Collaborative models are relevant to all application areas. Their adoption, combined with new business opportunities for non-food biomass crops, could revitalise small dedicated biotechnology firms in primary production and in industry. Integrator models could develop in health biotechnology to manage the complexity of predictive and preventive medicine, based on biomarkers, pharmacogenetics, shrinking markets for individual drugs, and the analysis of complex health databases.

An estimate of the "probable" bioeconomy in 2030 adopts a "business as usual" approach to institutional factors such as regulation and builds on research into the types of biotechnology products that are likely to reach the market by 2015. The results suggest that biotechnology could contribute to 2.7% of the GDP of OECD countries in 2030, with the largest economic contribution of biotechnology in industry and in primary production, followed by health applications. The economic contribution of biotechnology could be even greater in developing countries, due to the importance of primary production and industry in their economies.

Ultimately, the impact of the bioeconomy on GDP in 2030 will depend on the interplay between governance, including the level of international cooperation, and the competitiveness of biotechnological innovations. Two scenarios are developed to explore alternative futures. One scenario describes how a change in the funding system for health therapies encourages rapid innovation in regenerative medicine. In another scenario, public attitudes could result in some biotechnologies not reaching their potential. An example is predictive and preventive medicine, where the advance of this technology could be limited by public resistance to poorly planned and intrusive healthcare systems. The scenarios also explore different technological outcomes such as growing competition between biofuels derived from biomass, algal biofuels, and electrical transport systems.

As highlighted in the scenario analyses, the social and economic benefits of the bioeconomy will depend on good policy decisions. The required mix of policies is linked to the potential economic impacts of biotechnological innovations on the wider economy. Each type of

innovation can have incremental, disruptive or radical effects. In many (but not all) cases incremental innovations fit well within existing economic and regulatory structures. Disruptive and radical innovations can lead to the demise of firms and industrial structures, creating greater policy challenges, but they can also result in large improvements in productivity. The extensive discussion of policy options examines challenges in primary production, health and industrial biotechnology, looks at cross-cutting issues for intellectual property and integration across applications, evaluates global challenges, and finally reviews the types of policies that are required over both the short and long term.

Primary production provides a diverse range of policy challenges. Examples include the need to simplify regulation, encourage the use of biotechnology to improve the nutritional content of staple crops in developing countries, ensure unhindered trade in agricultural commodities, and manage a decline in the economic viability of some sectors when faced with competition from more efficient producers. The main challenges for health applications are to better align private incentives for developing health therapies with public health goals and to manage a transition to regenerative medicine and predictive and preventive medicine, both of which could disrupt current healthcare systems. Industrial biotechnology faces multiple futures due to competitive alternatives from both outside and within biotechnology. Efficient policies to support many industrial biotechnologies will need to be linked to life cycle analysis standards to identify the most environmentally sustainable alternatives.

Obtaining the full benefits of the bioeconomy will require purposive goal-oriented policy. This will require leadership, primarily by governments but also by leading firms, to establish goals for the application of biotechnology to primary production, industry and health; to put in place the structural conditions required to achieve success such as obtaining regional and international agreements; and to develop mechanisms to ensure that policy can flexibly adapt to new opportunities.

Chapter 1

Defining the Bioeconomy

Both OECD and developing countries face a range of environmental, social, and economic challenges over the next two decades. Rising incomes, particularly in developing countries, will increase demand for healthcare and for agricultural, forestry, and fishing products. At the same time, many of the world's ecosystems that support human societies are overexploited and unsustainable. Climate change could exacerbate these environmental problems by adversely affecting water supplies and increasing the frequency of drought.

Biotechnology offers technological solutions for many of the health and resource-based problems facing the world. The application of biotechnology to primary production, health and industry could result in an emerging "bioeconomy" where biotechnology contributes to a significant share of economic output. The bioeconomy in 2030 is likely to involve three elements: advanced knowledge of genes and complex cell processes, renewable biomass, and the integration of biotechnology applications across sectors. This book evaluates existing evidence and the characteristics of biotechnology innovation in order to estimate what the bioeconomy of 2030 might look like. It also develops a policy agenda to help guide the use of biotechnology to address current and future challenges.

By 2030, the global population is expected to increase by 28%, from 6.5 billion in 2005 to 8.3 billion, and average global per capita income by 57%, from USD 5 900 in 2005 to USD 8 600.[1] Both a larger and a more affluent population will increase world demand for health services that improve the quality and length of life, as well as demand for essential natural resources: food, animal feed, fibre for clothing and housing, clean water, and energy.

In order to meet future demand, the supply of natural resources will need to increase more quickly in the future than in the past. As shown in Box 1.1, the expected growth in demand for grain will require crop yields to increase at a much faster rate than the approximately 1% per year observed during the 1990s. Yet the way in which humanity is currently using and exploiting these natural resources is already straining the sustainability of the earth's ecosystems. The Millennium Ecosystem Assessment project estimates that 60% of the earth's 24 main ecosystems that support human societies – including rivers and lakes, ocean fisheries, forests, air quality and crop systems – are "being degraded or used unsustainably" (MEA, 2005).[2] A review of published research on fish stocks predicts the global collapse of all currently exploited ocean fish stocks by 2048 unless significant changes are made to fisheries management (Worm *et al.,* 2006, 2007). Climate change will exacerbate the stresses on ecosystems. These and other major trends that will shape the world in 2030 are identified in Chapter 2.

The solutions to the challenges posed by climate change, ecosystem degradation, poverty and global public health will require innovations in global governance, innovation policy, economic incentives and the organisation of economic activity. A crucial component, as with previous crises where humanity has confronted the threat of resource restraints, is technological innovation that creates new resources and allows efficient use of existing resources.

Biotechnology can provide a stream of such technological innovations. It can improve the supply and environmental sustainability of food, feed and fibre production, improve water quality, provide renewable energy, improve the health of animals and people, and help maintain biodiversity by detecting invasive species. Yet biotechnology is unlikely to fulfil its potential without appropriate regional, national and, in some cases, global policies to support its development and application.

This book evaluates the factors that will shape the emerging bioeconomy and the types of policies that might be implemented to maximise the benefits of biotechnology. Along the way, it summarises the types of biotechnologies that are in use today, analyses current data to

estimate the probable structure of the bioeconomy in 2015, and then uses scenario analyses to explore alternative futures for the bioeconomy in 2030.

Box 1.1. **Demand for grains in 2030**

In 2000, global grain production was 1.86 billion tonnes for a world population of 6.1 billion, providing an average of 305 kg of grain per person. The FAO predicts that global crop production will increase by 1.5% per year to 2030 (Bruinsma, 2003), which would produce 2.8 billion tonnes of grain in 2030. This is due to a 13% increase in arable land, mostly in South America and sub-Saharan Africa, and improved crop yields. The UN's medium projection is for a global population of 8.3 billion people in 2030 (UN, 2006). The increase in grain production works out to a small per capita rise of 11.5% over 30 years, to 340 kg of grain per person in 2030 compared to 2000.[1]

These estimates show that grain production would be sufficient to feed the world's population in 2030, if equally distributed. However, the consumption and production of grains per person varies widely across and within countries. The population of developed countries consumed approximately 612 kg per capita of grain in 2000,[2] slightly more than double the world average. This additional grain was primarily used to feed meat and dairy animals.

Due to rapidly rising incomes in developing countries, the demand for meat and dairy products is expected to rise considerably, increasing demand for grain for use as animal feed. The global demand for grain in 2030 would reach 5.1 billion tonnes if the world's population adopted approximately the same diet enjoyed by Europeans. This would create a global grain shortfall of 2.3 billion tonnes, compared with an estimated 2030 production of 2.8 billion tonnes.

Demand in 2030 will not reach 5.1 billion tonnes because many people in the world will still lack the necessary income to increase their consumption of animal protein. Nevertheless, this calculation shows the size of the potential demand for grain. Meeting this level of demand would require a sustained increase in grain production of 3.5% per year, well above historically observed growth rates.

These estimates assume that very little grain is used for biofuels. Adding in demand for biofuels could significantly increase global demand for grain, while increasing pest infestations and agronomic stresses such as drought, heat and salinity could make it difficult to increase yields. Clearly, there will be an enormous demand for agricultural biotechnology, not only to maintain yields in the face of these challenges, but also to substantially increase them.

1. The FAO estimated a 1.3% annual increase in grains, but the average for all crops of 1.5% is used here because livestock and dairy farmers can switch from grains to other feed crops such as soybeans, depending on relative prices.

2. Based on grain consumption in the United States and the European Union in 2000 (production + imports - exports). Per capita grain consumption was likely to be similar in other developed countries such as Australia, Japan, Korea, New Zealand and Singapore. Figure from FAOSTAT Data Archives, Food Balance Sheets.

What is a bioeconomy?

For the purposes of this study, the bioeconomy can be thought of as a world where biotechnology contributes to a significant share of economic output. The emerging bioeconomy is likely to be global and guided by principles of sustainable development and environmental sustainability (see Box 1.2). A bioeconomy involves three elements: biotechnological knowledge, renewable biomass, and integration across applications.

Box 1.2. **The bioeconomy and sustainable development**

Sustainable development requires the maintenance of the factors that support life and human societies. This requires the long-term preservation, in good condition, of *(1)* environmental factors essential to life, such as biodiversity, clean fresh water, clean air, soil fertility, and an amenable climate; *(2)* renewable resources such as water, timber, food, and fish; and *(3)* the technological capabilities to develop alternatives to the depletion of non-renewable resources such as minerals, rock phosphate and petroleum, or to manage other challenges, such as climate change.

Sustainable development depends on economic growth that maintains environmental sustainability (items 1 and 2 above). This requires decoupling economic growth from environmental degradation. A first step is to reduce the quantity of resources used and the amount of pollution created to produce a unit of economic output. Life cycle analysis (see Box 6.4) can help identify the most environmentally efficient production technologies. Over the long term, however, economic growth needs to not only reduce environmental damage to zero, but also repair degraded soil, water, and air.

Biotechnology can support sustainable development by improving the environmental efficiency of primary production and industrial processing and by helping to repair degraded soil and water. Examples include the use of bioremediation to remove toxic compounds from soil and water, improved crop varieties that require less tillage (reducing soil erosion) or fewer pesticides and fertilisers (reducing water pollution), genetic fingerprinting to manage wild fish stocks and prevent their collapse, and industrial biotechnology applications that reduce greenhouse gas emissions from chemical production.

Source: Diamond, 2005; Hermann *et al*., 2007; IAASTD, 2009.

The first has to do with using biotechnological knowledge to develop new processes for producing a range of products, including biopharmaceuticals, recombinant vaccines, new plant and animal varieties

and industrial enzymes. This knowledge includes an understanding of DNA, RNA, proteins and enzymes at the molecular level; of ways to manipulate cells, tissues, organs or whole organisms; and of bioinformatics for analysis of genomes and proteins (NZ MoRST, 2005). The development of this knowledge requires intensive R&D and innovation.

The second element is the use of renewable biomass and efficient bioprocesses to achieve sustainable production. Renewable biomass can be obtained from primary sources such as food crops, grasses, trees and marine algae, and from household, industrial and agricultural waste such as vegetable peelings, sawdust, used vegetable oils, bagasse and wheat straw. Bioprocesses can turn these materials into a range of products, including paper, biofuels, plastics and industrial chemicals. Alternatively, some of these products can be directly produced by genetically modified algae and micro-organisms, without the need for biomass feedstock.

The third element is integration between knowledge and applications, based on generic knowledge and value-added chains that cross applications. There are three main application fields for biotechnology: primary production, health, and industry.[3] Primary production includes all living natural resources, such as forests, plant crops, livestock animals, insects, fish and other marine resources. Health applications include pharmaceuticals, diagnostics, nutraceuticals and some medical devices. Industrial applications cover chemicals, plastics, enzymes, mining, pulp and paper, biofuels, and environmental applications such as bioremediation to clean up polluted soils. The current uses and research targets of biotechnology in each of these applications are described in Chapter 3.

In the mid 2000s, biotechnology probably contributed to less than 1% of GDP in the OECD countries (Zika *et al.,* 2007). In contrast, the *potential* economic value of biotechnology is much greater than this. In 2004, primary production, health and industrial sectors that either used biomass or with current or potential applications for biotechnology accounted for 5.6% of the GDP of the European Union and 5.8% of the GDP of the United States.[4] For comparison, the information and communication technology (ICT) sectors accounted for 7.4% of the GDP of the United States in 2004 (EU KLEMS, 2008).[5]

The economic potential of biotechnology can be increased through economies of scale and scope that increase the efficiency of research and applications. As a generic technology, research in biotechnology creates tools and inventions with multiple uses, creating economies of scope. One example is genome sequencing, used to identify drug targets in people, commercially useful genes in agricultural plants, and genes in micro-organisms with industrial applications. Another example is bioinformatics,

used to analyse large genomic, proteomic and other databases in all application fields.

Not all inventions are useful for all sectors. For example, directed evolution and gene shuffling are most frequently used in industrial applications to increase the output of enzymes or fine chemicals by micro-organisms. The use of pharmacogenetics is almost entirely limited to human health. The variety of uses for inventions often declines as research moves closer to market applications. Nevertheless, there are several cases where inventions developed for one application have been used for an entirely different purpose. Box 1.3 gives a few examples of such "spillovers".

Box 1.3. **Research spillovers**

At the Fred Hutchinson Cancer Research Center in Seattle, research in the late 1990s suggested that the growth rate for cancer could be reduced by turning "off" several genes that regulate growth. An agricultural scientist learned about this work in an informal discussion with researchers at the Center and saw the potential for a reverse application in agriculture. Instead of slowing growth, these genes could be manipulated to increase crop yields. This technology is now being used by the firm Targeted Growth to improve yields for biofuel crops.

Amyris Biotechnologies was established to exploit a method of modifying metabolic pathways in micro-organisms in order to reduce the cost of producing pharmaceuticals. The first application was to produce a precursor of artemisinin – an anti-malarial compound present in the plant *Artemisia annua* – in yeast. Amyris Biotechnologies then applied its knowledge of modifying metabolic pathways to the industrial production of biofuels. It is using this technology to produce high energy-density biofuels from sugar cane.

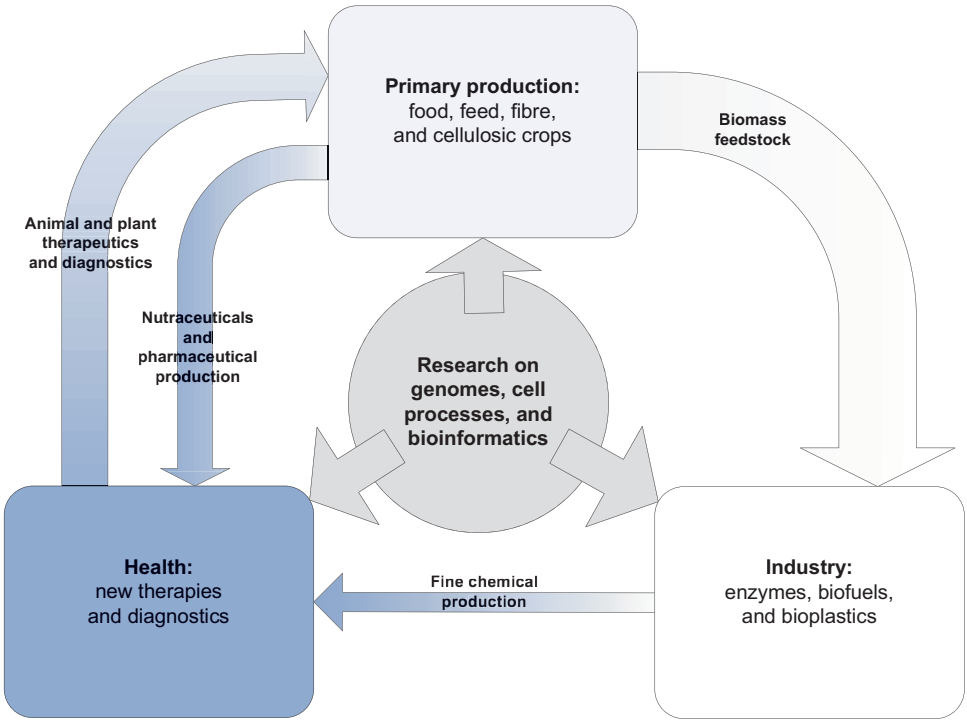
Aresa, a Danish biotech firm, is using GM technology developed for crop breeding to produce GM plants for environmental remediation. The GM plants change colour from green to red in the presence of explosives in the soil, providing a method for detecting mines.

Integration across research applications and value-added chains can lead to greater efficiency and economies of scale in the commercial use of biotechnology. Until recently, the use of biotechnology in one application was rarely integrated with its use in another application. In fact, the level of integration had declined over time. Between the late 1980s and the mid-1990s several large firms, including Monsanto, Novartis and Zeneca, had positioned themselves as "life science" firms in order to exploit synergies in the application of biotechnological research across agriculture and

pharmaceuticals. The strategy failed because of market, organisational and cultural differences in these two applications (Tait, Chataway and Wield, 2002). These firms separated their business activities into independent agricultural, health and industrial firms.

Recent developments have increased the level of integration across the three main application fields. Examples illustrated in Figure 1.1 include the enzymatic production of fine chemicals by industrial firms for use in the pharmaceutical sector, improved varieties of crops for biofuel and bioplastic production, the production of large-molecule biopharmaceuticals in GM plants, the use of recombinant vaccines and biodiagnostics in agriculture, and functional foods and nutraceuticals that are expected to improve health.

Figure 1.1. **Current and expected integration across biotechnology applications**



Note: Arrow width represents the relative importance of the integration.

Primary production, as a source of biomass and as a production vehicle for high-value chemicals, could play a central role in integrating biotechnology applications. For example, using biotechnology to produce

improved tree varieties for biofuels would integrate primary and industrial production, while producing pharmaceuticals in plants would link the agricultural and pharmaceutical sectors.

Foreseeing the emerging bioeconomy

Predicting the future of a technology is difficult. Predictions are often far off the mark, vastly under or over-estimating technical progress or the effects of technology on society.

Two characteristics of biotechnology that are not shared by many other technologies improve our ability to predict the future bioeconomy. The first consists of regulatory requirements for some agricultural and health biotechnologies. These leave a data trail that can be used to predict what will possibly reach the market up to seven years into the future, as shown in Chapter 4. These results also show that some of the optimistic short-term predictions for agricultural and health biotechnology are likely to be wrong.

The second characteristic is that biotechnology is frequently used as a process technology to make existing products such as fuels, plastics, and crop varieties. It can also be used to produce entirely new products such as cancer drugs. For all of these examples, the problems that need to be solved are known in advance. These include the problem diseases, the types of crop traits that would improve agricultural output, and the types of industrial products that can be replaced with biomass. In addition, the size of the potential market for products such as biofuels or anti-cancer drugs can be estimated with a reasonable degree of accuracy.

The above points do not mean that most of the predictions in this book for the emerging bioeconomy, although cautious, will be correct. There are many unknowns. How biotechnology is used and the rate and direction of technological developments will be affected by scientific serendipity, regulation, intellectual property rights, private investment decisions, the supply of highly skilled scientists, technicians and managers, public attitudes towards biotechnology and the cost of capital. Some of these factors are evaluated in Chapter 5. Firms must also find ways of building profitable business models that can turn new ideas into commercially successful products, as discussed in Chapter 6.

Chapter 7 describes one probable future and two scenarios for the future bioeconomy in 2030. Some readers may find that these descriptions of the future bioeconomy err on the side of caution and under estimate developments in biotechnology. The scenarios are certainly less futuristic than those of other reports, which describe a world well before 2030 with abundant and cheap biofuels, designer children, drugs with no side effects,

cures for many diseases including cancer, AIDS, Parkinson's disease and muscular dystrophy, and the replacement of diseased hearts and livers with new organs regenerated from stem cells (Kaku, 2004). Another futuristic article suggests that genetic engineering will be so simple that it will be used by consumers to design new genomes of plants and animals for fun (Dyson, 2007).

If the predictions in this book appear overly cautious in comparison with other studies, there are good reasons. One is a question of timelines. In the future, biotechnology could produce complex replacement organs from stem cells or eliminate severe side effects from drug treatment, but an assessment of past trends suggests that neither is likely to occur by 2030. Optimistic estimates of technological progress in biotechnology usually assume that the reductive engineering model, responsible for the rapid progress in computer and communication technologies over the past few decades, can be applied to living systems. This assumption frequently does not apply because of the complexity of living systems and because a long time is often required to determine if experiments with living systems will succeed or fail. This partly explains why, for many health technologies, progress has consistently lagged behind expectations. An example is the "war on cancer", launched in the United States in 1971 by President Nixon. Over the 37 years since 1971, an estimated USD 250 billion has been spent on cancer research in the United States alone. There have been notable technical breakthroughs for several types of cancer and the ability to detect many types at an early stage has improved survival, but no cure has been found so far.

This study could also be too cautious. Scientific breakthroughs could result in the successful application of the engineering model to synthetic biology, leading to the production of unimaginable new chemical compounds before 2030, with unpredictable applications and markets. The use of regenerative medicine in mid-2008 to construct part of a woman's trachea (BBC, 2008) also suggests that regenerative medicine, as well as other health biotechnologies, might progress far more rapidly than a cautious approach would envision.

Therefore, in evaluating the policy challenges in Chapters 8 and 9, this book adopts a framework that can adapt to varying rates of technological progress and more cautious or more optimistic scenarios for the future. The analysis covers the types of policies that will be needed to promote incremental, disruptive and radical technical developments in biotechnology. Disruptive and radical technologies generally have a longer time horizon than incremental technologies, and require a different policy approach. The challenge is to develop a policy framework that can flexibly support each type of technology.

The number of current and potential applications of biotechnology is too large to be adequately covered in a book of this length. Instead, a limited number of representative biotechnologies within each main application field are used to explore the factors that will influence the future of the bioeconomy.

Notes

1. Real GDP in 2001 USD.
2. The Millennium Ecosystem Assessment project involves the work of 1 360 experts worldwide. The estimate for fisheries is limited to wild fish stocks only and excludes farmed fish.
3. Some studies include environmental applications as a fourth application area. In this report we include these applications either under primary production (for example, the protection of biodiversity) or under industrial applications.
4. Sectors with biotechnology and biomass applications include agriculture, hunting, forestry and fishing, metal mining, textiles, leather goods, pulp and paper, chemicals, and pharmaceuticals.
5. The estimated value of the ICT sector includes that of all information and communication equipment hardware manufacturing (computers, radio and TV equipment, semiconductors, telecom equipment), telecommunication services, and software development and services.

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Chapter 2

What External Factors Will Drive the Bioeconomy to 2030?

Several factors will drive the emerging bioeconomy by creating opportunities for investment. A major factor is increasing population and per capita income, particularly in developing countries. The global population is expected to reach 8.3 billion in 2030, with 97% of the growth occurring in developing countries. GDP is expected to grow by 4.6% per year in developing countries and by 2.3% in OECD countries. These trends in population and income, combined with rapid increases in educational achievement in China and India, indicate not only that the bioeconomy will be global, but that the main markets for biotechnology in primary production (agriculture, forestry and fishing) and industry could be in developing countries. Increases in energy demand, especially if combined with measures to reduce greenhouse gases, could create large markets for biofuels.

An expected increase in elderly populations, both in China and in OECD countries, will increase the need for therapies to treat chronic and neurodegenerative diseases, some of which will be based on biotechnology. Many countries and healthcare providers will try to reverse rapidly increasing healthcare costs. Biotechnology provides possible solutions to reduce the cost of pharmaceutical R&D and manufacturing. Alternatively, biotechnology could improve the cost-effectiveness of health therapy, so that expensive treatments provide commensurate and significant improvements to health and the quality of life.

The shape of the future bioeconomy will depend on breakthroughs in basic and applied research in the biological sciences; commercial opportunities, and innovations in regulations and business models. However, the shape of the bioeconomy in 2030 will also hinge on external factors that will influence the location, size and types of markets for biotechnology products, including food, feed, fibre, fuel, plastics, fine chemicals and pharmaceuticals. These external factors include population and incomes, demographics and education, energy consumption, the availability and cost of key resources such as energy, food and water, access to healthcare, and both supporting and competing technologies.

Barring unexpected events such as a major global conflict or lethal pandemic, the expected population, income and energy consumption of the world can be estimated relatively accurately, as they follow long-term quantifiable trends. In addition, broad estimates can be made about climate change, human resources, food prices, water use and competing technologies, although the future trends for these factors are more sensitive to ongoing or proposed policy actions.

The broad trends are as follows. The economic importance of developing countries is rising and will continue to grow into the future, alongside an increase in their influence in global affairs. The populations in these countries will move from the countryside to the cities as people become better educated and opportunities in services and manufacturing grow. This could also impact health and food consumption patterns as obesity becomes more prevalent due to a more sedentary lifestyle and affluent dietary patterns. The share of agriculture in employment will decline through increased mechanisation. Coupled with burgeoning populations, large developing countries will support sustainable internal markets for goods and services, ranging from basic commodities to many advanced products.

The OECD countries will maintain higher per capita incomes and wealth compared to developing countries, but the gap will shrink over time. The demographic shift to an older population structure will continue to pose economic challenges. In the best case this will drive gains in productivity commensurate with demand, but in the worst case it will be a major burden on society, stifling growth. OECD countries will continue to see their economic future in services and innovation. This will propel the development of new medical technologies and advanced manufacturing techniques that require large amounts of capital for R&D and commercialisation. Some of these technologies will be too costly for many developing countries. Access to markets in large non-OECD economies will, however, be seen an essential driver for growth.

The majority of the workforce within the OECD countries and within several of the leading developing countries will have grown up with computers and will be comfortable with Internet-based learning and social networking, factors with profound impacts on the way people live, work, and interact. Global virtual communities of environmentalists, political movements and research scientists will promote the rapid diffusion of ideas, knowledge and technology around the world. Regions that were once considered remote will become increasingly connected to the world through the Internet and mobile communications. This will also cause major social shifts, as people are increasingly exposed to other cultures and ideas.

Energy demand and access will continue to be major global challenges. Despite increased use of renewables and low-carbon energy sources, fossil fuels will continue to supply a large percentage of energy. This could conflict with steps to address climate change, a phenomenon expected to increase the intensity of storms, droughts and heat waves; shift precipitation patterns; and cause a gradual rise in mean sea levels. These climatic factors, plus pollution and increasing stresses on freshwater supplies, will increase the cost of meeting the growing demand for food, animal feed, fibre and energy, at least over the medium term. Even if global agreement is reached over an equitable climate change agreement, environmental challenges are inevitable and will require new and innovative solutions.

The combined effect of all these global changes will be uneven across regions. Large swaths of the world will remain in poverty, and malnutrition will continue to be a major concern in some regions. Resource shortages and higher prices for basic commodities could create global tensions, as almost every country will be affected by them in an increasingly interconnected world.

The world of 2030 will be fraught with challenges, but these same challenges will create numerous opportunities for biotechnology. The bioeconomy of 2030 will depend on the ability of governments and firms to develop and apply biotechnology to address these challenges.

Population and income

The world population will reach approximately 8.3 billion in 2030 (UN, 2006; see Table 2.1).[1] Almost all population growth, 97%, is expected to occur in developing countries. Population growth in the developed countries will be very low and primarily the result of immigration. The population of several countries in Europe and of Japan could decline. As shown in Figure 2.1, Asia will continue to dominate the world's population, with China and India alone accounting for slightly over a third of the global

population. The population of sub-Saharan Africa will see the largest relative gains, increasing from just over 10% of the world's population in 2005 to nearly 16% in 2030.

World GDP is expected to increase by 57%, from an average of USD 5 488 per capita in 2005 to USD 8 608 per capita in 2030. Much of this growth will occur in non-OECD regions, where the share of real global GDP will increase from 21% in 2005 to 30% in 2030. Between 2005 and 2030, GDP will grow by 4.3% per year in non-OECD regions and by 2.26% in the OECD area. Per capita incomes in 2030 in the OECD countries will remain three to six times higher than the world average (see Table 2.1). Although there will be a large drop in the percentage of the world population living on less than USD 2 per day, chronic poverty will still affect more than 1.8 billion people in 2030, down from 2.7 billion in 2003 (World Bank, 2007).

Table 2.1. **Population and per capita GDP in 2005 and 2030, by region**

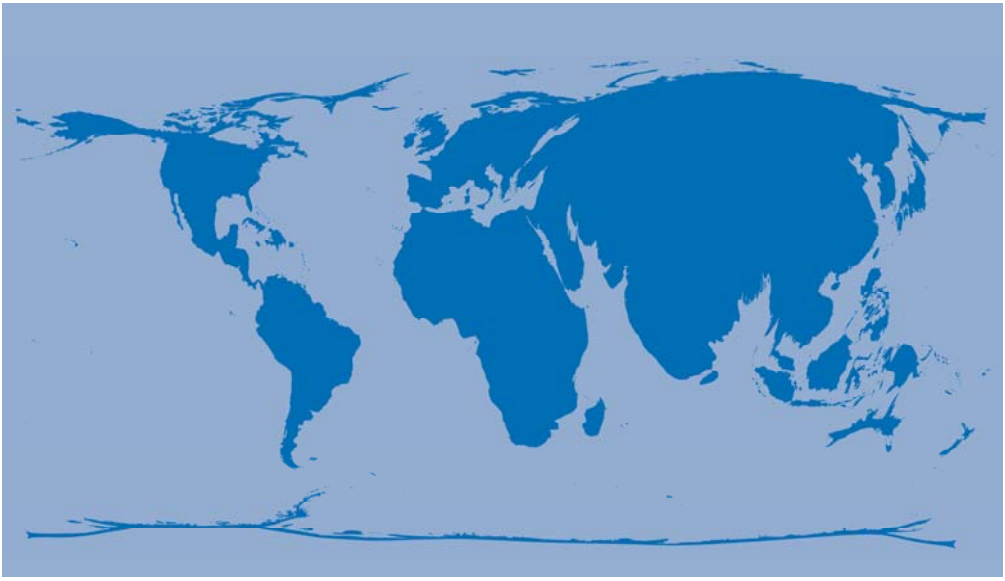
	2005		2030		Average annual growth rate, 2005-30	
	Population (millions)	GDP per capita[1]	Population (millions)	GDP per capita [1]	Population	GDP[2]
World	6 494	5 488	8 236	8 606	0.96%	2.79%
OECD	1 250	22 430	1 368	35 802	0.36%	2.26%
Europe	598	16 034	621	25 951	0.15%	2.10%
North America	429	30 253	522	47 495	0.79%	2.62%
Oceania	25	19 004	31	29 073	0.86%	2.59%
Asia	198	25 233	194	36 951	-0.08%	1.45%
Non-OECD	5 244	1 432	6 868	3 141	1.08%	4.31%
Africa	946	740	1 525	1 391	1.93%	4.53%
Eastern Europe, Central Asia and Middle East	483	2 826	570	6 246	0.66%	3.91%
Asia (excluding Central)	3 372	1 146	4 198	2 992	0.88%	4.83%
China	1 326	1 671	1 457	5 088	0.38%	4.95%
Southern Asia including India	1 483	559	2 035	1 426	1.27%	5.14%
South America	443	3 561	575	5 795	1.05%	3.04%
Brazil	179	3 162	226	4 980	0.94%	2.79%

1. GDP is in 2001 USD.

2. Average annual growth rate is for national or regional GDP instead of for per capita GDP.

Source: OECD, 2008a.

Figure 2.2. **World land mass by expected population in 2030**



Source: Figure produced by Salim Sawaya, using data for the UN's medium variant estimate of population growth (UN, 2006).

One of the drivers of future economic growth is the globalisation of trade and services, which is expected to continue to 2030 and perhaps enter a phase of increased intensity. This new phase will be characterised by the increased importance of trade in services and R&D – which will outpace other sources of growth (World Bank, 2007).

Sustained economic growth and higher incomes will be major factors in the development of the bioeconomy, although the global economic crisis of 2008 to 2010 could reduce expected income levels by 2030 (see Box 2.1). Higher global incomes, particularly in developing countries, will create additional demand for healthcare, meat, fish and specialty foods, consumer durables, automobiles, higher education, and travel. More income will also provide a source of corporate and personal savings, part of which will be invested in R&D. Major biotechnology research centres are beginning to spring up in several of today's developing countries. This trend will continue.

Box 2.1. **The global economic crisis**

By late 2008, a credit crisis had led to a global economic crisis. The depth and length of this crisis will depend on responsive actions taken by national governments and the true severity of the crisis. The economic projections to 2030, presented in Table 2.1, could be robust enough to resist periodic recessions. However, the developing economic crisis could end up being longer and deeper than those in recent memory. No historic guides exist that can help us gauge how long this current crisis will continue impacting on the global economy.

Two recent reviews of the international economic situation have concluded that the OECD area could experience between a 0.4% (OECD, 2008a) and 2.0% (IMF, 2009) fall in GDP in 2009. The studies expect GDP growth of 1.5% and 1.0%, respectively in 2010. This would reduce the estimated per capital GDP in Table 2.1 for the OECD area in 2030 by between 3.7% and 6.1%.[1]

The global economic crisis could also have two direct impacts on the emerging bioeconomy. A long term tightening of credit markets and a subsequent increase in borrowing costs could reduce the amount of capital available for investing in biotechnology R&D and in high risk start-up firms in the OECD area. This trend might occur even without the global economic crisis, with capital seeking better investment opportunities in developing countries with high growth rates. Conversely, the global crisis could provide a major push forward for the emerging bioeconomy. This would occur if the OECD countries respond to the economic crisis by increasing investments in research and in infrastructure for alternative energy and sustainable agriculture as a way to spur long term growth.

1. The estimated decline in per capita GDP in 2030 is by the authors.

Higher per capita incomes will increase the global demand for healthcare, but low average incomes in 2030 in developing countries could limit the market for expensive therapies to relatively high-income individuals. Without a global change in how health biotechnology research is funded and delivered, biopharmaceuticals and other advanced medical technologies could remain unaffordable for most people in the developing world.

Demand for agricultural products will rise from an increase in both population and income. The latter will increase demand for meat, fish and dairy products, which require large inputs of animal feed. As discussed in more detail below, increased demand for agricultural products could drive up food prices, cancelling out some of the benefits from increased incomes. NGOs and governments could support the use of biotechnology to develop

new crop varieties as part of an agricultural policy to reduce food shortages or improve food and feed quality.

An increase in intensive agriculture and rising demand for many goods resulting from increased population and income levels will exacerbate some of today's environmental problems. This may spur demand for industrial biotechnologies for environmental remediation or cleaner production technologies.

Demographics and human resources

By 2030, the share of the global population over age 60 will increase while the share under 15 will decrease. This demographic shift will occur in both developed and developing regions, but the increase in the share of older people will be more pronounced in the developed countries. An important result will be a decline in the working-age population between 15 and 59 in developed countries, from 62.9% to 56.0% of the total population. In contrast, the working-age population in developing countries will remain stable at approximately 61% of the total population (UN, 2006).

Since the total population of developing countries will grow by over 1.5 billion between 2005 and 2030, the global working-age population will increase from just over 3 billion in 2001 to more than 4.1 billion in 2030 (representing an annual growth of approximately 1%). In 2030, 90% of the global workforce will be in developing countries, with China and India alone accounting for 40% of the total. The workforce in developed countries will decline by about 0.16% per annum over this time period (World Bank, 2007). Most employment in developed countries will be in the service sector, while employment in developing countries will shift out of agriculture and into manufacturing and services. Agricultural workers will decline from about 43% to about 30% of the global labour force between 2001 and 2030. That shift will lead to an increase in energy demand; the increase could partly be met by agricultural by-products, as processes once done by humans are mechanised.

The educational qualifications of the global workforce will continue to improve. Investment in education is expected to result in a much larger share of the global working-age population in 2030 with some tertiary education.[2] In the OECD area, the share of the population with a tertiary degree is expected to increase from 26% in 2005 to 36% in 2025 (OECD, 2008b). In many non-OECD countries, the share of the population with some tertiary education is projected to grow substantially between 2000 and 2030. This share is predicted to double in size, from just over 5% to over 10% in China, and to increase from 6.5% to nearly 14% in both Brazil and

India (OECD, forthcoming). The share of individuals with a secondary education will also increase significantly, while the share with no education will decline in all regions (Lutz *et al.*, 2004).

Global demographic shifts and increasing education levels may create opportunities and pose challenges for the bioeconomy. The increase in elderly populations globally, but most dramatically in the OECD countries and China, will increase the prevalence of neurodegenerative and other diseases of old age, thereby increasing demand for long-term healthcare. Biotechnologies will be used to explore possible treatments for these diseases. In general, the increase in the oldest age cohort in the OECD countries should increase markets for healthcare firms, but the decline in the working age population could reduce the tax base for funding public healthcare services.

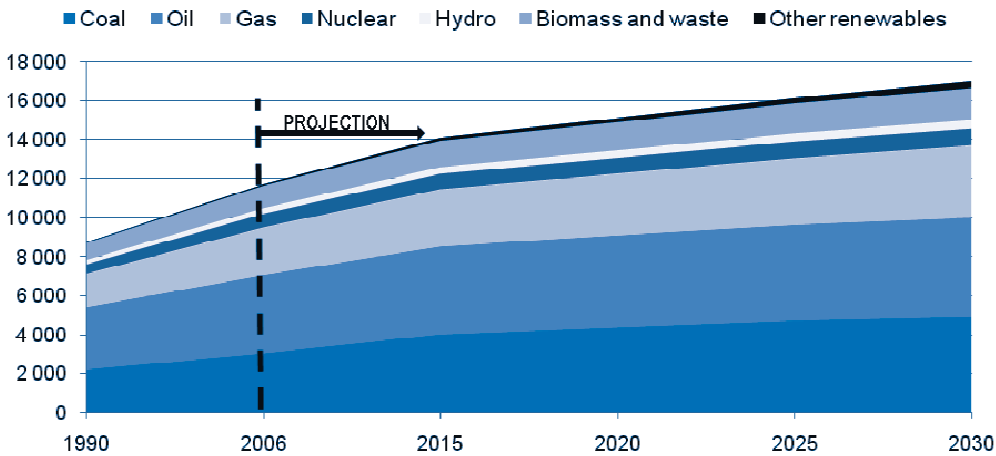
Given the high knowledge intensity of biotechnologies, an increase in the global population with a tertiary education will increase the size of the labour pool available for biotechnology R&D. In developing countries, a larger and better-educated workforce could support greater investment in industrial and primary production biotechnology.

Energy consumption and climate change

Without major policy changes to address energy use and climate change, the world will become more reliant on fossil fuels by 2030. Demand for coal, oil and gas will increase by over 44% from 2006 to 2030. The share of all energy demand met by fossil fuels will remain relatively steady at approximately 80% over the same period (see Figure 2.2). The increase in demand for energy will come primarily from the developing world, where demand will exceed that of the OECD countries around 2013.

There is a general scientific consensus that human activities, especially the emission of greenhouse gases (GHGs) from energy use, are a major contributing factor to the increase in global temperatures over the past century. The Intergovernmental Panel on Climate Change (IPCC) found that most of the increase in average global temperatures is "very likely" to be caused by the increase in GHG emissions due to human activities (IPCC, 2007).[3]

Figure 2.2. **Expected world primary energy demand (Mtoe)**



Note: Based on the IEA's reference scenario. This includes the effects of government energy policies and measures that were enacted or adopted by mid-2008.

Source: Authors, based on IEA, 2008.

As demand for fossil fuels continues to grow, GHG emissions are expected to continue increasing into the future, especially as many future fossil fuel sources will be dirtier than those currently being exploited. Global mean temperatures for 2030, relative to 1900 levels, are expected to increase from 1.4° to 1.6° C, with warming projected to accelerate after 2030 (IPCC, 2007).

Temperature increases in the range projected for 2030 will affect ecosystems and human activities. For example, both the Stern Report and the IPCC estimate that warming of approximately 1° C could decrease water availability and increase drought in low-latitude areas, as well as increase the risk of coral bleaching and wildfires. It could also decrease crop yields in low-latitude areas, although this might be partly compensated by increases in yields at higher latitudes. That beneficial effect would not, however, continue at higher warming levels, with expected crop yields declining in all areas with a 3° C temperature increase. Global warming may also increase health risks if infectious diseases spread to new geographic regions (Stern, 2006; IPCC, 2007).[4]

Global warming has very pronounced impacts on agricultural, environmental and industrial biotechnologies. Agriculture will face decreasing yields from stresses such as higher temperatures, drought and

salinity. The development and adoption of agricultural biotechnologies, particularly plant varieties with agronomic traits to increase stress tolerance, could help mitigate these effects. The increased demand for energy and the potential for sustained energy price increases could lead to more widespread use of bioenergy and industrial biotechnology in processes where it can reduce energy consumption.

The spread of diseases to developed countries could spur investment in sensors and diagnostics to detect disease vectors and infectious agents. It could also encourage investment in novel treatments and vaccines, but this effect is hard to gauge as many infectious diseases, such as malaria, can also be managed through public health measures.[5]

Agriculture, food prices and water

Due to growing world demand for meat[6] and biofuels, the average price of food, feed and energy commodities from 2008 to 2017, is likely to be significantly higher than the average price over the last decade and will reduce but not eliminate the long-term decline of prices in real terms. This is even the case after the sharp fall in prices in early 2008 (OECD-FAO, 2008). Given the multitude of factors involved, it is difficult to project food and feed crop prices beyond 2017. Supply-side solutions should increase output – for instance by extending the amount of land under cultivation, which increased by 10.4% between 1961 and 2005.[7] This may not be sufficient to overcome supply constraints, as the FAO estimates that the amount of new farmland for food production will grow more slowly in the future (FAO, 2002). The alternative solution is to increase yields through the adoption of intensive agricultural techniques in developing countries, but this will require above-average prices to stimulate investment. Therefore, while quantitative price estimates are unavailable for 2030, food prices could remain high, compared to historical levels, through to 2030.

By 2017, developing countries should surpass the OECD area in production of the most traded food commodities. They will also account for an increasing share of global food imports and exports (OECD-FAO, 2008). However, the conversion of land to agricultural use, primarily through forest clearing in South America and Africa, could have significant environmental consequences, including large CO_2 emissions and a loss of biodiversity.

The same factors that are contributing to increased demand for agricultural products will increase water use in the future. Agriculture is the largest consumer of water globally, accounting for about 70% of all water withdrawals (OECD, 2008a). Meat production is especially water intensive.[8]

These conditions, along with the potential for droughts caused by climate change, could result in a massive increase in the number of people living in areas under water stress (see Table 2.2). By 2030 the total population living in areas of high and medium water stress is expected to increase by 38% and 72%, respectively. Conversely, the increase in populations living in areas with low or no water stress will increase by only 4%. Water pollution could also increase, with 5 billion people (1.1 billion more than today) in 2030 without connection to a sewage system (OECD, 2008c).

Table 2.2. **Population living in areas under water stress**[1,2]

(In millions)

	2005	% of world population	2030	% of world population	Total % change (2005-30)
Severe	2 837	44%	3 901	47%	38%
Medium	794	12%	1 368	17%	72%
Low	835	13%	866	11%	4%
No	2 028	31%	2 101	26%	4%
Total	6 494	100%	8 236	100%	27%

1. The 2030 estimates are based on extrapolation of historical and current trends into the future and assume that no new policies are enacted.

2. The columns may not sum to 100% due to rounding.

Source: OECD, 2008c.

Sustained high demand and prices for food and water will likely put the international spotlight on agriculture as an area for action. Agricultural biotechnologies, especially those that increase yield and tolerance to salinity and drought in new plant varieties, are a possible solution in many parts of the world. Rising feedstock prices and water shortages will also pose challenges to the economic viability of biofuels and biorefineries. Water shortages and health risks from underdeveloped sanitary systems could also drive the development of industrial biotechnologies that reduce water consumption or purify polluted water sources.

Healthcare costs

Healthcare expenditures as a percentage of GDP, in both OECD and non-OECD countries, are likely to increase significantly by 2030. In 2005, public expenditures on health and long-term care amounted to an average of

5.7% of the GDP of OECD countries. Projections show that this could rise to 12.8% by 2050, assuming that expenditures grow 1% per annum faster than income (this corresponds to observed trends over the past two decades), or to 10.1% if policy actions are taken to curb the extra 1% growth (OECD, 2006). Estimates are higher if private healthcare contributions are included.

After rapid growth in the early 1970s, the share of healthcare in GDP stabilised through the 1980s, but increased steeply again in the early 1990s. New health technologies have played a major role in this increase. An OECD study noted that since "pure demographic factors have so far been weak, this upward trend in [healthcare] spending is probably due to the increased diffusion of technology and relative price changes" (OECD, 2006).

The rapid increase in healthcare costs as a share of GDP could have a dramatic impact on health innovation. The prospect of controls on prices and access to new health technology has been identified by a survey of industry analysts as the most important strategic risk facing health biotechnology companies (Ernst and Young, 2008). Controls on prices and access will be particularly challenging to current business models for health biotechnology, as downward pressure on health technology revenue decreases incentives for R&D – except where new technologies have the potential to reduce healthcare costs. For example, some studies have estimated that the application of agricultural biotechnology to produce complex pharmaceuticals in plants could reduce production costs for some pharmaceuticals by two-thirds compared to microbial production systems (Frost and Sullivan, 2004). Functional foods and nutraceuticals with proven health benefits could lower healthcare costs by reducing the risk of certain diseases. In addition, industrial biotechnologies could be applied to environmental remediation and water purification, thereby improving health outcomes. Alternatively, society could be willing to accept spending a higher share of GDP on health if balanced by commensurate improvements in health outcomes. Biotechnology offers potentially significant improvements to overall health and quality of life. This could play a positive role in shaping public opinion on acceptable expenditure levels.

Supporting and competing technologies

The bioeconomy will not develop in a bubble. Progress will continue in enabling and competing technologies, such as informatics and alternative energy sources. Supporting technologies will influence how biotechnology products are developed, while competing technologies will determine biotechnology's market size and share.

Supporting technologies

The two main supporting technologies for biotechnology are computing and nanotechnology.[9] To date, advances in computing technology and bioinformatics have been more important than the emerging science of nanotechnology, but the latter could have a large impact on biotechnology in the future, particularly for health applications.

Massive amounts of computing power and storage space, often measured in terabytes, are required for many bioinformatics applications. Over the last four decades, computing power has increased rapidly while costs have simultaneously decreased, allowing researchers to create, access and manipulate larger datasets and to construct more accurate models of biological systems. These trends are likely to continue. In addition, the increase in bandwidth available globally has opened up new ways for researchers to communicate and collaborate, including video and social networking websites.

A major application of nanotechnology is the production of nanoscale devices that can readily interact with biomolecules on both the surface of a cell and within cells. These devices can provide gene and drug delivery systems targeted to specific sites in the body. In addition, nanobiotechnology can be used to produce biocompatible replacements for body parts and fluids, self-diagnostics for use in the home, sensors for labs-on-a-chip, and material for bone and tissue regeneration. Bionanotechnology also has promising applications in environmental remediation.

Competing technologies

Many of the goods produced by biotechnology, such as fuels, plastics, and chemicals, can be manufactured using other technologies This creates potential competition between the social, economic and environmental advantages of biotechnology and those of alternative production methods. The potential for competition also exists when there are similar alternatives in product markets. For example, insect-resistant GM cotton competes with the cultivation of conventional cotton using integrated pest management techniques. Biofuels currently compete against fossil fuels and in the future could compete with electric cars. Likewise, public health measures may be a much more economical method of controlling disease outbreaks than performing costly R&D in an attempt to develop vaccines. The optimal technological solution will depend on how the social, environmental and economic advantages of biotechnology are valued in market economies in comparison with alternatives.

As research into biotechnological solutions continues to reduce costs and improve efficiencies, research into technological alternatives will also be moving forward. For example, research into solar array technology may yield large reductions in the cost of solar panel production and increased efficiency in converting sunlight to electricity. Especially if coupled with breakthroughs in electricity storage, solar arrays could be a cheaper source of renewable energy for automobiles than biofuels.

The competitiveness of both biotechnological and alternative solutions to these and other problems is unknown and will depend on several factors, including the amount of R&D invested in each option, the relative cost of different technologies, and government support through subsidies, tax credits or mandates. Major technological breakthroughs in a competing technology could divert private and public investment away from some biotechnologies.

Biotechnologies will continue to compete with alternative technologies in the future. In agriculture, advances in precision farming and water conservation techniques could compete with biotechnological solutions to environmental pressures. In health, competition with low-cost solutions to infectious disease, such as water purification, will continue. The toughest competition for biotechnology is likely to arise in industrial applications. Other renewable energies such as solar, geothermal and wind power could prove strong rivals to bioenergy, boasting fewer unintended side effects.

Summary of drivers

A summary of the key trends discussed in the preceding sections and their influence on the bioeconomy and biotechnology applications in primary production, health and industry are shown in Table 2.3. The influence of these trends on the bioeconomy will not be equal across all sectors. Population and income levels will have the most pronounced impact on the use of biotechnology in primary production. Demographic changes, especially in OECD countries, will have the strongest impact on health biotechnology. Climate change and environmental challenges will affect the future of agricultural biotechnology, but will probably be most influential in industrial applications.

Table 2.3. **Drivers for the bioeconomy**

	Situation in 2030	Implications for			
		The bioeconomy	Primary production	Health	Industry
Population and economics	World population rises to 8.3 billion. 97% of growth occurs in developing countries. World GDP doubles its 2005 level, but many still live on USD 2 per day. Per capita income in OECD countries remains 3 to 6 times the world average.	More money flows into R&D and investment. Centres of biotech R&D develop in non-OECD countries. Increased income in the developing world changes consumer habits with regard to food, healthcare, travel, etc.	Increased population and demand for meat and fish drive up food prices. Negative impact on poor populations increases the acceptance of biotechnology solutions for yield.	Higher income levels increase demand for healthcare for the world's larger populations.	Population growth poses environmental challenges that create opportunities for industrial biotechnology (IB).
Demographics and human resources	The global labour force increases by 25%. Working age and young cohorts decrease in OECD countries. Education levels rise and jobs move from agriculture to manufacturing and services.	Problems funding entitlement programmes. Increases in education levels, particularly the numbers of those with tertiary education, increase HR availability for R&D.	Mechanisation of agriculture in the developing world increases energy demand.	Elderly populations increase demand for healthcare, particularly long-term care. Prevalence of degenerative disorders increases. Biotech solutions may be limited.	As agriculture is increasingly mechanised in the developing world and fuel demand increases, IB is employed for the conversion of agricultural wastes to fuel.
Energy and climate change	Rising energy demand is met by fossil fuels and GHG emissions increase. Global temperature increases by 1.0 °C and sea levels rise.	Increase in R&D for low GHG energy and climate change mitigation.	Crop yields decrease and drought and salinity increase in some regions, driving the development and adoption of plant varieties with higher yield and stress tolerances.	Increased temperatures lead to the spread of some diseases to new geographic regions, but public health measures compete with biotech as a solution.	High energy prices and robust environmental regulations provide incentives for using IB to cut energy use and GHG emissions.

Table 2.3. **Drivers for the bioeconomy** (continued)

	Situation in 2030	Implications for			
		The bioeconomy	Primary production	Health	Industry
Food prices and water	Food prices remain high compared to historic levels as demand for biofuels and meat rise. There are large population increases in areas of water stress and 67% of the world lacks sewerage.	High food prices cancel out some economic gains. R&D investment in agriculture and environmental remediation.	Demand for food and water drive interest in agriculture. Advanced biotech plant varieties are seen as a solution in many regions.	Lack of clean drinking water/sanitation increases some disease.	IB is used to reduce water consumption and remediate polluted water. Feedstock prices and water shortages challenge the viability of biorefineries and biofuels.
Healthcare costs	New technology contributes to increased healthcare spending globally.	Cost concerns in health limit potential profitability of health R&D, helping to drive a diversification of biotech R&D into industrial and agricultural applications.	In an attempt to contain healthcare costs, prevention through eating healthy food and drug production in plants are explored for cost savings.	Downward pressures on cost decrease R&D incentives and add to the difficulty of implementing expensive new medical systems.	IB is explored to clean water in a bid to prevent illness.
Competing and enabling technologies	IT and nanotech spur the development of biotechnologies while competition with non-biotechnologies intensifies.	Increases in computing power benefit bioinformatics. Competition for R&D funds increases.	Precision farming and water conservation techniques are explored.	Advances in nanotech may solve some technical problems associated with drug delivery and experimental therapies.	Nanotechnologies spur development of environmental remediation techniques but bioenergy faces competition from other renewables.

Notes

1. The figure uses the United Nations median variant.
2. Tertiary education includes most post-secondary level (high school) programmes, including one or two year certificate programmes, three to four year university degrees, and post-graduate Masters and PhD degrees.
3. "Very likely" is defined as the assessed probability of occurrence at >90% (IPCC, 2007).
4. A recent report identified 12 diseases that could spread to new geographic regions as a result of climate change: avian influenza, babesiosis, cholera, Ebola, intestinal and external parasites, Lyme disease, Plague, paralytic shellfish poisoning (PSP) from an increase in dinoflagellates that cause toxic red tides, rift valley fever, sleeping sickness, tuberculosis, and yellow fever (Wildlife Conservation Society, 2008).
5. Public health measures, including the draining of swamps and the use of DDT to destroy mosquito vectors, were the primary factors in eradicating malaria from Europe (Bruce-Chwatt and Zulueta, 1980). More recently, public health measures such as quarantines and early detection halted the diffusion of SARS (Smith and Alvarez, 2008).
6. Annual per capita meat consumption in developing countries has already increased from 10 kg in 1964-66 to 26 kg in 1997-99 and is projected to rise to 37 kg in 2030, increasing demand for livestock feed such as grains and soybeans (FAO, 2002).
7. The FAOSTAT database shows that globally there were 1 280 780 ha in 1961 of arable land and 1 413 425 ha in 2005. This refers to "land under temporary crops … temporary meadows for mowing or pasture … and land temporarily fallow … abandoned land resulting from shifting cultivation is not included" (FAO, 2005).
8. Approximately ten times as much water is required to produce 1 kg of beef as 1 kg of wheat (FAO as cited by BBC, 2008).
9. Nanotechnology encompasses the production and application of physical, chemical, and biological systems at scales ranging from individual atoms or molecules to around 100 nanometres. A nanometre is one billionth of a metre.

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Chapter 3

The State of the Bioeconomy Today

Biotechnology today is used in primary production, health and industry. Platform technologies such as genetic modification, DNA sequencing, bioinformatics and metabolic pathway engineering have commercial uses in several application fields. The main current uses of biotechnology in primary production are for plant and animal breeding and diagnostics, with a few applications in veterinary medicine. Human health applications include therapeutics, diagnostics, pharmacogenetics to improve prescribing practices, functional foods and nutraceuticals, and some medical devices. Industrial applications include the use of biotechnological processes to produce chemicals, plastics, and enzymes, environmental applications such as bioremediation and biosensors, methods to reduce the environmental effects or costs of resource extraction, and the production of biofuels. Several applications, such as biopharmaceuticals, in vitro *diagnostics, some types of genetically modified crops, and enzymes are comparatively "mature" technologies. Many other applications have limited commercial viability without government support (*e.g. *biofuels and biomining) or are still in the experimental stage, such as regenerative medicine and health therapies based on RNA interference.*

The basic science underpinning biotechnology in primary production, health and industry is similar, with all three application fields sharing the same set of platform technologies or research tools. Some research discoveries that are closer to entering the market have been applied to more than one of these domains, but to date biotechnology has followed separate trajectories in each field. This is because primary production, health and industry have different regulations, industry structures and culture, while the firms active in each respond to their environment with different business models.

This chapter reviews the main platform technologies shared by each application area and provides a brief overview of today's use of biotechnology in the three fields. Those readers familiar with the current state of play in biotechnology may wish to simply review those sections covering unfamiliar applications or move directly to Chapter 4, where biotechnology applications to 2015 are discussed.

Platform technologies

Platform technologies, here understood as the main research tools and techniques for modern biotechnology, are used both for R&D and in nearly all biotechnology applications. Some of them are emerging technologies that could have major impacts on the future of the bioeconomy.

At present, the most important of these technologies relate to genetic information or modification. Genetic modification (GM), performed since the early 1970s, involves the insertion of one or more genes from one organism into the DNA of another organism (UN, 1997), usually in order to impart a desired genetic trait. While this used to be a very complex and laborious process, advances in amplifying DNA strands (using polymerase chain reaction, or PCR) and the development of new gene delivery methods (*e.g.* gene guns) have made this commonplace. Genetic modification is used in a wide variety of biotechnology applications.

An emerging platform technology that can be used to modulate gene function is RNA interference (RNAi). Saturating cells with small, targeted segments of double-stranded RNA can turn off (or turn on)[1] targeted genes. The ability to silence targeted genes could have numerous uses in all applications. No commercial RNAi applications for gene silencing are yet available,[2] but a few health therapies based on RNAi are in clinical trials.

Other important technologies concern the analysis of how cells function (metabolics) and the structure of cell molecules, including proteins (proteomics) and DNA. Proteomics involves the analysis of the full complement of proteins within an organism. It is much more complex than

genomics because proteins can be modified within the cell. Understanding how proteins function together will help in the development of new therapeutic agents and provide new ways to diagnose and treat reproductive disorders (Moore and Thatcher, 2006).

DNA sequencing identifies the "order of the nucleotides (the base sequence) in a DNA molecule" (NCBI, 2004). This is a key step in discovering the structure and function of genes. Once a reference sequence for a gene is known, this information can be used to identify errors in the genetic coding of individuals. The productivity of gene sequencing technologies, measured by the number of base pairs that can be sequenced by one operator per day, has increased 500-fold over the past decade, with costs declining by three orders of magnitude (Bio-Era, 2007). An increasing range of sequencing technologies are available, from those that rely on PCR to amplify genetic material before they can be used to those that require a single molecule to determine its sequence. DNA microarrays permit researchers to identify known genes for humans, animals, plants and insects. These open up many applications in monitoring.

Once desired DNA or RNA sequences are known, they can be synthesised for use in research or in the production of a product. As with gene sequencing, gene synthesis technology has improved dramatically. Synthesis productivity has doubled every year, improving 700-fold over the past decade, while costs have declined to a thirtieth of previous levels (Bio-Era, 2007). In addition, gene synthesis companies are active all over the world and can provide synthesised DNA sequences by mail from specifications received over the Internet. Gene synthesis companies are active all over the world and can provide synthesised DNA sequences by mail from specifications received over the Internet.

Bioinformatics covers the construction and analysis of databases containing information on genomes, proteins, and other complex cell processes. A number of biobanks have been established in several countries to collect genetic and other data from a large number of individuals. Analyses of databases containing human, animal and plant genomes are likely to lead to a better understanding of gene functions and improve the prevention, diagnosis and treatment of a wide range of illnesses.

As biotechnology evolves from a gene-based to a multidisciplinary science that takes into account full cellular modules and their interaction with the external environment, bioinformatics will play an increasingly important role. This will include systems modelling and the production of three-dimensional models of a wide variety of biological components.

Synthetic biology (synbio) is emerging as a new field for improving micro-organisms, based on an engineering approach that enables "the design

and construction of new biological parts, devices, and systems, [and] the re-design of existing, natural biological systems for useful purposes" (syntheticbiology.org, n.d.). The purpose of synbio is to increase biological efficiencies by designing a cell system for a specific function, thereby eliminating the production of unwanted products that waste the cell's energy.

One technique within synbio involves altering an organism's metabolic pathways, *i.e.* the set of chemical reactions by which a living organism or cell sustains itself. The aim is to induce a cell to either produce a desired substance or consume a substance (as for environmental remediation) (Nill, 2001). Metabolic pathway engineering has been used, for example, to develop micro-organisms that can produce the polymers polyhydroxybutyrate (PHB) (Rudnik, 2008), and propanediol (PDO) (DuPont, 2008a).

Another promising application of synbio is for biosensors. Recently, a biosensor able to detect arsenic in water, developed using synbio by the University of Edinburgh, was licensed to a non-profit spin-off from the university. Devices capable of detecting biofilm formation, responsible for causing infections and clogging in urinary catheters, are also under development.

The construction of a "minimal cell" or an "artificial genome" is a key theme in of synbio research. This can be done either using a fully synthetic genome which can then be inserted into a cell whose original DNA has been removed, or by constructing a synthetic cell from pre-designed biological components. Work on the former method has progressed significantly. In 2007 the US Patent and Trademark Office published a patent application from the J. Craig Venter Institute for the first fully synthetic bacterial genome (USPTO, 2007). Research is currently under way to insert this synthetic genome into a living bacterial cell (Kowalski, 2008; Pilkington, 2007).

Ongoing research in this area is assisted by several public databases[3] on metabolic pathways. The design of biological "parts" is facilitated by an open-access library of several hundred standard parts, or *BioBricks,* that can be assembled into various biological devices (IGEM, 2007). This could pave the way for an era in which "biodesign" can be carried out by people with expertise in systems design rather than biology.

Biotechnology applications in primary production

Modern biotechnology is used in primary production to develop new varieties of plants and animals with improved traits, new diagnostic tools, advanced propagation techniques for plants and animals, and therapeutics and vaccines for the treatment and prevention of veterinary illnesses. The following two sections discuss the current status of biotechnology in primary production related to plants and animals.

Plants

New crop varieties

Biotechnology is used to develop new varieties of food, feed and fibre crops that have commercially valuable genetic traits. One method is to use genetic modification to transfer genetic material across species that cannot interbreed. Other methods only use the genetic material of species that are naturally capable of interbreeding, such as gene shuffling and intragenics (Conner *et al.,* 2007; Jacobsen and Schouten, 2007). Biotechnologies such as marker assisted selection (MAS), which uses biological or chemical markers to identify traits, can also be used to improve accuracy and reduce the time required to develop new varieties based on conventional breeding techniques.

Both GM and non-GM research programmes focus on one or more of the following traits:

- *Herbicide tolerance (HT)* allows plants to resist the effects of specific herbicides. HT has been developed using both GM technology and other breeding techniques.
- *Pest resistance* improves the ability of the plant to resist harmful insects, viruses, bacteria, fungi and nematodes. The most common form of GM pest resistance uses a gene from bacteria (Bacillus thuringiensis, or *Bt*) to emit an organic toxin that kills some pest species.
- *Agronomic traits* improve yields and provide resistance to stresses that can reduce yields, such as heat, cold, drought and salinity.
- *Product quality characteristics* include modified flavour or colour, modified starch or oil composition that improves nutritional value or

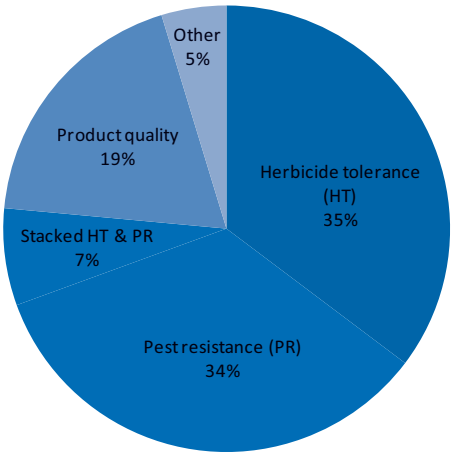
processing characteristics, and the production of valuable medical and industrial compounds.

- *Technical traits,* such as chemical markers, are essential for breeding programmes, but have no commercial value for growers.

Due to regulatory requirements, complete data on all field trials of GM plants are available for almost all OECD countries. The data provide information on the types of crops and traits that are under development and the firms and public research organisations that are active in GM research. In contrast, there are no consistent data sources for OECD countries for the use of non-GM biotechnologies in crop development, partly because registration of field trials is not required. There is strong evidence, however, that the majority of non-GM crop breeding programmes use biotechnologies such as MAS.[4]

Crop varieties with GM herbicide tolerance, pest resistance, or both have been used for over a decade and account for over 75% of the 85 GM varieties that were approved as of May 2007 in the United States (see Figure 3.1). Slightly less than 20% of the 85 varieties contained product quality or agronomic traits, but these two types of traits are the focus of many current research programmes. The remainder of approved GM varieties include traits for virus resistance or male sterility.

Figure 3.1. **USDA approved GM varieties as of May 2007, by trait**



Note: There are a total of 85 approved varieties. See Annex 3.A1 for details.

Source: Authors, based on USDA, APHIS GM approvals.

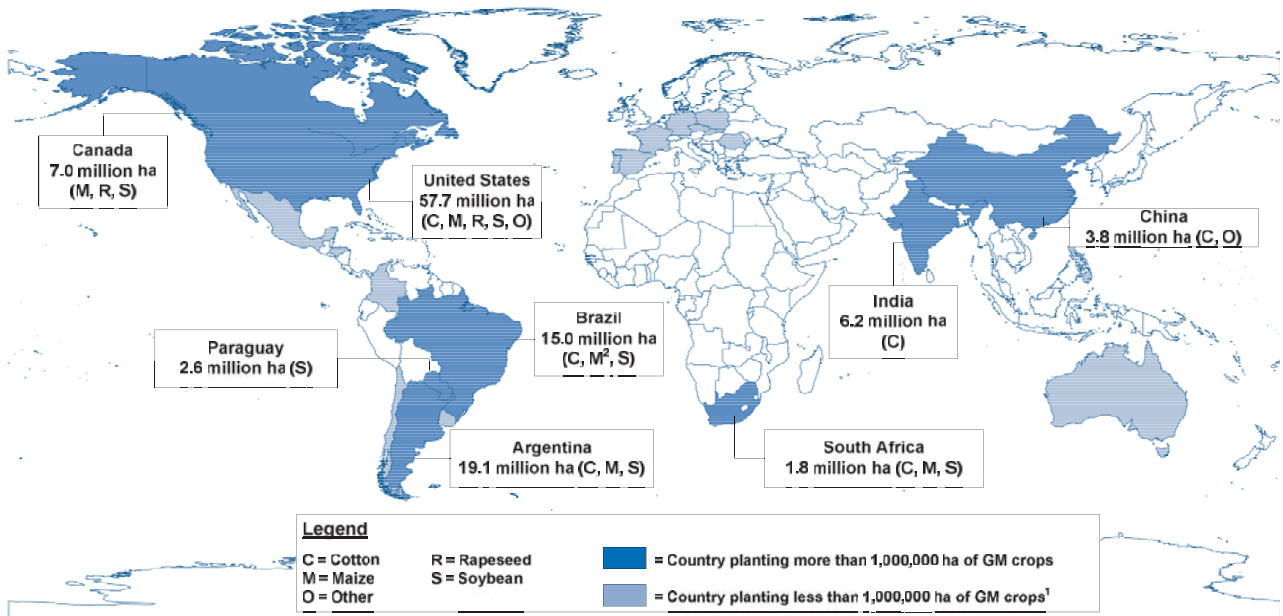
Although GM varieties of over a dozen different plant species[5] have received regulatory approval somewhere in the world, the large majority of GM plantings are for cotton, maize, rapeseed (canola), and soybeans. Uptake in many regions of the world, in both OECD and non-OECD countries, has been rapid, with GM crops planted in 10 OECD countries and in 13 non-OECD countries in 2007. Figure 3.2 displays all the countries that had approved biotech crop plantings in 2007, and highlights the eight countries (two OECD and six non-OECD) that planted a minimum of 100 000 hectares. Globally, around 107 million hectares were planted with GM crops in 2007, accounting for approximately 9% of global hectares planted with all crops and approximately one-third of the plantings of the four main GM crops noted above.[6]

While most commercialised GM plant varieties were developed in OECD countries, many developing countries are also active in using biotechnology to improve crop varieties. The FAO-BioDeC database lists 1 678 non-GM biotechnology crop projects and 929 GM crop projects in 88 countries. Approximately 8.5% of the non-GM projects and 6.2% of the GM projects have led to commercialised varieties. The major GM target crops (cotton, maize, rapeseed and soybean) comprise almost all of the commercialised GM varieties as well as a large majority of the GM crop R&D occurring in the developing world. Other research targets include, among others, sugar cane, barley, bananas, coffee, eggplant, oil palm, pineapple, sweet potato, and various beans and peas.

Forestry

The adoption of GM for forestry has been relatively slow compared with GM crops. This is due to the genetic complexity of trees, the long breeding times required, and multi-gene modification requirements for most traits. Almost all biotechnology programmes for tree species are in the research stage, with the exception of GM poplar tree plantations in China (Pearce, 2004). While GM field trials of commercially valuable traits for forestry have been conducted for quality characteristics, herbicide tolerance and pest resistance, the largest number of trials is for technical traits that are not destined for commercialisation but meant to assist further research. The pace of research into GM trees has, however, increased. Over 387 GM field trials were conducted with tree species from 2000 to 2007, versus only 93 field trials conducted from 1987 to 2000.[7]

Figure 3.2. **Approved GM crop plantings, 2007**



1. Countries planting less than 1 000 000 hectares in 2007 include the following countries (hectares of GM plantings in parentheses): Australia (100 000), Czech Republic (<50 000), Chile (<50 000), Colombia (<50 000), France (<50 000), Germany (<50 000), Honduras (<50 000), Mexico (100 000), Philippines (300 000), Poland (<50 000), Portugal (<50 000), Slovakia (<50 000), Spain (100 000), Romania (<50 000), and Uruguay (500 000).
2. Brazil did not approve GM maize until 2008 (Reuters, 2008). GM maize is therefore not included in the number of hectares planted in Brazil in 2007.
Source: Figure produced by Salim Sawaya, using data from James, 2007 and Reuters, 2008.

Biotechnology is currently being used to develop tree varieties with modified lignin that can reduce paper production costs, particularly for specialty paper. Faster-growing tree species for timber, pulp and paper, and biofuel production are another important goal.

Biotechnology is also applied to the propagation of trees. The goal is to propagate genetically identical seedlings of genetically superior trees. Biotechnology-based propagation technologies, sometimes coupled with MAS, can significantly speed up tree breeding programmes. A common technique is micropropagation, which allows rapid propagation, *in vitro*, of vegetative stock from tissue cultures (Forest Resources Development Service, 2004; McCord and Gartland, 2003). While non-biotech root cutting techniques are widely used for angiosperms (broadleaf trees), it is more difficult to use this technique for conifers. An option for conifers is somatic embryogenesis, a type of micropropagation in which ordinary plant tissue is used to produce genetically identical seedlings. This technology has been commercialised and can produce substantial yield gains of 30%-60%, compared to 8%-13% from traditional open pollination. Somatic embryogenesis can also be used to ensure that desired genetic traits are maintained during reproduction (Cellfor, n.d.).

Developing countries are also applying biotechnology to forestry, with a number of commercialised applications. The FAO-BioDeC database contains 810 non-GM and 46 GM projects related to forestry. Micropropagation and biotechnology-based plant breeding account for 51% and 33% of the non-GM research projects, respectively, while the rest of the forestry research projects are on diagnostics or biobased pesticides and fertilisers. Over 41% of all the GM forestry research in the developing world focuses on insect resistance, 13% on bacterial and fungal resistance, 11% on salinity resistance, and 4% on wood quality/lignin content.[8]

Plant diagnostics

Diagnostics can identify a plant disease before it causes significant economic damage, allowing the farmer to either treat the affected crop with pesticides or prevent the spread of disease to unaffected crops. Estimates of the economic losses from plant disease vary widely depending on the underlying assumptions. Two studies for the United States estimate annual losses of USD 9.1 billion (Fermin-Munoz *et al.*, 2000) and USD 33 billion (Pimentel, Zuniga and Morrison, 2004). In relative terms, developing countries suffer greater economic losses than developed countries because of the economic importance of agriculture and because many farmers cannot afford to purchase plant protection products.

Several diagnostics to detect diseases through the presence of specific genes or proteins (*e.g.* an antibody) are being used to detect plant pathogens.[9] Diagnostics are available for 954 plant diseases, of which over 90% are for bacterial, fungal or viral pests. These diagnostics cover the most important pathogens of developed countries (Ward *et al.,* 2004), but many must be conducted in a laboratory and require specific skills. The goal of much current research is to develop real-time diagnostics for use in the field.

Animals

Biotechnology has three main applications for livestock, poultry and aquaculture: breeding, propagation and health (diagnostic and therapeutic). The identical set of biotechnologies (*e.g.* MAS and GM) used in plant breeding can be applied to animal breeding. In addition, diagnostics can be used to identify serious inherited diseases in order to remove afflicted animals from the breeding population. Biotherapeutics, due to their high cost, are primarily used for companion animals (household pets) or for valuable animal breeding stock.

Animal breeding

The largest commercial application of biotechnology in animal breeding is the use of MAS to improve the accuracy and speed of conventional breeding programmes. This technology is widely used in both OECD and non-OECD countries. As an example, MAS is used by European pig breeders to screen for genetic problems and remove defective stock (Menrad *et al.*, 2006). MAS is less widely used to identify the presence of desirable genes, partly because of a lack of adequate knowledge of genetic markers for target animals. MAS varieties of fish are estimated to account for 30% of salmon and trout revenues and 10% of oyster revenue from aquaculture in the European Union. MAS varieties are also estimated to account for 15% of total sales from fish farming (Zika *et al.*, 2007).

R&D into breeding GM animals has aimed at producing desirable compounds in their milk or blood, improving food characteristics, or imparting traits that reduce some of the harmful environmental impacts of large-scale animal production. In February 2009, the US Food and Drug Administration (FDA) approved the first drug – ATryn for treating hereditary antithrombin deficiency –produced in genetically modified goats (Vedantam, 2009). In addition, transgenic fish species are being developed with improved growth rates and greater resistance to viruses, bacteria and cold temperatures (Kapuscinski *et al.,* 2007).

Propagation

Somatic nuclear transfer cloning is the primary advanced biotechnology technique used in the propagation of animals. It consists of removing the nucleus of an egg cell and replacing it with the nucleus (and DNA) of a donor individual of the same species. The cloned animal is identical to the animal that donated the DNA. Although costs are decreasing and will probably continue to do so, this technique is too expensive to be widely used for basic animal breeding. Its use is limited to the reproduction of high-value animals such as breeding bulls and niche animals such as pets. Cloning can also be used for GM animals, since conventional breeding of GM stock could result in the loss of the genetic trait. Although technologies are being developed to improve cloning success, such as pre-implementation genetic diagnosis (PGD) that screens embryos for genetic defects, problems associated with survival rates and birth defects continue to be problematic.

Animal diagnostics and therapeutics

The animal diagnostics sector is based on genetic and immunological tests that were developed for the human diagnostic industry, with minor variations. There are two main markets for animal diagnostics: companion animals (pets) and farm animals. The former is particularly valuable, because pet owners are willing to spend more on healthcare per animal than livestock farmers.

In 2007, 160 veterinary diagnostic kits using 69 different methods – 39 of them based on biotechnology – were available to detect 57 diseases.[10] Eighteen of the diagnostics only detect diseases of companion animals. The available diagnostic kits cover 26 of the 91 diseases that the World Organisation for Animal Health (OIE) has deemed as "of serious socio-economic or public health consequence" (OIE, 2005). There is evidence that the development of veterinary diagnostics is increasing, as over one-third of the 160 diagnostics on the market in 2007 were launched between 2002 and 2007, but most of these were not based on biotechnology (USDA, 2006).

Biotechnology has also contributed to several diagnostics for aquaculture. These use DNA to detect pathogenic viruses in farmed fish and crustaceans.[11] The goal is to develop biotech-based microarrays for detection of aquatic animal diseases. For example, the Fisheries Research Agency in Japan has developed a chip that can diagnose 23 different bacterial infections in one test (TheFishSite, 2005).

Very few biopharmaceuticals or biovaccines have been approved for animal use. The FDA's Center for Veterinary Medicine lists only two approved biopharmaceuticals. The small number is probably due to poor

cost-effectiveness in livestock or a lack of applications in valuable animals such as family pets and racehorses. The only recombinant vaccine approved for livestock in the United States as of December 2006 is for West Nile Virus (USDA, 2006), although recombinant rabies vaccines are approved for wild racoon populations and for cats. In 2007, 13 biotechnology treatments for fish disease were available. However, despite the existence of some extremely virulent viruses that can kill up to 100% of the affected population (OIE, 2006), there are only two vaccines for fish.

Other biotechnology applications for animals

In addition to its uses for farmed fish, biotechnology has a number of applications for marine resources (see Box 3.1) such as wild fish, molluscs and other marine species. DNA fingerprinting to distinguish between different stocks of migrating fish can be used to manage wild stocks and close fisheries when stocks become endangered. DNA fingerprinting can also be used to determine the factors that improve survival of wild species released from hatcheries (Gaisser *et al.*, 2006).

Box 3.1. **Ocean and marine applications**

Oceans cover more than two-thirds of the world and contain 97% of all water. They also contain about 80% of life on earth, are responsible for nearly 40% of global photosynthesis (Hourigan, 1998), and hold 90% of the world's biomass (ISIS, 2006). Those figures show the potential for ocean and marine resources to become an integral part of the bioeconomy.

The wealth of living marine resources and their genetic characteristics could form the basis for countless new biotech applications. For instance, bacteria known as thermophiles thrive in very hot water conditions ranging from around 50°C to 80°C. Other bacteria known as hyperthermophiles can survive at temperatures over 120°C (NSF, 2003). The genetic characteristics that permit survival in high temperatures could be applied to applications in resource extraction – for example, where hot environments are a major challenge.

The oceans are thus a key location for bioprospecting, or the search for naturally useful genetic resources. During a two-year circumnavigation of the world, the Sorcerer II Global Ocean Sampling Expedition sampled sea organisms and their genes. The expedition produced a publicly available dataset of more than 7.7 million sequences or 6.3 billion base pairs of DNA, which is thought to be the largest publicly available metagenomic dataset in the world (JCVI, 2007).

Another potentially useful characteristic of some marine species is an ability to reproduce very quickly. Numerous algal species have growth rates that are many times faster than land-based crops. If harvested, these could be used as a source of biomass for electricity generation. Some algae can (or can be designed to) produce compounds useful for fuel, chemical, or nutraceutical production. Nutraceuticals, such as omega three oils, can also be extracted from fish.

In order to ensure that the oceans' potential as a benefit to the bioeconomy is realised, biodiversity needs to be protected. Biotechnology can make an impact here, too. Fishery depletion has become a major problem, with an estimated 25% of world fish stocks overexploited or depleted, and 52% of stocks near their maximum sustainable limits (OECD, 2008). DNA fingerprinting can help to preserve fish stocks by identifying overfishing (Gaisser *et al.*, 2006).

Biotechnological applications for insect pollinators and pests are still in the research stage. Current research aims to reduce the reproductive viability of insect pests and improve the ability of valuable pollinators such as honeybees to resist pests and diseases.

Biotech applications in health

There are three main areas in which biotechnology has been applied to health: therapeutics, diagnostics, and pharmacogenetics. There are in addition two other areas where biotechnology could have applications for health: functional foods and nutraceuticals (FFN) and medical devices.

Therapeutics

For the purposes of this report, therapeutics developed using biotechnology are classified into three groups:

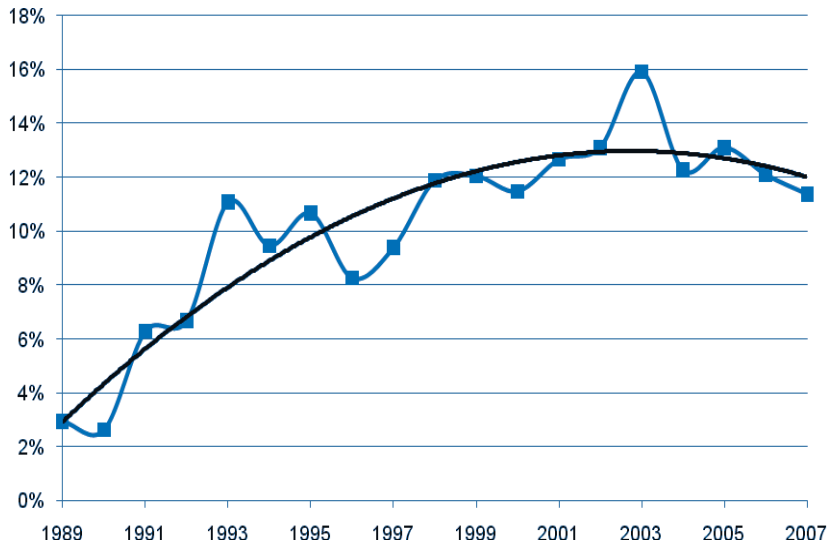
- *Biopharmaceuticals* are large-molecule therapeutics with molecular weights of several thousands or even tens of thousands of daltons. They include monoclonal antibodies (mAbs) and recombinant versions of proteins, amino acids, vaccines, enzymes and hormones. Many of them are produced by recombinant micro-organisms or cell-lines of higher organisms and even in GM plants and animals. Some biopharmaceuticals can be produced without using recombinant technology – for example, pigs can be used to produce porcine insulin. These "biologics" are not covered in this report.
- *Experimental treatments* include a disparate group of biotechnologies with very few, if any, products on the market, *e.g.* tissue engineering, therapeutic vaccines,[12] stem cell research, and gene, antisense, and RNAi therapies. Tissue engineering is based on knowledge of the growth and differentiation of cells, and includes bone and skin scaffolds and (potentially) the engineering of other complex organs. Therapeutic vaccines stimulate the immune system to attack proteins that cause an existing disease, for example those associated with tumour cells. Stem cell research could lead to the repair or production of entire organs. Gene, antisense and RNAi therapies involve the modification of genes or their functions in living cells.
- *Small-molecule therapeutics* are usually produced through chemical synthesis. Biotechnology can be used to identify new therapeutic targets, to provide a means to more effectively screen drug candidate molecules in pre-clinical research. Genetic testing

technologies also support the design of more targeted clinical trials and more informed prescribing practices. Recombinant biotechnology or metabolic pathway engineering can be used to manufacture small-molecule precursors and chiral forms of drugs, as well as some pharmaceuticals that cannot be synthesised at low cost or in sufficient quantities.

Biopharmaceuticals

Since 1989, the biopharmaceutical share of all new pharmaceutical compounds (new molecular entities or NMEs)[13] that received market approval increased from 2% to 16% in 2003. As shown in Figure 3.3, this share has been relatively stable between 1999 and 2007, at between 12% and 14% of NME registrations. This equates to approximately seven new biopharmaceuticals per year.

Figure 3.3. **Share of biopharmaceutical NMEs out of all pharmaceutical NMEs (three-year moving average), by year of first registration for market approval, 1989-2007**



Note: First registration refers to the first time a drug received marketing approval in any jurisdiction in the world.

Source: Authors, based on data from Pharmaprojects (Informa, 2008).

An important measure of the impact of new drug approvals on public health is their additional therapeutic value, defined as their effectiveness in treating a medical condition compared to existing therapies. Many biopharmaceuticals have delivered substantial therapeutic value. Just a few of the numerous examples include imiglucerase for treating Gaucher's disease, trastuzumab (Herceptin) for treating breast cancer, and alpha and beta forms of erythropoietinfor treating several types of anaemia.[14] On the other hand, a new drug that offers no improvements over an existing drug already on the market provides little additional therapeutic value. Examples include the many different versions of cholesterol-lowering drugs or insulin on the market. These types of drugs are commonly known as "me too" drugs. Since the early 1980s, they have accounted for approximately two-thirds of all new drugs (GAO, 2006).

France's *Haute Autorité de Santé* (HAS)[15] evaluates the additional therapeutic value of drugs that have been approved for the French market. As shown in Table 3.1, an analysis of HAS ratings for 53 of 109 biopharmaceuticals approved for use in the United States or the European Union, plus 1 476 other drugs, shows that biopharmaceuticals provided a substantially higher level of therapeutic value than their non-biotechnology-based counterparts.[16]

A single drug can be approved for multiple indications.[17] For example, HAS evaluated 53 biopharmaceuticals for 103 different indications. The second column of Table 3.1 gives the highest rating given to each biopharmaceutical for at least one approved indication. The comparison with all other drugs is based on all indications for which the drug is approved. In this comparison, a much higher percentage of biopharmaceuticals, 47.6%, compared to 12.4% for all other drugs, provide a "moderate improvement" or better. In addition, only 38.8% of biopharmaceuticals are rated as offering no therapeutic advance over existing drugs on the market, versus 77.2% of all other drugs. These results show that biopharmaceuticals have, so far, offered substantially greater therapeutic advances than other types of drugs.

Generic versions of biopharmaceuticals, known as biosimilars, could significantly reduce the cost of these drugs. At the end of 2008, five biosimilars were approved for use in Europe, but only one in the United States. The number could increase in the future as many biotherapeutics are approaching the end of their patent life. The United States has lagged Europe in approvals of biosimilars because of concerns over the ability of firms to replicate the manufacturing processes for complex biomolecules.

Table 3.1. **HAS evaluations of the therapeutic value of biopharmaceuticals and all other drugs**

January 2001 - December 2007

Evaluation class	Biopharmaceuticals				All other drugs	
	Highest rating		All indications		All indications	
	No.	%	No.	%	No.	%
Major therapeutic progress	5	9.4	9	8.7	35	2.4
Important improvement	13	24.5	22	21.4	52	3.5
Moderate improvement	12	22.6	18	17.5	96	6.5
Minor improvement	8	15.1	9	8.7	105	7.1
No improvement ("me too")	11	20.8	40	38.8	1 139	77.2
Judgement reserved	4	7.5	5	4.9	49	3.3
Total	53	100	103	100	1 476	100

Notes: For a full definition of each evaluation category, see Annex 3.A2. Analysis includes therapeutics but excludes diagnostics, vaccines and generic drugs.

Source: Authors, based on data from the French *Haute Autorité de Santé* (HAS).

Experimental therapies

Many new experimental therapies are also being developed. These include regenerative technologies such as cell and tissue engineering, stem cells and gene therapies; and antisense and RNAi therapies. Some experimental therapies have the potential to prevent and cure diseases rather than treat them.

Despite many years of research only a few experimental therapies, such as simple tissue engineering, have reached the market (BBC News, 2008). Many of these treatments have been held back by strong immune system reactions to the treatment that cause adverse effects and limit effectiveness. However, R&D pipelines remain robust with products in all phases of clinical trials. A few products have completed Phase III clinical trials and await market approval.

Small-molecule therapeutics

Small-molecule (SM) drugs, usually less than 500 daltons in weight (Cheng *et al.,* 2007), account for approximately 86% of all new chemical entities (NCEs) approved since 1999. Biotechnological knowledge can be applied to develop, produce, test and manage the use of SM drugs. This application creates opportunities to improve the productivity of SM drug development in four ways:

- *Drug discovery:* Genomics and genetic databases, plus analytical methods such as gene transfer, gene expression profiling and gene knockout techniques are used to identify human drug targets (Pisano, 2006; Hopkins *et al.*, 2007).
- *Clinical trials:* Biotechnological knowledge, such as pharmacogenetics, toxicogenomics and gene-based diagnoses can improve the safety and efficacy of drug development and clinical trials by identifying population groups that respond or do not respond to treatment.
- *Manufacturing:* Microorganisms developed through GM or metabolic pathway engineering can manufacture compounds that are too expensive to synthesise or derive from natural sources.
- *Patient care:* Pharmacogenetics can identify individual patients who will respond to specific drugs and exclude patients for whom the drug has few therapeutic benefits or potentially adverse side effects.

Diagnostics

Diagnostic tests based on modern biotechnology are used to identify both genetic diseases and non-genetic diseases. Diagnostics can be either *in vivo* (invasive and inserted into the body), in which case they are closely regulated through clinical trials, or *in vitro* (non-invasive) in which case the regulatory requirements are often considerably less demanding.

Biotechnology-based *in vivo* diagnostics are a relatively small market; only 13 have obtained market approval and 11 are in development or clinical trials. The majority of these *in vivo* diagnostics are aimed at detecting cancer.

By contrast, the *in vitro* diagnostic (IVD) market is relatively large. Regulations for *in vitro* diagnostics are usually considerably less demanding than for *in vivo* diagnostics because the former are not traditionally seen as damaging to health. Without stringent registration guidelines, it is difficult to know the exact number of *in vitro* diagnostic products using biotechnology. An indication of the biotech market share can be drawn from revenue data. Zika *et al.* (2007) estimated the biotech share of 2004 IVD revenues at 30%, ranging from 37% in the United States to 29% in the EU-5[18] and 21% in all other countries.

In general, there are two main types of biotechnology-based *in vitro* diagnostic tests: immunological (based on the specificity of antibodies to bind to a target molecule) and molecular genetic (based on the binding properties of similar gene sequences). Antibodies specific to a very wide

range of molecules can be generated and used to detect signs of diseases or to detect foreign substances in a variety of human fluids, such as blood or urine. A well-known immunological test uses mAbs to detect a hormone in a woman's urine to determine if she is pregnant.

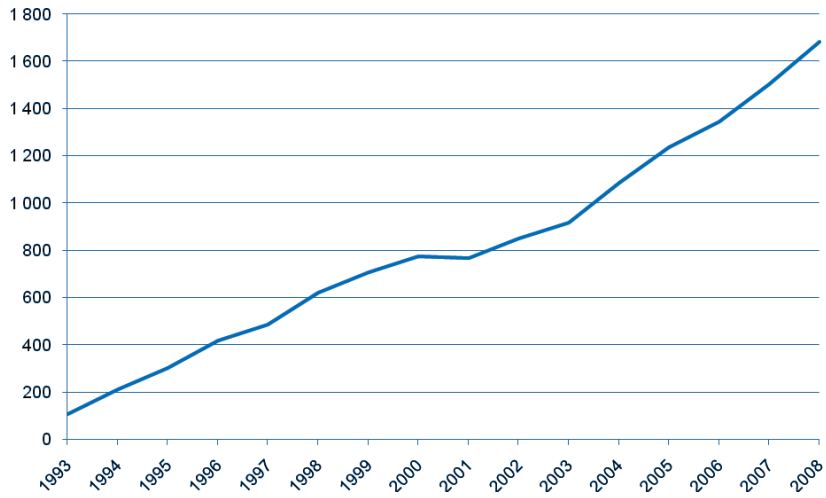
Genetic tests can identify specific genes, and determine the presence or absence of mutations or other changes in an individual's genetic material. Genetic testing can yield information in a wide variety of circumstances from pre-implantation screening of embryos during *in vitro* fertilisation (IVF), screening of foetuses, or of children or adults to diagnose genetic conditions, to identify a person's risk profile for developing or passing on certain medical conditions, or even to detect infectious agents such as the Human Papilloma Virus. Genetic tests are increasingly being developed to detect variations in several genes at once. For example, a diagnostic test for seven genes has recently been developed to assess the risk of common forms of breast cancer (deCODE, 2008).

The GeneTests website catalogues over 1 600 diseases for which genetic tests are currently available (see Figure 3.4). Submissions to GeneTests are voluntary. This means that the catalogue might not include all genetic tests available worldwide, although it does provide a lower limit of the number of diseases for which genetic testing is available. Many of these tests target single genes that are linked to rare diseases. Other tests identify genetic risk factors for several diseases with a high frequency, such as cancer, AIDS/HIV or anaemia. The use of genetic tests is also increasing rapidly. An OECD survey of 1 306 genetic testing laboratories found that the number of genetic tests performed increased by 60.2%, from 874 608 in 2000 to 1 401 536 in 2002 (OECD, 2007).

Pharmacogenetics

Pharmacogenetics examines the way in which genes and drugs interact. The method uses diagnostics and bioinformatics to identify subgroups that respond or do not respond to specific drugs. This technology could pave the way to more targeted health therapies. A small number of drugs have only been approved for population subgroups with certain genetic characteristics.

Figure 3.4. **Number of diseases for which genetic testing is available as reported to GeneTests, by year**



Source: Authors, based on GeneTests, 2008.

The OECD has identified three ways in which pharmacogenetics is currently applied in clinical practice:

- "to help identify responders and non-responders to a treatment;
- to aid in establishing appropriate dosages for responders;
- to identify susceptibility to adverse drug reactions (ADR) and possibly exclude some patients from treatment." (OECD, forthcoming)

The widespread use of pharmacogenomics and pharmacogenetics[19] could lead to personalised medicine, where the type of prescribed drug and dosage are determined by an individual's genome. The use of these technologies in drug development and delivery could decrease drug development time and cost, due to smaller, targeted clinical trials and shorter drug approval times. Benefits to healthcare include personalised, more effective dosages and fewer adverse drug reactions.

Pharmacogenetics requires validated genomic biomarkers.[20] As of September 2008, the FDA has identified 27 validated markers for 25 drugs for which genetic testing is required, recommended or suggested for information before prescribing (see Table 3.2). This number has increased

from 18 validated biomarkers in October 2006. The share of FDA-approved drugs containing pharmacogenetic information on their labels has increased as well, from only 5% of drugs approved in 1990 to 37% of drugs approved in 2005 (Frueh, 2006).[21]

Table 3.2. **Valid FDA genomic biomarkers and genetic testing requirements, September 2008**

FDA category	Validated biomarkers[1]
Test required	4[2]
Test recommended	10[3,4]
Information only	14
Total	27[5]

1. For detailed information on each drug, see FDA, 2008.

2. Required tests are for drugs treating breast cancer, colorectal cancer, HIV and leukaemia.

3. One drug (Warafin) has three associated genomic biomarkers for which testing is recommended.

4. Testing for one drug (Carbamazepine) is only recommended for at risk persons.

5. One drug, Cetuximab, is counted twice because its testing is required for colorectal cancer and recommended for head and neck cancer.

Source: Authors, based on FDA, 2008.

Functional foods and nutraceuticals (FFN)

Health Canada defines a functional food as "similar in appearance to … a conventional food that is consumed as part of a usual diet and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions, *i.e.* they contain bioactive compounds." A nutraceutical is "a product isolated or purified from foods that is generally sold in medicinal form … and demonstrated to have a physiological benefit or provide protection against chronic disease" (Health Canada, 1998). Nutraceuticals can also be extracted from non-food plants such as marine algae.

Many nutraceuticals, such as fish oils, and functional foods with added nutrients have been available for decades and are not produced using

modern biotechnology. Biotechnology can be used to engineer or select plant or animal specimens with increased levels of certain nutrients or functional components. These can then be consumed or the components extracted for use. There are no data on the share of FFN products or sales derived from biotechnology, but the share is probably very low.

In developed countries with diverse diets, the health need for functional foods is generally low. Due to the high R&D and regulatory costs of using biotechnology to improve the nutritional content of foods, the most economically viable application of biotechnology is for staple foods that are purchased in large quantities. To date, mandatory rules based on proven health benefits have often been required to create functional foods. Examples include regulations to increase the content of folic acid in bread or vitamin D in milk (Food Safety Authority of Ireland, 2006). These requirements have been met through fortification instead of through enhanced crops.

Biotechnology has been used to develop functional foods with improved oils[22] and fruits such as tomatoes with high levels of anti-oxidants, such as lycopene and anthocyanins, that are thought to offer protection against cancer and cardiovascular disease (Hayden, 2008). Consumers in developed countries may be willing to pay a premium for these products, sufficient to cover R&D and regulatory costs, if they believe that they offer health benefits.[23]

Medical devices

Medical devices include surgical instruments and equipment, *in vitro* diagnostics, tissue engineering, medical imaging equipment and products that affect the biological structure of a person but which do not achieve their effects through a chemical or biological reaction (*e.g.* implants, prostheses, neuroprosthetics to restore vision, hearing or motor function, pacemakers, infusion pumps, dialysis machines). Many medical devices do not involve biotechnology, but tissue engineering and many diagnostics are part of biotechnology and have therefore been discussed above. Another type of medical device is a biosensor that uses proteins to detect molecules. Biosensors utilising enzymes can mediate chemical reactions that indicate the presence of substances without becoming exhausted, and consequently have a long lifetime. Enzyme-based biosensors are currently used with insulin pumps to monitor glucose levels in diabetics.

Biotech applications in industry

Industrial biotechnology (IB) is used in the production of chemicals and derived biomaterials, with additional applications in mining and resource extraction. There are many industrial applications based on enzymes that are either produced by GM micro-organisms or selected using modern biotechnology. Activity is also under way to combine a number of biobased industrial processes into a single production line known as a biorefinery.

Production of chemicals

Biotechnology can be used to produce a large number of biofuels and bulk and specialty chemicals, including enzymes, solvents, amino acids, organic acids, vitamins, antibiotics, and biopolymers. Bulk chemicals, including some organic acids, have high global production volumes of over 3 million tonnes per year and low prices and profit margins. Specialty and fine chemicals have low production volumes and high prices and profit margins; they are often for use in medicines. In many cases these biotechnology processes compete with other production methods such as chemical synthesis.

In chemical production, biotechnological processes can substitute one or more chemical steps. They thus can have several advantages over traditional chemical synthesis, including include more specific reactions, less demanding production conditions (such as lower temperature and pressure, and milder pH conditions) and lower energy inputs, waste, and environmental impacts. Despite these advantages the uptake of biotechnology in chemical production is limited, due to the high costs of enzymes or bioreactors and the costs of building or modifying production facilities to use biotechnology. The USDA (2008) estimated that biotechnological processes produced 1.77% of the estimated worldwide chemical production value of USD 1.2 trillion in 2005.

Ongoing research aims to make biotechnology more cost-competitive through improved production methods such as process intensification and *in situ* product recovery, as well as through the use of genetic modification and metabolic pathway engineering to increase the output efficiency of micro-organisms. Research is also under way to develop fermentation processes that are effective at pH levels conducive to the product being developed. For instance, low pH production of organic acids reduces the demand for neutralisers and the need for downstream processing because no salt is produced as a by-product. Fermentation systems that permit more than one strain of a micro-organism in a bioreactor could dramatically reduce

production costs. This approach is already established for ethanol production.

Production of biomaterials

In addition to traditional biobased materials such as wood and cotton, biobased chemicals can be used to create packaging and containers, fabrics and consumer durables (*e.g.* electronics casings and car components). While some niche applications exist, the most important biomaterial to date has been bioplastics, manufactured from biopolymers. Some bioplastics are biodegradable while others, similar to most common petrochemical-based plastics, are not but can be recycled. At present, the development of biodegradable bioplastics is more advanced than non-biodegradable plastics, but research is under way into non-biodegradable bioplastics.

Some bioplastics, including the most common starch-based polymers, can be produced without modern biotechnology, but many others require advanced fermentation or designer micro-organisms for the production of polymers and monomers (the building blocks of polymers). In addition, advances in agricultural biotechnologies, especially those related to product quality traits that increase the quantity of certain plant components, could have a major positive impact on biopolymer production by increasing production yields. For example, research has advanced on the production of PHB (a type of polyester) in switchgrasses. GM switchgrass is currently capable of producing 3.7% of its weight in PHB, but a minimum PHB weight of 5% is required for commercial viability (Kram, 2008).

There are generally four broad categories of polymers that are currently being examined for biobased production. These are, from the most to least technically advanced, polysaccharides, polyurethanes, polyesters, and polyamides (nylons). They differ in the type of monomers and the type of chemical bond that joins them. They also vary in their functionality and usability since their physical, chemical, mechanical and thermal properties differ.

Estimates of current (2008) annual bioplastic production range from 300 000 metric tonnes (European Bioplastics, 2008) to nearly 600 000 metric tonnes (USDA, 2008). As shown in Table 3.3, several large biopolymer production plants have been built and many others are under development all over the world. For instance, in the United States 225 000 metric tonnes of capacity were expected to be available by the end of 2008. While these are substantial quantities, they represent a very small share of overall polymer production. It was estimated that in 2003 biopolymers accounted for only 0.07% of Japan's polymer production (Web

Japan, 2003) and in 2007 only 0.21% of Europe's polymer production (European Bioplastics, 2008).

Table 3.3. **Examples of biopolymer production facilities in use or development**

Country	Type of polymer (class)	Capacity (metric tonnes)	Launch date
United States	Polyester (PLA)	140 000	2002[1]
United States	Polyurethanes (PDO)	45 000	2006[2]
United States	Polyester (PHB)	50 000	2008 (expected)[3]
Italy	Starch polymers	60 000	2008 (expected)[4]
China	Polyester (PHB)	10 000	2009[5]
Brazil	Polyester	350 000	2011[6]
France	Polyester (PBS)	Unknown	2011[7]

1. *http://pubs.acs.org/cen/news/85/i41/8541news6.html.*

2. *www2.dupont.com/Government/en_US/news_events/article20060620.html.*

3. *http://seekingalpha.com/article/33404-metabolix-archer-daniels-midland-announce-production-of-mirel-natural-plastics.*

4. *www.epobio.net/newsletter/news040703.htm.*

5. *www.euroinvestor.co.uk/news/shownewsstory.aspx?storyid=9756295.*

6. *www.csrwire.com/News/9270.html.*

7. *www.rrbconference.com/bestanden/downloads/142.pdf.*

Industrial enzymes

Enzymes are proteins that can repeatedly catalyse biochemical reactions without being damaged by those reactions. In addition to being used to produce chemicals, they have numerous industrial uses in food and feed, detergent, textile, biofuel (see below), and pulp and paper production.

The use of enzymes typically replace the use of chemicals and has a significant effect on the environmental load of industrial processes; *e.g.* the CO_2 emission is often decreased due to lower energy consumption when processes are carried out at lowered temperatures.

Food, feed, and beverages

Enzymes are frequently used in food and beverage production, including that of cheeses, breads, and fermented beverages; they reduce raw material inputs, substitute traditional chemicals and lower the energy used during production. Many enzymes are produced using genetically engineered micro-organisms to improve production efficiencies – the enzyme itself is

not necessarily modified. MAS and high-throughput screening are used to select micro-organisms that produce unique enzymes or to optimise enzyme production.

Enzymes can also be added to animal feed to improve the digestibility and nutrition of many materials. For instance, somewhere between 50% and 80% of all phosphorous in pig and poultry feed is bound in a molecule known as phytate. Enzymes, called phytases, can be added to animal feed to break down phytase. This increases the nutritional value of the feed by releasing phosphate and, by optimising the animal's phosphorous intake, reduces the release of phosphorous into the environment, thus reducing water pollution (Novozymes, 2008).

Detergents, textiles and pulp and paper[24]

The use of enzymes in detergents, textiles and pulp and paper offers many advantages over traditional methods, such as improved performance; reduced energy and water consumption due to lower required temperatures and increased efficiency; lower environmental impacts via reduced harmful by-products, and improved product quality.

Enzymes have been added to detergents since the early 1930s to improve washing quality at low temperatures. Enzymes were also adopted quickly by the textile industry, where they are used to provide desired textile effects and remove starch and impurities like wax from cotton.

Enzymes in the pulp and paper industry have only been used for the past two decades or so, but adoption has occurred rapidly. The industry uses enzymes to modify starch for the production of coated papers and to break down lignin in order to reduce the consumption of bleaching chemicals. Other widely used applications include enzymes to reduce pitch (which can create holes in paper and interfere with machinery during production) and to facilitate recycling by removing sticky residues and improving the de-inking process.

There are many different enzymes currently on the market for these application areas. A good number are produced using modern biotechnologies and current research is aimed at expanding the range of useful enzymes. Biotechnology can create new enzymes through the use of a number of techniques including genetic manipulation, protein engineering, directed evolution, and by advanced selection techniques.

Environmental applications

In addition to the environmental benefits from the use of biotechnology in primary production and industrial processing, biotechnology can be used in the environmental services sector to repair or monitor environmental conditions. Two main applications include:

- *Bioremediation* – "uses micro-organisms to reduce, eliminate, contain, or transform to benign products contaminants present in soils, sediments, water, or air" (DOE, 2003)
- *Biosensors* – are devices "that use an immobilised biologically-related agent (such as an enzyme, antibiotic, organelle or whole cell) to detect or measure a chemical compound" (FAO, n.d.)

Bioremediation technologies have been used for many years and form the technological foundation of most modern sewage treatment plants. Waste from industry (*e.g.* heavy metals), agriculture (*e.g.* chemical fertilisers) and nuclear plants pose a modern and more challenging problem.

The most important work now carried out for bioremediation is to improve the ability of micro-organisms to neutralise harmful compounds. While MAS can be used to select candidate organisms, given the difficult compounds to be treated, it is likely that GM and metabolic pathway engineering will be required to significantly improve efficiencies. In view of the extreme conditions at many sites requiring bioremediation, work is also under way to increase the resistance of micro-organisms to toxins and metals so that they are suitable for use.

Biosensors can be used for long-term monitoring of environmental conditions and biodiversity. Compared to biosensors, sensors based on chemical analysis are generally cheaper to develop, but more expensive per test. They are consequently less suited than biosensors when multiple readings are required over time. However, very few environmental monitoring systems have required high sample volumes, resulting in limited commercial applications for environmental biosensors.

While comprehensive R&D figures are not available, a review by the authors of biosensor R&D in the European Union, Japan and the United States found very little investment by the private sector and no significant increases in public sector funding over historical levels. Research is ongoing, however; a 2003 study identified research into 31 biosensors aimed at detecting pesticides, organic compounds, metals, and biological parameters (*e.g.* toxicity, identification of micro-organisms) (Sharpe, 2003). A more recent study found 34 companies involved in developing biosensors

(Reiss *et al.,* 2007). Many of these are large companies for which biosensors are a minor activity.

In addition to bioremediation and biosensors, biotechnology can be applied as a pre-treatment for chemicals or fuels to reduce the presence of harmful compounds. For instance, microbes could be combined with traditional hydrotreatment to remove sulphur compounds, a cause of acid rain, from fossil fuels.

Biotechnology in resource extraction

Biotechnology can be used in metal ore mining and for enhancing oil recovery, but at present very little R&D and commercial activity has occurred.

Bioleaching uses bacteria in a liquid solution to extract metals from ore and is employed in copper and gold mining operations. Bio-oxidation, another biomining technique, uses bacteria to release encapsulated metals of interest. Both techniques have several advantages over traditional extraction methods: improved recovery rates, which can reach up to 85-95% rather than 15-30% for gold recovery (Acevedo, 2000); low capital and energy costs; usability in remote locations; and low skill requirements (BIOX, 2006).

Biotechnology can also be applied in oil extraction. Microbial enhanced oil recovery (MEOR) uses micro-organisms to increase the amount of oil recoverable from wells. Acids or gases produced by micro-organisms can increase oil extraction by freeing oil pockets in reservoir rock or increasing pressure. The percentage of oil that can be recovered from a standard well has generally been in the range of 15-50% (Mokhatab and Giangiacomo, 2006) but some estimate that MEOR can increase oil recovery rates to over 80% (CSIRO, 2007). MEOR technology is in use in several small-scale oil fields where the technology is economically competitive.

At present, all micro-organisms used in mining and oil recovery are from wild populations. Advanced biotechnologies have been used to select micro-organisms that can substantially improve desirable characteristics such as leach rates (Watling, 2006). There is no information on the use of advanced biotechnology to modify micro-organisms for use in resource extraction, but a range of biotechnologies could be used to further increase leach rates, increase tolerance to harsh conditions associated with high metal levels, or produce novel characteristics that improve oil recovery.

Biorefineries

A biorefinery is "a facility that integrates biomass conversion processes and equipment to produce fuels, power, and chemicals from biomass. The biorefinery concept is analogous to today's petroleum refineries, which produce multiple fuels and products from petroleum" (NREL, 2008). Ideally, the biorefinery concept would differ from petroleum refineries by being able to use a comparatively wider range of feedstocks.

Many industries, including food processing and pulp and paper, already process biomass to produce a product (*e.g.* food, food additives, paper) with energy as a by-product. In general, these production plants do not use modern biotechnology. For instance, a pulp and paper mill can produce a variety of types of paper from wood while using wastes and residues to generate electricity. Likewise, the production of ethanol from sugar cane relies on conventional fermentation, while bagasse, the by-product from sugar fermentation, is simply burned to generate electricity. There are also a good number of existing biorefineries that use amylases – enzymes produced from modified micro-organisms – to convert starch into sugars that are then fermented into ethanol.

In addition to producing biofuels (*e.g.* ethanol, biodiesel) and human food or animal feed by-products, biorefineries increasingly produce chemicals and biomaterials. For example, in 2006 a biorefinery was opened in Italy which produces a range of biobased chemicals and plastics from vegetable oils and maize starch (Smith, 2008).

Biorefineries are also being designed to use non-food biomass or to integrate the processing of non-food waste. This can include grasses, waste products (wood, agricultural, and other), and micro-algae or seaweeds. Several new types of biorefineries are listed in Table 3.4. All use biomass feedstocks that are treated with a biotech or combined chem-bio process to produce a variety of products.

Table 3.4. **Characteristics of new types of biorefineries**

Concept	Type of feedstock	Predominant technology	Phase of development
Green biorefineries	Wet biomass: green grasses and green crops, such as lucerne and clover	Pre-treatment, pressing, fractionation, separation, digestion	Pilot plant (and R&D)
Whole crop biorefineries	Whole crop (including straw) cereals such as rye, wheat and maize	Dry or wet milling, biochemical conversion	Pilot Plant (and demonstration plant)
Lignocellulosic feedstock biorefineries	Lignocellulosic-rich biomass, *e.g.* straw, chaff, reed, miscanthus, wood	Pre-treatment, chemical & enzymatic hydrolysis, fermentation, separation	R&D/Pilot plant (EC), demonstration plant (United States)
Two platform concept biorefineries	All types of biomass	Combination of sugar platform (biochemical conversion) and syngas platform (thermochemical conversion)	Pilot plant
Thermo chemical biorefineries	All types of biomass	Thermochemical conversion: torrefaction, pyrolysis, gasification, HTU, product separation, catalytic synthesis	Pilot plant (R&D and demonstration plant)
Marine biorefineries	Aquatic biomass: microalgae and macroalgae (seaweed)	Cell disruption, product extraction and separation	R&D (and pilot plant)

Source: Ree and Annevelink, 2007.

Biofuels

Although comprehensive data are not available, many biorefineries to produce biofuels are in use or under construction within the OECD area. As of January 2009, 172 ethanol biorefineries were in operation in the United States for a total annual capacity of 40.1 billion litres (10.6 billion gallons) (RFA, 2009), representing approximately 4.5% of gasoline consumption (OECD-FAO, 2008). All but 10 of these biorefineries use maize as a primary feedstock. In addition, a second report identified 13 cellulosic ethanol pilot and demonstration plants under construction in the United States (USITC, 2008). These cellulosic biorefineries are expected to use a variety of grasses, woods, and agricultural and municipal wastes as feedstock. The first commercial scale plant is not expected to be complete until the end of 2009 and is expected to begin producing 38 million litres (10 million gallons) in 2010 (Range Fuels, 2008). Another report identified 18 biorefinery initiatives in the Netherlands (including 1 biorefinery network, 8 R&D projects, 6 pilot plants, and 3 demonstration plants) and

33 biorefinery initiatives in Europe and the United States (including 1 commercial venture, 5 networks, 14 R&D projects, 8 pilot plants, and 5 demonstration plants) (Ree and Annevelink, 2007).

Many biofuels are produced without using modern biotechnology. For instance, ethanol is produced from sugar cane through fermenting sugars with yeast, a method well known for millennia. There are two places in biofuel production where biotechnology is used: the development of crop varieties tailored to bioenergy production (enhanced quality traits such as increased oil content or maize that contains the enzyme amylase) and new processes that improve the conversion of biomass to fuel.

Biofuel crop varieties

Agricultural biotechnologies that increase plant yields, decrease pesticide use and improve agronomic performance will indirectly reduce the cost of biofuel production. Biotechnologies can also be used to alter plants' composition to produce biofuels more efficiently. However, only a small share of biofuel research is focused on developing improved plant varieties for biofuel production. The total number of biofuel patents has increased rapidly, from 147 in 2002 to 1 045 in 2007. Agricultural biotechnology patents, however, made up only 59 of the biofuel patents in 2006 (9.2% of the 2006 total biofuel patents) and 51 in 2007 (4.9% of that year's total) (Kamis and Joshi, 2008).

Despite low patent numbers, research into product quality traits could improve biofuel production efficiencies. While some of this research deals solely with biofuels, improved oil, seed, and starch content traits that are currently in field trials for several major food crops could also benefit biofuel production.[25] Table 3.5 shows the percentage of all field trials conducted from 1987 to 2006 for maize, rapeseed, soybean and wheat that involve traits that are potentially applicable to biofuel production. While relatively little activity has gone into modifying the composition of maize and wheat (3% and 2% of all field trials, respectively), significant activity has gone into rapeseed and soybean (19% and 21%, respectively). As discussed in Chapter 4, several varieties of these product quality traits are likely to appear on the market by 2015.

Grasses and trees are also being explored for use in biofuel production. While trees can be used for energy generation through combustion (usually in the form of wood pellets), advanced biotechnologies offer the prospect of converting grass and forest biomass into liquid fuel through cellulosic fermentation. A major technical challenge is the removal of lignin from the biomass feedstock to free the cellulose and hemicellulose for fermentation into ethanol (Lin and Tanaka, 2005). While industrial biotechnology

processes can be used to remove or breakdown lignin, biomass feedstocks (such as trees and grasses) can also be designed with reduced lignin content, thereby making the delignification process less costly.

Table 3.5. **Percentage of all field trials in select food crops involving potential biofuel traits, 1987-2006**

Crop	Total field trials	% involving potential biofuel traits[1]
Maize	7 250	3
Rapeseed	1 715	19
Soybean	1 276	21
Wheat	890	2
Other oilseeds[2]	225	9

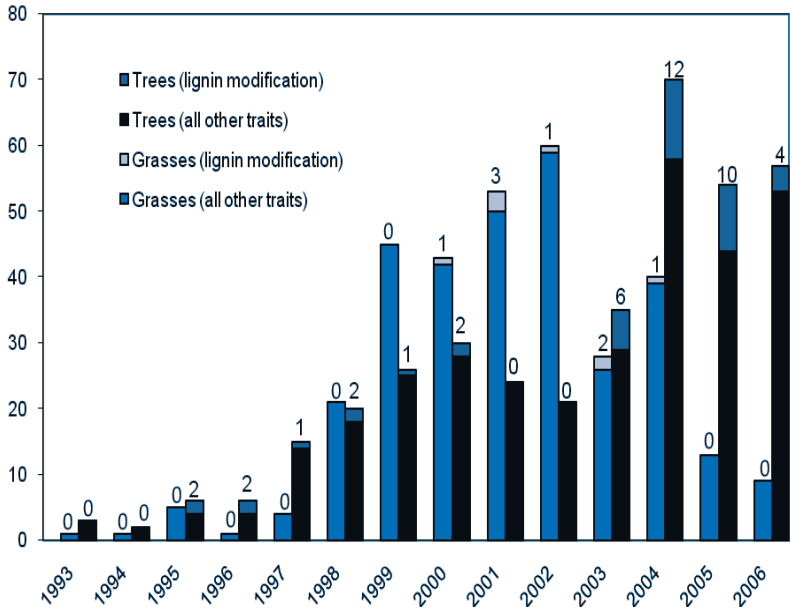
1. Potential biofuel traits include the modification of amylase, lignin, oil, seed, and starch content.

2. Other oilseeds include flax, mustard, and sunflower.

Source: Authors, based on the UNU- MERIT, 2008.

Figure 3.5 gives the number of all GM field trials in grasses and trees and the number of these trials that involved lignin modification. For example, 70 field trials were conducted using tree species in 2004. Twelve of these trials concerned lignin modification. There have been fewer field trials of lignin modification for grasses. Only eight field trials were undertaken between 2000 and 2004, and none has been conducted since. It is noteworthy that all eight trials involved forage grasses, since a lower lignin content has nutritional benefits for grazing animals. However, given the recent interest in the use of grasses as a biofuel source, research under way in the lab could move to field trials in the near future. For instance, the 2008 US Farm Bill committed USD 4.5 billion to biomass research over the next four years, much of which is aimed at research into cellulosic ethanol.

Figure 3.5. **Number of GM field trials for trees and grasses for lignin modification and for all other traits**



Note: The number at the top of each column gives the number of field trials that involve modifying lignin content.

Source: Authors, based on the UNU-MERIT, 2008.

There has been more activity recently to reduce the lignin content in trees, possibly to reduce the cost of removing lignin in paper manufacturing. While from 1993 to 2002 there were no more than two field trials per year, there were 6, 12, 10, and 4 field trials conducted in 2003 to 2006, respectively.

Widespread, open-release, of low-lignin grasses or trees will depend on meeting environmental regulatory requirements to prevent the spread of low-lignin genes to wild plants, or strong evidence that natural selection would quickly eliminate this gene from wild species.

The Jatropha plant in India and sweet sorghum in China have also been identified as potential feedstocks for mass production of biofuels. Jatropha is not used as a food crop and the market for sweet sorghum as a food source is very small. Both can be grown on marginal lands, though yields are

correspondingly low. Research is under way to develop drought-resistant GM varieties of jatropha (Anon, 2005). With improved yields, some of these varieties are expected to be available for use in 2012 (Fitzgerald, 2006). Mycorrhiza, a beneficial root fungus, is used with jatropha to extend roots, allowing for improved phosphorus and nitrogen uptake. This would improve yields on marginal lands. The mycorrhiza is produced by modifying jatropha in a lab with agrobacterium rhizogenes to express hairy roots (TERI, 2008).

Industrial processes for biofuels

Biotechnology can reduce the cost of producing biofuels through improved industrial biotech processes that facilitate the conversion of biomass into fuel or energy. The main types of biofuels in use today include bioethanol and biodiesel. Government policies, particularly subsidies and mandated blending volumes or percentages, coupled with high energy prices in the 2004 to 2008 period, have spurred a large increase in production capacity.[26]

Large-scale bioethanol and biodiesel production has aroused concerns over the impact of biofuel production on the environment and on food prices. This has driven interest in both cellulosic fermentation and the use of microbes to produce biofuels. The latter can benefit from using metabolic pathway engineering or synthetic biology to design microbes that can produce a wide range of potential biofuels.

Table 3.6 summarises the different methods in use and under development for producing biofuels.

Table 3.6. **An overview of some current biofuel production technologies and research goals**

Production type	Technology overview
Transesterification (*e.g.* biodiesel)	Biodiesel is produced from animal fat and vegetable oil via a chemical process called transesterification. Feedstock is mixed with alcohol and a catalyst to produce esters (biodiesel) and glycerol as a by-product. Biotechnology could be used to produce biodiesel but has been held back by the high cost of lipase enzymes that are required as a catalyst. Given the need for animal fat or vegetable oil, large-scale biodiesel production raises environmental concerns (*e.g.* deforestation and land use change) and may increase food prices if food crops are used.
Fermentation processes (*e.g.* bioethanol and biobutanol)	Fermentation is commonly used to produce bioethanol from feedstocks including maize and sugar cane. Ethanol is produced either by the direct fermentation of sugars (not modern biotechnology) or by using amylase enzymes, produced with GM micro-organisms, to break down starches into sugars that are fermented. Challenges arise in ethanol production and transport as a result of its solubility in water, which complicates extraction from the fermentation broth and eliminates pipelines as a transport option. Butanol can also be produced through traditional fermentation of biomass. Recent high fossil oil prices, and recognition of butanol's potential as a transport fuel, have renewed interest in biotech production. Research is under way to improve fermentation – including through development of bacteria that are more stable (*i.e.* not degraded by fermentation) – and to increase conversion efficiency. Biomass requirements and the use of food crops have led to environmental and food price concerns similar to those for transesterification.
Lignocellulosic conversion	Due to concerns over environmental impacts and the effect of competition between food and feed, lignocellulosic ethanol is seen as a desirable supplement to transesterification and fermentation. It involves the extraction of polysaccharides (cellulose and hemicellulose) from lignin, which are then converted into simple sugars, and fermented into fuel. In addition to expected cost reductions, lignocellulosic biofuels increase the fossil fuel saved per unit of energy produced. Other attractive aspects include the ability to use agricultural wastes and non-food crops such as grasses that can be grown on marginal, nutrient-poor lands and harvested throughout the year. Lignocellulosic fuel production is still in the R&D pilot plant stage. Public and private research is under way around the world to develop bacteria and enzymes that would reduce lignocellulosic fuel production costs.[1]
Microbial production	Some naturally occurring microbes produce chemicals closely resembling those used in fuels. Research focuses on using metabolic pathway engineering and synthetic biology to reconfigure microbes so as to produce a large variety of molecules that could be used in gas and liquid fuels. These fuels include, *inter alia,* alcohols, alkanes (*e.g.* methane, propane, octane), ethers, and hydrogen. For instance, modified algae could be used to photosynthesise carbon dioxide from the air into a substance similar to vegetable oil that can be used to produce biodiesel. Research is also under way, in a joint venture between Amyris and Crystalsev, to produce isoprenoids – a fuel similar to diesel – from sugar cane using modified microbes and DuPont and BP have created a partnership to explore the microbial production of biobutanol based on metabolic pathway engineering (DuPont 2008b). Numerous micro-organisms of importance to biofuel research have had, or are in the process of having, their genome sequenced completed.[2] Many of these potential fuels have attractive properties, including high energy-density and low water solubility.

1. Important industrial players in the development and production of enzymes for the hydrolysis of (hemi)cellulose are Novozymes, Genencor, Dyadic, Iogen and Diversa.
2. A representative list of some of these micro-organisms of importance to biofuel production is available in Wackett, 2008.

The bioeconomy today

The biotechnology products and applications discussed in the preceding sections make up the bioeconomy of today. These technologies are all strongly linked through the same advanced platform biotechnologies. As one takes a broader view, however, major divergences in the way these products are applied and linked to one another become clear. Within sectors, many applications are only lightly integrated with other biotechnology applications in the same area. In health, only a handful of the hundreds of available human genetic diagnostic tests are used in the prescription of biotherapeutics and other drugs.

Some integration has occurred across application fields, but only for some products, and in most cases existing supply chains are weak. Agricultural biotechnology products are used as biomass feedstocks for industrial production, but very few agricultural biotechnologies have been applied to designing biomass optimised for a specific industrial biotechnology process. Veterinary biotechnology products, including therapeutics and diagnostics, are an exception, as they can be adapted easily from human health biotechnology.

The lack of strong supply chain integration across applications creates inefficiencies, which makes it difficult for today's bioeconomy to play a major role in solving the environmental, social and economic challenges discussed in Chapter 2. Using biomass to significantly reduce demand for fossil fuels requires fuel crops and conversion technologies that increase energy yield. Feedstock crops that are not well suited to energy production reduce the efficacy of biomass as a solution. In health, a slow stream of marginally innovative biopharmaceuticals may actually increase healthcare costs at a time when they already account for a large share of public and private budgets. Scant use of genetic tests to identify responding populations does little to quell healthcare spending, as costs associated with adverse drug reactions remain high. Likewise, genetic tests that determine risk factors for untreatable diseases may reduce wellbeing by creating anxiety, and tests that return false positives or negatives could potentially change behaviour to the detriment of health.

New approaches to applying biotechnology could provide solutions to these challenges, but the current level of technological maturity, along with structural conditions that dictate the way products are developed and delivered, prevent biotechnology from achieving its full potential. Future technology developments may improve efficiencies and open the door to the broader use of biotechnology to achieve health, environmental and economic goals. How biotechnology develops in the medium term (to 2015) will influence the long-term future of the bioeconomy. These medium term developments are examined in Chapter 4.

Notes

1. Recent studies have found the inverse (RNAa) in which small segments of RNA can activate or turn "on" genes (Janowski *et al.*, 2007).

2. There is a single approved antisense drug, fomivirsen (Vitravene™), available for treating cytomegalovirus retinitis, a virus that can cause blindness in AIDS patients. Antisense differs from RNAi in that it acts directly on DNA rather than RNA.

3. See for example, *www.wikipathways.org/index.php/WikiPathways*.

4. Interviews with five French and German firms active in maize breeding found that all five firms used MAS. The larger firms used MAS in every maize-breeding programme; 100% of sales were from varieties developed using MAS. The one smaller firm estimated that only a third of its turnover was from MAS maize (Menrad *et al.,* 2006). Another interview study of 18 agricultural biotechnology SMEs in Australia, North America and Europe found that 78% of the firms used MAS (Blank, 2008).

5. As of 1 May 2007, approval has been received or pending in the United States for one or more GM varieties of the following plant species: alfalfa, beet, chicory, corn, cotton, creeping bentgrass, flax, papaya, plum, potato, rapeseed, rice, soybean, squash, tobacco and tomato (see Annex 3.A1 for details).

6. The FAOSTAT database shows that globally 1 214 310 000 hectares were planted in 2006. Soybean accounted for 81 613 000 hectares, maize 46 047 000 hectares, cotton 21 358 000 hectares, and rapeseed 8 808 000 hectares. Data for 2007 were not available at the time of writing.

7. Analysis by the authors, based on UNU-MERIT, 2008.

8. Eight GM forestry R&D projects, or 17.4%, were classified as "other" or "not specified".

9. The most commonly used tests are ELISA (53.9% of all commercial diagnostic tests), which can detect antibodies, and PCR (40.4% of all commercial diagnostic tests) which detects genetic variations. Some variants of these methods are also used. For example, the Reverse

Transcription-PCR (RT-PCR) method, or the Double-Antibody Sandwich-ELISA (or DAS-ELISA) method, which is used to detect pathogenic *Verticillium* species (Koppel and Sebots, 1995).

10. Four are genetic tests for DNA or RNA and 35 use a method such as ELISA or PCR to identify a protein.

11. The firm Aqua Bounty markets diagnostic systems using PCR that identify five shrimp and salmon viruses (SybrShrimp and SybrSalmon), see *www.aquabounty.com*.

12. For further information on therapeutic vaccines see Sela and Helleman (2004).

13. A new molecular entity (NME) refers to an active drug molecule that has never been approved for use in a drug in any other jurisdiction.

14. France's *Haute Autorité de Santé* (HAS) considered all of these drugs as providing a "major therapeutic progress". See Table 3.1 and Annex 3.A2.

15. HAS is an independent French public body with financial autonomy. It is charged with improving patient care and equity within the French healthcare system.

16. HAS has not evaluated many biopharmaceuticals that were introduced before 2001, nor have all recently approved biopharmaceuticals been evaluated. This is why an evaluation is only available for 53 biopharmaceuticals. A similar analysis based on ratings from *Prescrire,* an independent French organisation funded by doctor subscriptions, produced similar results, using a longer data series for 73 biopharmaceuticals evaluated between 1986 and end-2007 (See Annex 3.A3.). The *Prescrire* group takes two to three years to evaluate a drug once it receives market approval in France. This explains most of the missing evaluations.

17. The indication refers to the medical condition that is treated by a specific drug or treatment.

18. The EU-5 comprises France, Germany, Italy, Spain and the United Kingdom.

19. Pharmacogenomics differs from pharmacogenetics in that it studies the effect of the entire genome (or systems of genes) on drug response.

20. The FDA classifies a biomarker as validated if "*(1)* it is measured in an analytical test system with well-established performance characteristics and *(2)* there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results" (FDA, 2005).

21. Of all FDA drugs currently approved for use, 10% contain genomic information on their product labels (Frueh, 2006).

22. There is extensive research on developing soybeans and canola with improved oils and fats, but the main market for these varieties is for food processing. Healthy olive and other oils are already available for consumers.

23. Of note, many standard foods are good sources of anti-oxidants, including blackberries, cranberries and black soybeans.

24. This section draws extensively from Novozymes, 2008.

25. For example, a maize variety is under development that expresses large levels of amylases (the enzymes required to convert starch into sugar for ethanol production) (Syngenta, 2008).

26. The path to economically viable biofuels is likely to be uneven. In the autumn of 2008, the fall in petroleum prices combined with high maize prices led to the closure of several bioethanol plants in the United States.

Annex 3.A1

USDA-Approved GM Varieties

Table 3.A1.1. **USDA-approved and pending GM crop varieties as of 1 May 2007**

Plant	Number of varieties	Status[1]	First approval /pending[3]	Traits[2]							
				HT	HT-IR	IR	VR	PQ	AG	MS	PQ trait
Alfalfa	1	P		1							
Beet	1	A	1998	1							
Chicory	1	A	1997							1	
Corn	21	A	1994	6	5	8		1		1	High lysine
Corn	2	P	2005			1		1			Starch processing[4]
Cotton	11	A	1994	5	1	5					
Cotton	2	P	2006	1		1					
C.bentgrass	1	P	2003	1							
Flax	1	A	1998	1							
Papaya	1	A	1996				1				
Papaya	1	P	2004				1				
Plum	1	P	2004				1				
Potato	8	A	1994			5	3				
Rapeseed	9	A	1994	6				1		2	Improved oil profile
Rice	2	A	1999	2							
Soybean	5	A	1993	4				1			Improved oil profile
Soybean	3	P	2006	2				1			High oleic acid
Squash	2	A	1992				2				
Tobacco	1	A	2001					1			Low nicotine
Tomato	11	A	1992			1		10			Fruit ripening altered
Total	85			30	6	21	8	16		4	

1. A = approved, P = pending.

2. HT = herbicide tolerance, HT-IR = combined herbicide tolerance and insect resistance, VR = virus resistance, PQ = product quality trait, AG = agronomic trait, MS = male sterility.

3. Gives the date of first approval of a GM variety of each plant species. Many varieties will have received the approval status after this date. The date for "pending" refers to the earliest date for varieties still in the pending application status.

4. Variety includes thermostable alpha-amylase, which accelerates the conversion of starch to sugar and should decrease the cost of ethanol production. See "Klevorn, T.B., Syngenta's Product Pipeline", *www.bio.org/foodag/action/20040623/klevorn.pdf* (accessed 7 January 2008).

Source: USDA, APHIS GM approvals.

Annex 3.A2

Haute Autorité de Santé (HAS) Therapeutic Value Classifications

Medical service rendered (MSR)

The MSR takes into account:

- The efficiency and undesired effects of the medication.
- Its utility, especially when compared with other existing therapies.
- The severity of the indication to be treated.
- The preventative or curing characteristics of the medication.
- The value of the medication for public health.
- Whether the MSR is qualified as major, important, moderate, minor, or insufficient to justify reimbursement.

Improvement of the medical service rendered (IMSR)

The levels of IMSR are as follows:

I. Major therapeutic progress.

II. Important improvement in terms of therapeutic effectiveness and/or reduction of adverse effects.

III. Moderate improvement in terms of therapeutic effectiveness and/or reduction of adverse effects.

IV. Minor improvements in terms of therapeutic effectiveness and/or reduction of adverse effects.

V. No improvement.

An improvement in the methods of administration, likely to lead to better care of the patient with a clinical benefit, could be a factor in determining IMSR (*Haute Autorité de Santé*, translation by the OECD).

Annex 3.A3

Analysis of *Prescrire* Therapeutic Value Evaluations

Table 3.A3.1. ***Prescrire*** **evaluations of the therapeutic value of biopharmaceuticals and all other drugs (January 1986–December 2007)**

	Biopharmaceuticals				All other drugs[1]	
	Highest rating		All indications		All indications	
Evaluation class[2]	N	%	N	%	N	%
Major advance	0	0.0	0	0.0	8	0.4
Important advance	6	8.2	8	5.5	57	3.0
Some advance	16	21.9	23	15.9	196	10.2
Minimal advance	21	28.8	42	29.0	449	23.4
No advance ("Me too")	20	27.4	41	28.3	964	50.3
Not acceptable	8	11.0	15	10.3	127	6.6
Judgement reserved	2	2.7	16	11.0	114	6.0
Total	73	100	145	100	1 915	100

1. Includes therapeutics but excludes diagnostics and vaccines. Generics are excluded after 1996.

2. See Table 3.A3.2 for a definition of each evaluation category.

Source: Authors, based on data from *Prescrire* issues between January 1986 and December 2007. All other drugs: 1986-2000 data on page 59, *Prescrire* January 2001; 2000-2007 data on page 136, *Prescrire*, Feb 2008; data for 2008 from individual *Prescrire* issues. The evaluations for biopharmaceuticals were subtracted from the totals for all drugs.

Table 3.A3.2. **Definition of** ***Prescrire*** **evaluation categories**

	English	*(French)*	Definition
1	Major advance	*Bravo*	The drug is a major therapeutic innovation in an area where previously no treatment was available.
2	Important advance	*Intéressant*	The product is an important therapeutic innovation but has certain limitations.
3	Some advance	*Apporte quelque chose*	The product has some value but does not fundamentally change present therapeutic practice.
4	Minimal advance	*Éventuellement utile*	The product has minimal additional value and should not change prescription practices except in rare circumstances.
5	No advance ("Me too")	*N'apporte rien de nouveau*	The product may be a new molecule but is superfluous because it does not add to the clinical possibilities offered by previously available products. In most cases it concerns a "me too" product.
6	Not acceptable	*Pas d'accord*	Product without evident benefit but with possible or real disadvantages.
7	Judgement reserved	*Ne peut se prononcer*	The editors postpone their judgement until better data and a more thorough evaluation of the drug are available.

Source: English definitions are from *Prescrire International*.

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Chapter 4

The Bioeconomy to 2015

What types of biotechnology applications are likely to reach the market by 2015? Regulatory requirements in agriculture and health provide data that can be used to estimate the types of genetically modified (GM) plant varieties and health therapies that will be available by then. There are far less data for other biotechnology applications, with estimates based on past trends in scientific discoveries, production, or employment.

Based on past trends, GM field trial data, and company reports, it is estimated that by 2015 approximately half of global production of the major food, feed and industrial feedstock crops is likely to come from plant varieties developed using one or more types of biotechnology. These biotechnologies include not only GM but also intragenics, gene shuffling and marker assisted selection. Several novel agronomic and product quality traits will reach the market for a growing number of crops. Biotechnologies, other than GM, will be used to improve livestock for dairy and meat. GM will be increasingly used to develop animal varieties that can produce valuable pharmaceuticals or other compounds in milk. In health, biotechnological knowledge will play a role in the development of all types of therapies. It will no longer be meaningful to separate the pharmaceutical sector from the health biotechnology sector. Pharmacogenetics will develop rapidly, influencing the design of clinical trials and prescribing practices. The value of biochemicals (other than pharmaceuticals) could increase from 1.8% of all chemical production in 2005 to between 12% and 20% by 2015. Biofuel production could partly shift from starch-based bioethanol to higher energy density fuels manufactured from sugar cane or to bioethanol from lignocellulosic feedstock such as grasses and wood.

Despite the influence of exogenous factors such as business strategies, regulation, and the supply of funds for R&D, the development of some biotechnology applications can be forecast with a fair level of confidence up to 2015. The regulatory structures in place for pharmaceuticals and the open release of GM organisms produce several types of data that can be used to estimate when new biopharmaceuticals and GM plant varieties are likely to reach the market. Major diversions from expected trends for these products are unlikely to occur unless there is a large increase in R&D, a rapid decline in the time it takes to develop new products, or a substantial increase in the success rates for R&D projects.

The regulatory environment for industrial biotechnology does not leave a useful data trail for estimating the types of products that will reach the market by a specific date. Alternatively, some information on the future of industrial biotechnologies can be obtained from the academic literature and from publicly available information on private and public sector R&D efforts. Trend data for sales of biotechnology products provide another alternative method of estimating the impact of industrial biotechnology in 2015.

Many of the new biotechnology products and processes currently under development are produced by separate research programmes in each of the main application areas. Each programme is following its own technological trajectory and set of goals. The exception is the dependence of all applications on a similar set of platform biotechnologies. However, technology, regulatory systems, institutional conditions and business models are evolving simultaneously. Up to 2015, these changes are expected to increase the level of integration across different applications of biotechnology, particularly between agriculture and industry. As an example, technological developments and market opportunities could lead to integrated supply chains between agricultural feedstocks and industrial biorefineries.

The following sections describe expected technology developments, by application area, to 2015.[1] Summary tables for each application area explain the main biotechnologies in use, their current status, and expected developments to 2015.

Platform technologies to 2015

Platform technologies facilitate the development of biotechnology applications in all sectors. Technologies focusing on genes, such as those for genetic modification, will continue to play a major role in these applications to 2015.

The platform technologies that will probably have the greatest impact over the near future are RNA interference (RNAi), bioinformatics, gene sequencing, metabolic pathway engineering, DNA synthesis, and possibly synthetic biology (synbio).

While techniques that are widely used today, such as genetic modification, will continue to be extensively used, advanced techniques will become increasingly important. For example, several RNAi based therapeutics currently in clinical trials could reach the market by 2015.

The construction and analysis of databases will continue to be two of the main uses of bioinformatics, with rapid growth supported by an increase in computing power expected to 2015. These databases are likely to be commonly measured in terabytes and become more complex, integrating information from gene sequencing, biology, computer science, imaging, physics and chemistry (Kanehisa and Bork, 2003) in order to model cells as systems and predict functions (Tsoka and Ouzounis, 2000). Contributing to this trend will be the decrease in gene sequencing costs. If costs continue to fall as projected, it will be possible to sequence the human genome for approximately USD 1 000 around 2020 (Bio-Era, 2007). This could even be achieved sooner: one company has announced that it will begin offering full human genome sequencing for USD 5 000 in 2009 (Pollack, 2008a).

Metabolic pathway engineering techniques will continue to broaden the range of compounds that can be produced through biotechnology. They are likely to be extensively used before 2015 to economically produce non-biodegradable plastics, high-density biofuels and pharmaceuticals (Zimmer, 2006). This is supported by the significant amount of research currently under way and the entry of a number of large corporations into the field.

These techniques could well form a bridge to other synbio techniques involving the use of "artificial genomes" or modular biological parts, which are likely to take longer to develop. Following recent advances, synthetic genomes and/or biological parts could be used by 2015 to construct a small number of purpose-built micro-organisms for the production of valuable compounds that are difficult or impossible to produce using other technologies. Given strict regulations for agricultural and health products, the first uses of these synthetic micro-organisms are likely to be in drug discovery and in the production of compounds in closed systems.

Table 4.1 summarises the current status of platform technologies and their possible development and use up to 2015.

Table 4.1. **The current status and prospects to 2015 of some important platform technologies**

Technology	Definition	Current status	Status to 2015
Bioinformatics	The use of computers in compiling, analysing and modelling life science data. It mainly involves the creation of electronic databases on genomes, protein sequences, etc. as well as techniques such as the 3-D modelling of biomolecules.	Widely used. Numerous large, international databases are publicly available with a diverse range of genetic information across all kingdoms of living organisms and some complete genomes. Bioinformatics tools are also available for designing gene sequences.	Decreasing gene sequencing costs will increase the number of genetic databases. These will become more complex, integrating information from numerous disciplines in order to model cells as systems and predict function.
DNA sequencing	The process of determining the order of the nucleotides (the base sequences) in a DNA molecule. This is a key step in discovering genes and their function.	The first full human genome was completed in 2003 and it is now possible to sequence all human genes with a *known* function for around USD 1 000 (Herper and Langreth, 2007). Full human genome sequencing for USD 5 000 is expected to be available in 2009.	Spurred by private and public investment as well as prizes (*e.g.* the Archon X-Prize), costs will continue to fall as productivity increases. If costs decrease as projected, it will be possible to sequence the human genome for approximately USD 1 000 before 2020.
DNA synthesis	The assembly of a known sequence of DNA using synthetic chemicals.	Technology has improved at a rapid pace and has driven the development of a robust commercial industry. Companies in at least 18 countries offer DNA synthesis services, and private and public laboratories have the same capability.	Gene synthesis costs will continue to decline, and increased competition will spur companies to offer increasingly sophisticated design tools (*i.e.* bioinformatics).
Genetic modification	The insertion of one or more genes from one organism into the DNA of another organism. It is used *inter alia* to impart new traits to plants, modify micro-organisms for chemical production, and develop new drugs.	A very widely used and important biotechnology. It forms the basis for many current biotechnology applications and those in development. At one time GM was somewhat of an art, but new technologies have simplified techniques and improved efficiency.	Genetic modification will continue to form the basis of a wide variety of biotechnology applications. Better understanding of genetic functions will make more complex and stacked traits commonplace.
RNA interference (RNAi) and RNAa	The silencing (turning off) of genes by interfering with RNA production. RNAa does the opposite by switching genes on.	The RNAi mechanism was described in 1998. Research has been intense and products are in development in all sectors including health, where several clinical trials are under way. RNAa was discovered in 2006.	A few products based on RNAi are likely to reach the market. The technology will be heavily used in research to determine the function of individual genes.
Synthetic biology (synbio)	The design and construction of new biological parts, devices and systems, and the redesign of existing, natural biological systems for useful purposes. A subset of synbio is metabolic pathway engineering, which alters chemical reactions within a living organism to induce the production or consumption of a desired substance.	Most synbio is still in early research, but this science's potential has generated much excitement. To date, metabolic pathway engineering has only been used in a few commercial applications. High energy and commodity prices have led a number of large industrial players to invest in R&D, notably for the production of valuable chemicals.	Metabolic pathway engineering will be used to produce a number of chemicals, including high-density fuels and some pharmaceutical compounds and polymers that previously were not possible to synthesise. The future of other synbio applications is difficult to determine, given many technical uncertainties. If technical problems are solved, it could be applied quickly to industrial biotech applications such as chemical production. Current regulations will render it less likely that applications in health or primary production will be available.

Biotech applications to 2015 in primary production

The use of biotechnology in primary production is expected to increase greatly to 2015, particularly in the development of new varieties of plants and animals. New biotech crops with product quality and agronomic traits are expected to arrive on the market, providing notable benefits to farmers and industrial processors and potentially to consumers as well. Biotechnology is likely to play a significant role in animal breeding and propagation, with MAS used in most modern breeding operations by 2015. Research into GM animals and cloning will continue, but high costs and consumer opposition will limit commercial opportunities. Biotechnology will, however, increasingly be used to diagnose and treat diseases that affect livestock, poultry and farmed fish.

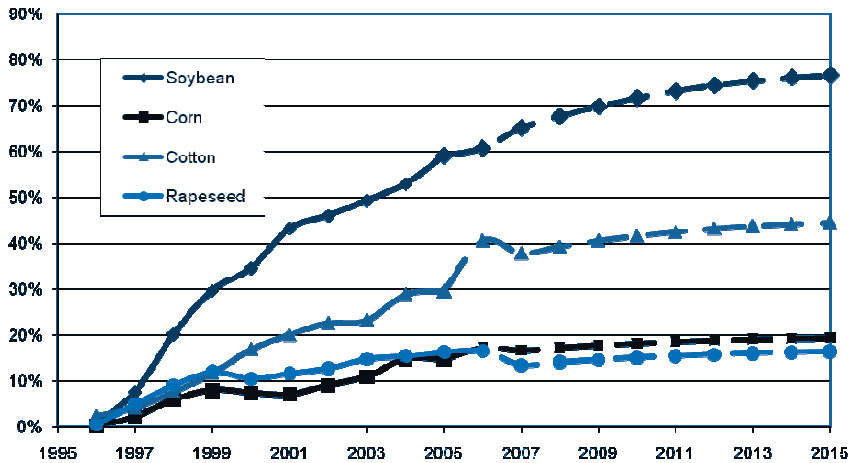
Biotech applications to 2015 for plants

The share of all cultivated crops from varieties developed through GM, MAS, or other biotechnologies has been rising rapidly over the past ten years. This trend will continue into the future. New product quality and stress resistance traits should also become available. Both MAS and GM will be used in forestry to improve pest resistance and growth rates and to reduce the lignin content of tree varieties for pulp and paper or biofuel production.

Food, feed and industrial feedstock crops

By 2015, approximately half of global production of the major food, feed and industrial feedstock crops is likely to come from varieties developed using biotechnology. Figure 4.1 presents estimates of the probable GM share of future hectares of four main GM crops, using past growth rates in GM plantings up to 2007 and global data on the number of hectares planted with each crop. By 2015, GM varieties could account for 76% of worldwide hectares planted with soybeans and 45% of hectares planted with cotton. The lower forecasts for the share of GM rapeseed (canola) and maize (both less than 20%) are mainly due to major producing countries, such as Brazil and China, not yet planting GM varieties of these two crops.[2] Brazil approved GM maize in late 2007 for planting during the 2008 harvest (Reuters, 2008), so the GM share of maize and rapeseed should increase faster in the future than estimated in Figure 4.1. Adoption of GM maize and rapeseed in Brazil, China and India would substantially increase the estimated GM share for these crops because 33% of global maize hectares and over 50% of rapeseed hectares are found in these three countries.

Figure 4.1. **Observed (to 2005) and forecast (2006-15) GM share of global area cultivated, by crop**



Source: Authors, based on world hectare data from the FAOSTAT Database, 2005; and GM plantings data from James, 2007.

Ongoing GM research programmes in Brazil, China and India also indicate that GM crop plantings will increase in these countries. All three are currently conducting approximately 30 field trials for each of the four GM crops (FAO, n.d.). They have all adopted GM cotton. Brazil has also approved GM soybeans and China has approved GM varieties of five small market crops (James, 2007). India is estimated to be investing USD 100 million per year in biotech crop R&D and Brazil intends to invest approximately USD 5 billion over the next ten years (Reuters, 2007). China's R&D expenditures for biotechnology are approximately USD 600 million, including USD 120 million on GM rice, the country's main staple crop (James, 2007). Furthermore, Chinese Premier Wen Jiabao has recently expressed support for continued use and research into transgenic plants (Xinhua, 2008).

The types of new GM crop varieties that will reach the market by 2015 can be estimated from analysing the GM field trial record in OECD countries and publicly available information on the R&D pipelines of four of the world's largest seed firms. The results indicate that the two most common traits to date, herbicide tolerance and pest resistance, are expected to be available for varieties of barley, sugar beet, peanuts, peas, potato, rice, and safflower by 2015.

Current research on agronomic traits focuses on improved yield and resistance to stresses such as drought, salinity and high temperatures. Research on product quality traits mainly deals with industrial processing characteristics. Some of these agronomic and product quality traits will be available for the main food and feed crops (maize, rapeseed and soybean) by 2010. Similar traits should be available by 2015 for other food and feed crops such as alfalfa, apple, cotton, lettuce, potato, rice, tomato, and wheat.

The economic benefits of herbicide tolerance and pest resistance traits have been shared between seed development firms and farmers. These traits decreased the cost to farmers of fertilisers and pesticides, increased yields, gave farmers more free time, and reduced their exposure to hazardous pesticides. The main beneficiaries of new product quality and agronomic traits, in addition to seed developers and farmers, will be industrial processors. Consumers could benefit from greater food security derived from higher yields and possibly from product quality improvements that impart beneficial health traits to crop varieties. While higher crop yields will also increase supply, a benefit to the consumer in the form of lower prices could be obscured by higher demand.

Forestry

There is a large commercial potential for improved tree varieties. GM varieties of faster-growing tree species could be ready for commercialisation by 2012 and tree varieties with altered lignin for use in pulp or bioethanol production by 2015. Biodiversity concerns in some countries could, however, slow commercialisation. MAS and other biotechnologies that do not involve GM will also be widely used in breeding programmes in countries such as Canada and New Zealand where forestry is a major industry. In all regions, improved pest resistance is an important goal for tree breeding programmes.

The economics of tree plantations for wood, fibre and biofuels favours the tropics and semi-tropics, where annual biomass production is many times greater than in temperate zones. Not surprisingly, GM breeding programmes have focused on new varieties of fast-growing, short-rotation trees such as pine and eucalyptus species that are adapted to warm climates (Sedjo, 2005). In part due to a surplus of wood in Northern OECD countries, there has been less private sector interest in developing new tree varieties for temperate zones, with the exception of poplar species. Once current temperate forests have been fully exploited, most production of wood fibre and an increasing share of structural timber production could shift to warmer countries.

Plant diagnostics and therapeutics

The goal in plant diagnostics is to develop real-time tests for multiple diseases that can be used by farmers in the field. Although 24 real-time biotech diagnostics (using PCR) are currently available, they can only detect single pathogens and are mostly not suitable for field use (Ward *et al.*, 2004).[3] A more useful technology is a microarray that detects plant pathogen DNA. An experimental DNA microarray can detect 24 potato pathogens (European Commission, n.d.). The method is still costly and difficult to achieve, but by 2015 DNA microarrays for some large market crops could be available for a large number of plant pathogens.[4]

Biotech applications to 2015 for animals

Biotechnologies such as MAS and diagnostics for pests and diseases can improve the quality and reduce the costs of livestock and poultry production, aquaculture, and honeybees.

Livestock and poultry

Up to 2015, MAS and other biotechnology techniques that do not involve GM are likely to be widely used to improve commercial livestock species such as pigs, cattle, dairy cows, and sheep. Due to high costs and public opposition, the use of cloning for food animals within the OECD area, if feasible at all, is likely to be restricted to the reproduction of improved breeding stock. The most likely use of both GM and cloning by 2015 is to produce valuable pharmaceuticals or other compounds in animal milk. A small market for cloning could develop for reproducing household pets.

Marine and aquaculture

To 2015, the largest potential for biotechnology in marine applications is the use of DNA fingerprinting to manage wild fish stocks and the use of MAS and other techniques that do not involve GM to develop improved varieties of fish, molluscs and crustaceans for aquaculture. GM transgenic fish species have already been developed (Kapuscinski *et al.*, 2007), but the commercial use of these varieties has been held back by concerns over public acceptance.

Honeybees and insects

The most probable biotechnology applications for insects are the use of MAS or GM to develop insecticide- and pest-resistant varieties of honeybees, and the development of diagnostic tests for pathogens that attack honeybee hives. Improved honeybee varieties are unlikely to be commercially available before 2015, but new diagnostic tests should appear around 2015. GM can also be used to reduce the survival rate of agricultural pests, but this technology will compete with well-established alternatives for pest control such as insect-resistant crop varieties and insecticides.

Animal diagnostics and therapeutics

As with plant diagnostics, the goal for animal diagnostics is to develop microarrays that farmers can use in the field to detect a variety of animal pathogens. A 2005 study predicted that on farm genetic testing for disease would be widely available for livestock by 2010 (NZ MoRST, 2005). Although the market is growing rapidly, this is unlikely, given the small number of genetic diagnostics for animal disease that have reached the market so far. R&D is under way however, and some products could reach the market by 2015. The USDA lists 41 animal diagnostics, testing for 15 diseases, under development. Of these, four are for diseases that the OIE has classified as "of serious socio-economic or public health consequence" (OIE, 2005) and 12 are for use with pets. Another potential market is DNA-based microarrays to test for harmful or beneficial genes in livestock breeding programmes (Bendixen, Hedegaard and Horn, 2005).

Several biotherapeutics for livestock, such as a growth hormone for pigs, treatments for parasites, and recombinant vaccines, could reach the market by 2015. Due to their high manufacturing costs, the market for the use of biopharmaceuticals to treat chronic disease in animals is limited to valuable breeding stock and particularly to the companion animal market. Pharmaceutical firms that develop biopharmaceuticals for humans will continue to market similar products for companion animals (Bellingham, 2007).

Table 4.2 summarises the current status of biotechnologies for primary production and their possible development and use up to 2015.

Table 4.2. **The current status and prospects to 2015 of some important biotechnology applications in primary production**

Technology	Definition	Current status	Status to 2015
Plants			
New crop and tree varieties	Modern biotechnology, including GM and non-GM methods such as MAS, can be used to develop improved varieties of all types of commercial crops. Several methods are available for propagation.	GM crops have been available since 1996 and are cultivated in 10 OECD and 13 non-OECD countries. Dozens of varieties are on the market, mainly of cotton, maize, rapeseed and soybean. Over 75% of approved varieties contain traits for either herbicide tolerance, pest resistance, or both. Non-GM biotechnologies are widely used to improve other types of crops.	Biotech's share of global plantings of cotton, maize, rapeseed and soybean will increase to 2015. New crop varieties with agronomic and product quality traits will appear on the market along with biotech varieties of some smaller market crops. MAS will be used in the development of most new non-GM varieties of commercial crops and many trees. A few GM tree varieties could be commercialised.
Plant diagnostics	Diagnostics detect harmful pathogens in crop and tree populations. Early detection can limit economic losses and environmental damage.	Hundreds of laboratory plant diagnostics are available, but tend to focus on pathogens prevalent in developed countries. 24 real-time diagnostics are currently available for single pathogens.	R&D aims to develop low cost, real-time diagnostics that are usable in the field for the detection of multiple pathogens that cause disease. DNA microarrays would meet these requirements. They should become available for a large number of plant pathogens in important commercial crops.
Animals			
Animal breeding and propagation	Biotechnology can be used to improve the speed and accuracy of animal breeding (*e.g.* MAS) and impart novel traits (*e.g.* GM). There are also applications for propagation, such as cloning.	MAS is widely used to improve the speed and accuracy of animal breeding programmes for both livestock and fish. Cloning is also used for propagation, but costs are currently prohibitive for all but high-value breeding animals and pets. GM animals have been developed, on an experimental basis, for the production of desirable compounds.	MAS will continue to be the dominant biotechnology used in animal breeding and will expand into most breeding operations. Concerns over consumer acceptance and cost may limit the use of GM and cloning, except for production of novel compounds and breeding of high-value animals.
Animal diagnostics and therapeutics	Animal diagnostics and therapeutics derive from products developed for human health. Biotechnology products include genetic diagnostic tests, biotherapeutics, and biovaccines. The main markets for animal diagnostics are companion and farm animals.	Several dozen biotech-based animal diagnostic tests are available. These cover several diseases for pets and some economically important livestock and fishery diseases. Only a few biopharmaceuticals or biovaccines have been approved for animal use.	A number of new animal diagnostic tests are under development and should be commercialised by 2015. Livestock diagnostics will move towards microarrays that can be used by non-specialists in the field. Several additional vaccines will be developed for costly infectious diseases that affect livestock. Several biopharmaceuticals that enhance growth or meat quality could reach the market.

Biotech applications to 2015 in human health

The main biotechnological products for human health are pharmaceuticals, experimental and emerging therapies (including cellular, gene, and stem cell research) and diagnostics. Health biotechnology will deliver approximately 10 to 14 new biopharmaceuticals per year to at least 2015. By this time several new regenerative biotechnologies could also obtain market approval, while a large number of diagnostics should reach the market every year.

Biotechnological knowledge is likely to be used in the discovery and development process for *all* new pharmaceuticals by 2015, for example to identify potential drugs or drug targets, or to assess safety. Consequently, even though there will still be small and large molecule drugs, it will no longer be useful to separate the pharmaceutical and health biotechnology sectors.

In addition to a gradual increase in the supply of health therapies, biotechnology has the potential to bring substantial improvements to healthcare delivery through more effective personalised therapies and the development of predictive and preventive medicine (see Box 4.1). The research necessary to support these two developments is already under way, as shown by the increasing number of diagnostic tests, identified gene-drug interactions, and submissions of pharmacogenetic information to regulatory authorities. Assisting this trend will be the continual decrease in genome sequencing costs discussed above. The main challenge to 2015 is to create and analyse data on individual genomes, validated biomarkers, and treatment outcomes.

Therapeutics

How many and what types of biotherapeutics are likely to obtain market approval by 2015? As noted in Chapter 3, biotechnology can be used to develop three types of therapeutics: large-molecule biopharmaceuticals, experimental treatments, and small-molecule therapeutics. Due to a lack of data, it is impossible to forecast the percentage of small-molecule drugs, developed through biotechnology, that are currently in clinical trials and which are likely to pass each clinical trial phase and consequently obtain market approval by 2015. Conversely, clinical trial data can be used to identify biopharmaceuticals and experimental therapies and therefore to estimate the number of these drugs that are likely to reach the market by 2015.[5]

Box 4.1. **Predictive and preventive medicine**

The goal of predictive and preventive medicine is to predict the development of disease before symptoms are visible and to prevent or delay the onset of disease through treatment. The future success of predictive and preventive medicine depends on large declines in the cost of genetic sequencing diagnostics (particularly the significant potential of microarray technology), and validated biomarkers that can accurately signal the risk of disease well before the appearance of symptoms. Obtaining the full benefits of predictive and preventive medicine would require an integrated system of biomedical research based on electronic patient records that include data on the patient's genotype, environmental exposures, complete drug prescription history, and health status over time. Equivalent data for thousands or millions of patients from a variety of ethnic groups will need to be analysed over long time periods to identify genes or biomarkers that can predict the risk of developing disease, as well as the adverse effects or benefits of drugs and other preventive therapies.

Once proven preventive therapies are available for clinical care, frequent monitoring of patients will be required to determine if these therapies are effective and to personalise treatment, depending on the patient's genetic and phenotypic responses to therapy. One of the most potentially challenging aspects to achieving effective prevention is the requirement for individuals to participate in maintaining their health by following prescribed drug, diet or exercise therapies.

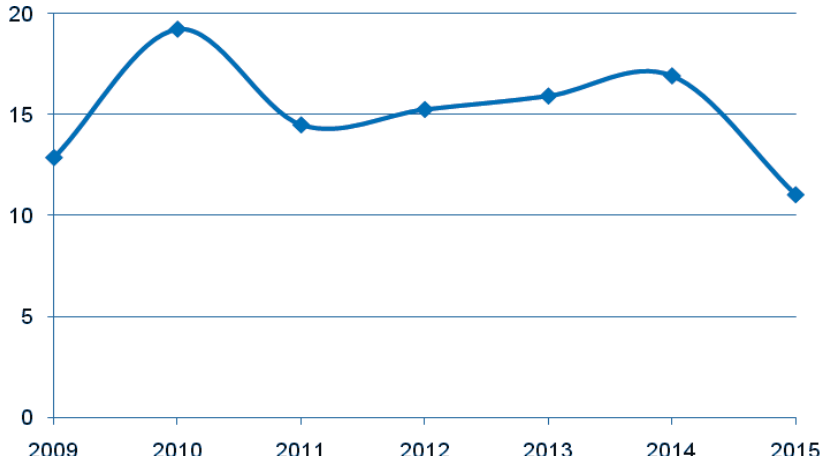
A transition from current healthcare models to a predictive and preventive health system has already begun, but could be slowed due to high costs, the need for long-term follow-up, and a poor fit with existing business models.

Of note, the importance of biotechnological knowledge in small molecule drug development is expected to increase significantly over the next decade so that a growing percentage of small molecule pharmaceuticals that enter clinical trials are likely to be developed or produced using biotechnology. For instance, biotechnology could be used to fight against antibiotic resistance through the development of new antibiotics. At some point after 2015, almost all drugs that succeed in clinical trials and obtain marketing approval will have used biotechnology at some point in their development.

An analysis of current clinical trials and historical success rates for biopharmaceutical new molecular entities (bio-NMEs) estimates that approximately 15 bio-NMEs will receive market approval each year to 2015 (see Figure 4.2). This is substantially higher than the average of nine bio-NME market approvals per year between 2000 and 2007 inclusive. The increase is due to a large number of drug candidates in Phase III clinical trials or in the pre-registration stage in biotherapeutic drug classes

(*e.g.* monoclonal antibodies and recombinant interferon) with high past success rates.

Figure 4.2. **Number of biopharmaceutical NMEs expected to obtain marketing approval, by year**



Notes: All results exclude changes in the formulation of existing bio-NMEs. The analysis uses historical success rates from Pharmapredict to estimate the probability of a drug within a defined class moving from each clinical trial phase to market approval. The decline in the projected number of biotherapeutics reaching the market after 2014 is partly due to the long lead times for drug development, with no data for many drugs in the preclinical stage.

Source: Authors, based on data from Pharmaprojects and Pharmapredict (Informa, 2008a, 2008b).

Between 2000 and 2007, biopharmaceuticals and the few experimental therapies on the market accounted for slightly more than 12% of all NMEs that obtained market approval. An analysis by the authors of all drugs in all clinical trial phases and past success rates indicates that this share is unlikely to increase significantly to 2015, probably not exceeding 20%.[6] Furthermore, this estimate assumes that the success rate for experimental biotherapies is equal to the average success rate for other biotherapeutics, which is unlikely to be the case. As the proportion of biopharmaceuticals by clinical trial phase is roughly constant, it is highly unlikely that there will be a future surge in the share of biopharmaceuticals out of all drugs on the market in the coming five to ten years. The only factors that could cause a

significant change in the share are either an increase in the percent of biopharmaceuticals that succeed in clinical trials, or a significant decrease in development time as compared to non-biopharmaceutical NMEs.

An important question is whether the expected increase in the number of biopharmaceuticals reaching the market to 2015 will provide substantial improvements over currently available therapies. Although the OECD analysis of the HAS data (Chapter 3) finds that a higher percentage of biopharmaceuticals than other new drugs offers a therapeutic advance compared to existing treatments, this advantage has been declining, partly because of firms bringing "me too" biopharmaceuticals onto the market.[7] The share of biopharmaceuticals offering some therapeutic advance or more declined from 52.1% of 25 indications evaluated between 2001 and 2004 inclusive, to 43.6% of 24 indications evaluated between 2005 and 2007. Over this period, the percentage of "me too" ratings for an indication increased from 25.0% to 50.9%.

The experimental biotherapies in the pipeline, with novel modes of action, could provide major medical advances and reverse the declining trend in the additional therapeutic value of biopharmaceuticals. However, the extent of any improvement is difficult to estimate. First, experimental therapies only account for about 40% of all bio-NMEs in the clinical trial process (Table 4.3), and their success rate is likely to be much lower than that for proven biotherapeutics. Secondly, many of these therapies, some of which have been in development for decades, elicit a strong immune system response that detracts from the value of the treatment. Furthermore, many of these technologies are so new that they are not clearly understood, suggesting that more time will be required to use them effectively. For instance, recent studies have raised doubts about the current understanding of RNAi and point to a mode of operation that involves the immune system rather than silencing genes (Pollack, 2008b). Finally, at the present level of technology maturity, the best candidates for many experimental therapies are rare diseases caused by single gene mutations (Human Genome Project Information, 2007). This limits the potential public health benefits of experimental biotherapeutics to small groups of individuals, at least in the near term.

Table 4.3. **Share of all biotechnology clinical trials in proven and experimental biotherapies, by phase**

	Phase I	Phase II	Phase III	Pre-registration	Total
Proven biotherapeutics[1]	63.2%	55.6%	62.8%	61.1%	59.3%
Experimental therapies[2]	36.8%	44.4%	37.2%	38.9%	40.7%
	100.0%	100.0%	100.0%	100.0%	100.0%

1. Biotherapeutics include monoclonal antibodies, recombinant therapeutics, and recombinant vaccines.

2. Experimental therapies include antisense therapy, cellular therapy, gene delivery vectors, gene therapy, immunoconjugates, immunotoxins (toxins conjugated with mAbs), non-antisense, non-RNAi oligonucleotides, RNA interference, and stem cell therapy.

Source: Authors, based on Informa, 2008b.

Diagnostics

The importance of diagnostic tests, including diagnostics based on biotechnology, will continue increasing to 2015. This will be particularly apparent if trends towards the increased use of pharmacogenetics (see below) and preventive medicine continue in unison.

Although there are only a small number of *in vivo* biotechnology diagnostics in clinical trials, these products have a short development time and high success rates. It is therefore likely that several of the products currently in development will reach the market before 2015.

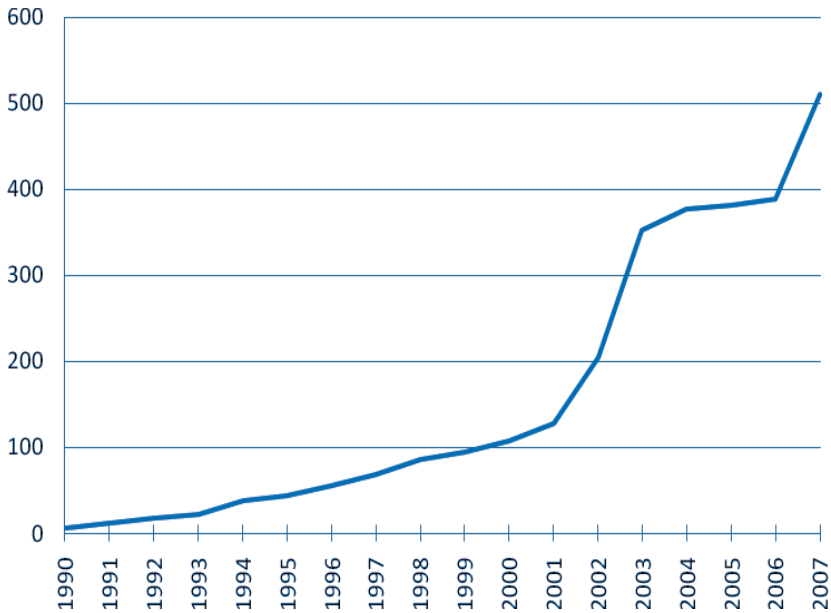
As noted in Chapter 3, the availability and use of *in vitro* diagnostics, and in particular genetic tests, has increased substantially since the mid-1990s. There are no data available that can be used to predict the number of genetic tests that will reach the market in the future. There are about 6 000 known genetic disorders (Human Genome Project Information, 2008), but many of the disorders which currently lack a diagnostic test are very rare. The very small diagnostic market for these disorders will limit commercial and academic interest in developing a genetic test for them. This could reduce the discovery rate for new genetic tests in the future.

Genetic testing is likely to shift from identifying single genetic mutations to tests for multiple genes that increase the risk of diseases caused by a large number of different factors. These tests could use microarray technology to identify multiple gene variations simultaneously.

Pharmacogenetics

There have been real advances in all of the key technology components required for developing pharmacogenetics. Bioinformatic tools are increasingly powerful; tremendous amounts of information are being stored and processed, including in public databases accessible over the Internet. DNA sequencing costs have decreased dramatically and are expected to continue to do so in the future. There has also been a rapid increase in the number of identified gene-drug relationships (see Figure 4.3), publications on pharmacogenetics and pharmacogenomics, and drug labels containing pharmacogenetic information.

Figure 4.3. **Number of identified gene-drug relationships, three-year moving average, by year of first publication**[1,2]



1. As of 10 December 2007.

2. Gene-drug relationship refers to the identification of a gene variant that influences a patient's reaction to the drug.

Source: Authors, based on PharmGKB, 2007.

The main regulators for health therapies, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA), are

collaborating on the harmonisation of rules for pharmacogenetic data submissions. This is essential for reducing the cost to firms of providing pharmacogenetic data. It is also possible that pharmacogenetic data submissions for new drug applications will become mandatory (PwC, 2005). The collection of standardised data as a result of these regulatory changes could have a major positive impact on the use of pharmacogenetics in drug development.

Along with the positive development listed above, there are numerous challenges in several domains that are influencing the large-scale development of pharmacogenetics to 2015:

- *Scientific* – The validation of biomarkers, which is one of the most important aspects of pharmacogenetics, is proving a daunting task. Roche CEO Franz Humer has stated, "It is as complex to find a biomarker as it is to find a new drug" (Hirschler, 2007). In addition, most drug responses are polygenetic, further increasing scientific complexity.

- *Regulatory* – Historically, diagnostics and drugs have been regulated independently (Phillips, 2006), and until recently, no regulation was in place for the use of pharmacogenetic information in the approval process for drugs.[8] Furthermore, although the majority of clinical trials now collect genetic data, this is a recent trend and the information is not yet uniformly used to evaluate differences in drug response. Positive steps are being taken however, for instance through work of The International Conference on Harmonisation (ICH). The ICH, which comprises regulatory authorities of Europe, Japan and the United States and aims to harmonise regulations for pharmaceuticals across jurisdictions, endorsed a concept paper laying out guidelines for the validation of biomarkers (ICH, 2008).

- *Economic* – By identifying subgroups of patients that do not respond to a drug, pharmacogenetic research could reduce the market for approved drugs and consequently the revenue earned per drug by pharmaceutical firms. Alternatively, pharmacogenetics could decrease the cost of drug development or allow firms to charge higher prices for more effective drugs.[9] Pharmacogenetics also has wider benefits. It could reduce the massive human and economic costs associated with adverse drug reactions (ADR), which are estimated to cost USD 136 billion and 100 000 deaths per year in the United States alone (CDER, 2002). This is a powerful economic argument for pharmacogenetics.

- *Human resources* – Pharmacogenetic research is very labour-intensive and requires the integration of numerous disciplines. The widespread application of pharmacogenetics will entail changes to the way in which some healthcare providers, such as doctors, work. For instance, the "off-label prescribing" of drugs for unapproved indications accounts for about 20% of all prescriptions in the United States (Radley, Finkelstein and Stafford, 2006). This practice could become obsolete as prescribing practices are increasingly determined by the patient's genetic status.

- *Public acceptance and access* – Drugs designed for small groups of genetically similar people could exacerbate adverse drug reactions in people with a different genetic code unless prescribing practices are strictly controlled. A small number of high-profile errors could reduce public confidence in the development and consumption of pharmacogenetic products. In addition, genetic variations associated with ethnicity can affect responses to drugs. Ensuring safe and effective access to drugs could therefore require different ethnic groups to be included in clinical trials. At present, most of the participants in clinical trials are Caucasian (OECD, forthcoming).

- *Lifestyle choices* – Not enough is known about the interaction between genetics and lifestyles (*e.g.* exercise, diet, alcohol consumption and smoking) as a factor in how individuals respond to medicines.

Due to the highly varied nature of the challenges facing pharmacogenetics, and the lower pipeline visibility of some components such as diagnostics, it is impossible to estimate the number of pharmacogenetic products that are likely to reach the market by 2015. The interaction of technology developments, regulatory policies and business models will determine the future trajectory of these technologies. Nevertheless, a few general observations can be drawn.

An increasing number of drugs tailored to groups of people who share specific genetic characteristics are likely to reach the market by 2015, with a focus on improving efficacy and reducing ADRs.[10] Concern over high-profile drug withdrawals (*e.g.* Vioxx) should also encourage firms to use pharmacogenetics during drug development to minimise severe ADRs. This could prevent expensive lawsuits and the loss of markets for unsafe drugs. Another application is to use pharmacogenetics to identify subgroups of responders. This could "rescue" drugs that fail in clinical testing by identifying subgroups of patients for which the drug is safe and effective (De Palma, 2006).[11] However, this could be more difficult and expensive than identifying subgroups at high risk of ADRs.

Functional foods and nutraceuticals (FFN)

In OECD countries, the market for functional foods is constrained by alternative and lower cost sources of compounds, such as anti-oxidants or healthy oils, compared to the cost of using biotechnology to produce these traits in food plants. However, several crop varieties with product quality traits for healthier oils are expected to reach the market by 2012-2015. This could influence the FFN market.

The largest potential market for functional foods is in developing countries where diets are restricted to a few staple crops. Under these conditions, improved varieties of staple crops such as rice or cassava are economically cost effective in health terms (Pew Initiative, 2007), although subsistence farmers are unlikely to be able to pay higher prices for improved seeds. Given adequate public sector support for crop development and distribution, several improved staple crop varieties with improved provitamin A, vitamin E, folate, iron, calcium, or higher protein levels could reach the market by 2015.

Compared to functional foods, nutraceuticals offer greater market opportunities for biotechnology in developed countries because of lower development and regulatory costs compared to improved food varieties and because supplements can be marketed at a high price.

Medical devices

Due to a lack of data, it is difficult to forecast developments to 2015 for medical devices based on biotechnology. However, a number of drug delivery systems and biosensors under development appear likely to reach the market by then.

One novel drug delivery system involves modified autologous cells that produce biopharmaceuticals in the patient, avoiding the need for ongoing injections.[12] Another early-stage innovation that could reach the market by 2015 is a nanodevice that releases drugs in response to over-expression of undesirable proteins.

Tissue engineering is currently regulated as though it were a medical device. The next generation of tissue engineering products is likely to consist of simple scaffolds to support cells that produce insulin. These too could reach the market before 2015.

Table 4.4 summarises the current status of biotechnologies for human health and their possible development and use up to 2015.

Table 4.4. **The current status and prospects to 2015 of some important biotechnology applications in health**

Technology	Definition	Current status	Status to 2015
Therapeutics	Therapeutics include biopharmaceuticals (large-molecule therapeutics produced by recombinant technologies), experimental treatments (tissue engineering, therapeutic vaccines, stem cell research and gene therapy), and small-molecule drugs that use biotech in their development, manufacture or use.	Since the late 1990s, approx. seven biopharmaceuticals per year reached the market. These have provided a significant therapeutic advantage over other drugs. Few experimental therapies are on the market. Biotech is increasingly used to develop small molecule drugs, particularly during discovery.	The number of biotherapeutics per year will increase slightly, but this will not result in a noticeably higher share of all drugs. While the therapeutic value of these biotherapeutics has been declining slightly, the approval of experimental therapies could reverse this trend. Biotech is likely to play at least some role (*e.g.* target identification) in the development of almost all new drugs.
Diagnostics	*In vivo* (invasive) and *in vitro* (non-invasive) diagnostic tests based on modern biotechnology can diagnose diseases and identify an increased risk of developing disease.	There is more activity in *in vitro* than *in vivo* diagnostics, much of it to detect genes, and mutations within genes and patterns of gene expression. Molecular genetics is the fastest growing segment of the diagnostics industry. There are over 1 600 diseases for which genetic tests are available, and usage has increased significantly.	An increase in the number of biotech-based *in vitro* diagnostics is expected, although growth may be slower than in the past. Gene tests will shift from identifying single genetic mutations to identifying risk factors associated with multiple genes.
Pharmacogenetics	Pharmacogenetics studies gene-drug interactions using diagnostics, bioinformatics and biomarkers. It is used to identify subgroups of responders and non-responders to a treatment, establish proper dosages, and reduce adverse drug reactions (ADRs).	In addition to the four drugs in the United States that require it, genetic testing is recommended for two dozen other drugs. The number of known biomarkers has increased rapidly, along with the number of drugs containing pharmacogenetic information on their registration labels.	Despite a variety of challenges facing pharmacogenetics, the key technological components are moving in the right direction. An increasing number of drugs for groups of people who share specific genetic characteristics will be approved, but they will primarily focus on improving efficacy and reducing ADRs. They will also be used to "rescue" drugs that fail in clinical testing by identifying responder subgroups.
Functional foods and nutraceuticals (FFN)	Functional foods have a claimed health benefit beyond basic nutritional functions, while nutraceuticals are dietary supplements isolated or purified from plants or animals.	Most FFNs on the market are not based on biotechnology. Biotech can be used to develop plant or animal varieties with increased levels of certain nutrients or functional components, but this is a very small share of the market.	By 2015, biotechnology could be used to develop nutritionally enhanced crops for developing countries. In the OECD, biotech plant varieties with product quality traits will be commercialised and could increase biotechnology's share of the FFN market.
Medical devices	Medical devices assist health but are not metabolised. Most do not use biotechnology.	Most potential applications are still in the research phase, including biosensors and tissue engineering based devices.	A few simple tissue engineering based devices to produce insulin could reach the market by 2015.

Biotech applications to 2015 in industry

Robust data on product development are unavailable for industrial biotechnology. The state of the sector in 2015 can only be estimated from general innovation indicators for patents, venture capital and R&D investment, and from case studies of specific technologies. These indicators point to continued growth in industrial biotechnology, but there are no consistent data for estimating the likelihood that specific biotechnologies will be commercially viable by 2015.

Estimating the future of industrial biotechnology is even more challenging than for health and primary production biotechnology because of the potential impact of unforeseeable developments. One large unknown for the future is the development rate of synthetic biology, including metabolic pathway engineering. These technologies could radically change the types of products that can be produced by living cells, particularly in closed industrial system applications. Regulatory restrictions will limit the impact of synbio in agriculture and health prior to 2015. A second unknown is the rate of development of competing technologies. While in some regions biorefineries could be major providers of low-carbon energy, in other regions solar, wind, wave, geothermal or nuclear power could provide more environmentally benign and cheaper sources of carbon-neutral energy and materials. A third unknown involves the relative prices and availability of petroleum versus biomass feedstocks, which will influence the commercial viability of biotechnological production processes compared to processes based on petroleum.

General innovation indicators

Industrial biotechnology patents, venture capital funding, and private sector R&D all point to a rapid increase in investment in industrial biotechnology that is likely to continue into the future, resulting in new products and processes reaching the market by 2015. In addition to technical barriers, the main limitation to the ability of industrial biotechnology to replace other industrial processes will be the relative prices of commodities such as petroleum and biomass feedstock.

On average, 500 industrial biotechnology patents were granted by the USPTO between 1975 and 1999. This doubled to over 1 100 per year between 2000 and 2006 (USITC, 2008).

The amount of US venture capital investment in industrial biotechnology is small compared to the total invested in biotechnology, but

it is increasing rapidly – from an annual average of approximately USD 85 million between 1999 and 2005 to USD 225 million and USD 290 million, respectively, in 2006 and 2007.[13] In addition, over the same period the number of industrial biotechnology companies receiving venture capital investment climbed steadily, from less than 5 per year in the late 1990s to approximately 10 per year from 2002 to 2006, peaking at over 20 in 2007. The average venture capital investment per company grew from less than USD 2 million in 1995 to approximately USD 14 million in 2007 (USITC, 2008). These increases match similar trends in the increase of venture capital investment in "clean tech" companies. While venture capital investment in 2008 is down, it is likely that the decline is temporary, given the potential for industrial biotechnology to address persistent concerns over climate change and energy independence.

A survey of US companies active in liquid biobased chemicals collected data on R&D investments in industrial biotechnology between 2004 and 2007. As shown in Table 4.5, biobased chemical R&D expenditures increased 70.4%, from just over USD 2 billion in 2004 to USD 3.4 billion in 2007. The rate of increase of full-time R&D employees, at 30.3%, was slower than R&D spending, but still represents an increase of more than 1 750 full-time R&D employees.

Table 4.5. **Bio-based chemical R&D: US survey respondents' expenditures and employment, 2004-07**

Item	2004	2005	2006	2007	2004–07 (% change)
Expenditures (1 000 USD)	2 014 363	1 953 849	3 425 432	3 432 427	70.4
Full-time employees	5 819	6 386	7 424	7 584	30.3

Source: USITC, 2008.

These recent increases in R&D spending, employment, patenting, and venture capital investment in industrial biotechnology suggest that the use of industrial enzymes and biotechnology in chemical production will continue to increase up to 2015. This will be most notable in bioplastics, where new technologies will open the door to the production of complex (in many instances non-biodegradable) biopolymers. Other industrial application areas, such as biomining and environmental services, will see more modest growth.

Chemical production

While hard figures are unavailable, the use of biotechnology for chemical production has increased over the past decade and is likely to continue to increase, driven by rising energy costs, new chemical legislation (*e.g.* REACH in Europe), and increasingly stringent environmental regulations.

Table 4.6 provides estimates by the USDA (2008) of the percentage of chemical production based on biotechnology in 2005, 2010 and 2025. Biotechnology's share of all chemical production is estimated to increase from less than 2% in 2005 to between 9% and 13% in 2010, reaching approximately one-quarter of all chemical production by 2025. Biotechnological processes are expected to account for approximately half of fine chemical production in 2025. By value, speciality chemicals will account for up to 60% of the total value of all biotech chemical production in 2025 (USD 300 million out of USD 483 million). The biotech share of commodity and polymer chemicals will be smaller, but the share will increase for both groups between 2005 and 2025.[14]

Table 4.6. **Projected value of world chemical production: 2005, 2010 and 2025**

USD billions

	2005			2010			2025		
Chemical sector	Total value	Biobased value	Biobased share	Total value	Biobased value	Biobased share	Total value	Biobased value	Biobased share
Commodity	475	0.9	0.2%	550	5-11	0.9-2.0%	857	50-86	5.8-10.0%
Specialty	375	5	1.3%	435	87-110	20.0-25.3%	679	300-340	44.2-50.1%
Fine	100	15	15.0%	125	25-32	20.0-25.6%	195	88-98	45.1-50.3%
Polymer	250	0.3	0.1%	290	15-30	5.2-10.3%	452	45-90	10.0-19.9%
All chemicals	1 200	21.2	1.8%	1 400	132-183	9.4-13.1%	2 183	483-614	22.1-28.1%

Note: The value of pharmaceuticals is excluded.

Source: USDA, 2008.

An evaluation of current research funding and targets leads to several predictions for the use of industrial biotechnology for chemical production to 2015. A number of new biocatalysts and advanced fermentation processes will be developed that are faster, less expensive and more versatile than comparable chemical catalysts. In addition, metabolic pathway engineering is being explored for the production of several chemicals.[15] Many processes will rely on specialty enzymes tailored to specific production processes and environmental conditions. While all of these techniques are expected to increase biotechnology's share in chemical production and permit its use for a wider range of chemicals, an increase in the biotechnology share of

chemical production will require advances in R&D and success in scaling up production.

Production of biomaterials

The development of biomaterials is expected to continue seeing strong growth to 2015, particularly if petroleum prices remain above previous levels. Many biomaterials, such as insulation and composite panels, can be manufactured without using modern biotechnology. Growth in other biomaterials, such as bioplastics, will depend on technical advances in biotechnology.

The market for biopolymers – the building material for many bioplastics – relies heavily on the relative commodity prices of biomass compared to petroleum, the traditional feedstock for polymers. Recent increases in petroleum prices have renewed interest in biopolymers, but the interest has been dampened by the corresponding increase in maize prices, an important biomass source for biopolymers. Nonetheless, concern about sustained agricultural and petroleum commodity prices should spur R&D into biopolymers, especially those based on waste biomass or non-food crops.

The USDA (2008) estimates that the upper limit for the substitution of petroleum-based plastics with bioplastics is 33%. Few assume that this limit will be achieved in the near term. Estimates of the global production of biopolymers in 2010 or 2011 range from approximately 500 to 1 500 kilo tonnes, or 0.2% to 0.6% of the expected production of all polymers (Wolf *et al.*, 2005; European Bioplastics, 2008).

Continued research into advanced fermentation processes are likely to increase the range of plastics that could be produced by biotechnology. Advances have occurred rapidly in the past, with some polyesters moving from the research phase to commercialisation within three years.[16] An entirely new prospect is the production of PVC from bioethanol.

Industrial enzymes

The market for enzymes is expected to experience strong growth to 2015. In the United States alone, demand is expected to increase by 6% annually to USD 2.5 billion by 2012, with the fastest growth occurring in biofuel, pharmaceutical, and pulp and paper applications (Freedonia, 2008). Reiss *et al.* (2007) estimate a 6.5% annual growth in the global enzyme market, with global sales in 2015 of USD 7.4 billion. R&D will continue to focus on developing and selecting more effective enzymes and production processes. The benefits would include cost savings as well as a smaller

environmental footprint for some industrial production processes through reduced energy consumption and the elimination of harmful by-products.

Environmental services

The use of biosensors in environmental monitoring is progressing at a slow pace, mainly due to regulatory systems that favour validated chemical analysis over new methods. While biosensors could replace chemical analyses that need extensive pre-processing and/or expensive analysis, many environmental parameters can be measured with cheap and widely accepted chemical techniques.

Biosensors are likely to be used increasingly over conventional methods when rapid results are paramount (*e.g.* monitoring of bioterrorism, chemical weapons, explosives and drinking water), or when biosensors have a competitive advantage such as in monitoring of biodiversity. There is no evidence of a surge in investment for environmental biosensors, but spin-off effects from large biosensor R&D efforts in medicine and biosecurity could be beneficial.

There is high potential for the use of modern biotechnology in environmental remediation, especially to clean up heavy metals and chemicals. While carefully selected wild strains of micro-organisms could be used in some cases, genetically modified organisms that are customised for the specific conditions of each cleanup site are likely to be more efficient bioremediators. These organisms would need to meet expensive regulatory requirements, even if they are useful only for specific locations. Consequently, bioremediation using GM micro-organisms is unlikely to be economically viable without either public financial support or a change in regulatory requirements. An alternative is to develop customised micro-organisms using metabolic pathway engineering, which is less stringently regulated.

Resource extraction

There are no consistent data on R&D investments or current or future sales of the use of biotechnology in resource extraction. Recent high demand for resources could stimulate research into developing micro-organisms to assist in the extraction of valuable minerals such as gold or copper from ores, or petroleum from oil wells. The use of biotechnology in resource extraction faces the same set of problems as with bioremediation, such as the need for customised micro-organisms suited to unique environments and high regulatory costs for the open release of GM organisms.

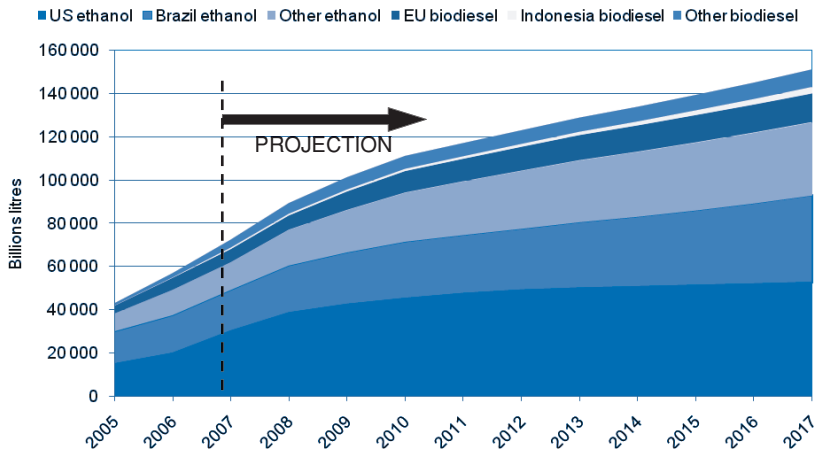
Biorefineries

New technological developments and private and public investment in pilot biorefinery facilities and demonstration plants could lead to new types of biorefineries by 2015, including lignocellulosic biorefineries and biorefineries that can use several types of biomass as feedstock. In addition, novel and versatile ways of using biorefinery by-products could improve commercial viability, such as new processes to convert glycerine, a by-product of biodiesel production, to a biopolymer.

Biofuels to 2015

From 2000 to 2007, biofuel production increased dramatically. This was primarily due to ethanol production, which tripled to 52 billion litres, and biodiesel production, which saw an 11-fold increase to 11 billion litres (OECD-FAO, 2008). As shown in Figure 4.4, biofuel production is expected to continue increasing rapidly to more than twice 2007 levels by 2017.

Figure 4.4. **World ethanol and biodiesel production: projections to 2017**



Source: Authors, based on OECD-FAO, 2008.

Given ambitious production mandates and the spectre of sustained high energy prices, R&D for biofuels is likely to increase. This will lead to new agricultural feedstocks and the development of new enzymes to increase

production capacity, reduce biomass and energy input requirements, and reduce the costs of using cellulosic biomass.

Biofuel crop varieties

The debate over the use of food crops and cropland for biofuel production, as well as debates over the environmental benefits of using maize, wheat and soybeans to produce fuels, could lead to substantial changes in biofuel production. The most likely outcome is a faster-than-expected shift in research priorities to non-food crops such as grasses and tree species that can be grown on land unsuitable for crop agriculture.

Low-lignin GM varieties of eucalyptus and pine with improved processing characteristics for cellulosic production of bioethanol could be available by 2015, but are more likely to appear later. Most research on "biofuel" grasses is still in the laboratory or greenhouse stage, but the number of field trials for low-lignin grasses tailored to biofuel production is likely to increase over the near future. It is possible that some GM grass varieties for biofuel production will be commercially available by 2015 provided that they meet environmental regulatory requirements.

Industrial processes for biofuels

Industrial processes for biodiesel and bioethanol derived from sugar cane or starch are unlikely to see any revolutionary technological changes to 2015. Research on the use of lipases for biodiesel production is underway, but production based on transesterification could still be more cost-effective in 2015. Bioethanol from starches derived from maize and wheat requires pre-treatment (usually through boiling) of starch prior to its conversion to sugar using amylases. New types of amylases that can convert raw starch to sugar have been tested in several full-scale production plants. The elimination of pre-treatment would save time and money and improve the energy efficiency of starch-based bioethanol.

Research into improved enzymes for converting lignocellulosic biomass to sugars is advancing. These are expected to reduce the cost and time to produce lignocellulosic ethanol. While advances in efficiency are expected, it is impossible to determine whether they will be sufficient to make cellulosic ethanol commercially viable on a mass scale by 2015. Rapid advances could however reduce or eliminate some of the environmental and food security concerns associated with biofuel production (OECD, 2008).

The development of high-density biofuels, mostly based on microbial production, has become a major focus of current research. These fuels, such

as alcohols, alkanes (*e.g.* methane, propane, octane) and ethers, could be produced by microbes and offer major advantages over ethanol and biodiesel due to their high energy content and low water solubility. The latter would facilitate transport in pipelines. A number of R&D efforts by large industrial companies, small innovative players, or a combination of the two bode well for future development. Some fuels produced by microbes could reach the market as early as 2010 (Amyris, n.d.). Other microbial-based fuels such as biodiesel from algae are unlikely to be available on a commercial scale by 2015, but they could reach the pilot plant stage. Biohydrogen is unlikely to be a viable alternative motor fuel by 2015 due to numerous challenges, including the costs associated with infrastructure development. Even if these problems are overcome, biohydrogen will compete with other hydrogen production methods such as the electrolysis of water.

Table 4.7 summarises the current status of industrial biotechnologies and their possible development and use up to 2015.

Table 4.7. **The current status and prospects to 2015 of some important biotechnology applications in industry**

Technology	Definition	Current status	Status to 2015
Production of chemicals	The biobased production of biofuels as well as of bulk and specialty chemicals, including enzymes, solvents, amino and organic acids, vitamins, antibiotics and biopolymers. These processes often compete with production methods using chemical synthesis.	A small but notable share (about 2%) of all chemical production. This ranges from a high of 15% of fine chemicals to less than 1% of polymers. Biotech production has advantages such as less demanding production conditions and lower energy inputs, waste and environmental impacts. R&D aims to increase competitiveness through increased efficiency.	Biobased chemicals are expected to grow to over 10% of the chemical market. Growth will be most notable in specialty chemicals and polymers. This will be driven by the development of new biocatalysts and advanced fermentation techniques as well as advances in metabolic pathway engineering. Many biobased processes will rely on enzymes tailored to specific production and environmental conditions.
Production of biomaterials	Biobased chemicals can be used to create various biomaterials, most importantly bioplastics, derived from biopolymers. Some bioplastics are biodegradable while others, similar to most petrochemical-based plastics, are not but can be recycled.	Though a very small share of the plastic market, several large biopolymer plants are in operation and more are in development. A goal of R&D is to develop non-biodegradable bioplastics.	Bioplastics will constitute an important (though still relatively small) share of the global plastics market. The range of plastics that are produced by biotechnology will expand to include many non-biodegradable plastics.
Industrial enzymes	Enzymes are proteins that act as a catalyst for biochemical reactions in a living cell. In addition to being used to produce chemicals, they have numerous industrial uses in food and feed, detergent, textile, and pulp and paper production.	Enzymes produced using modern biotech are widely used as additives in food, animal feed, and detergents. They are also used in many textile operations to save energy, and in pulp and paper to reduce imperfections in the final product. Biotechnology is applied to create and select enzymes through GM, directed evolution, and MAS.	The use of industrial enzymes is already mature and growth is expected to continue. More effective enzymes and production processes will become available. This will provide cost savings as well as a smaller environmental footprint for some industrial production through reduced energy consumption and the elimination of harmful by-products.
Environmental services	Biotechnology can be used to monitor environmental conditions through the use of biosensors. Bioremediation uses micro-organisms or plants to remove contaminants from the environment.	Uptake of biotechnology in environmental services has been slow. This is due to issues of cost competitiveness in the case of biosensors and the need for uniquely suited micro-organisms or plants in bioremediation.	Competitiveness with other technologies will continue to dictate the uptake of environmental biotechnologies. The development of new micro-organisms will increase the use of bioremediation. Biosensors will be the best solution in areas where continuous monitoring is essential, such as drinking water. R&D will depend on public support and spin-offs from health, agriculture and biosecurity research.

Table 4.7. **The current status and prospects to 2015 of some important biotechnology applications in industry** (continued)

Technology	Definition	Current status	Status to 2015
Resource extraction	Micro-organisms are used to increase the efficiency of resource extraction operations. This can include extraction of minerals from ores as well as changing conditions within oil wells to boost production.	Little R&D or commercial activity has occurred, but biotechnology has been demonstrated as a way to increase extraction efficiencies.	High demand for metals and oil could lead to an increase in the use of biotechnology. However, harsh onsite environmental conditions limit use to selected wild strains or GM organisms.
Biorefineries	Biorefineries integrate various conversion processes to produce fuels, power and chemicals from biomass. While similar to today's petroleum refineries, biorefineries could accommodate numerous varieties of biomass feedstocks.	Hundreds of biofuel refineries are operating worldwide. Most use food crops such as maize and sugar. Many pilot and demonstration plants have been set up to produce cellulosic ethanol and other chemicals out of a variety of other feedstocks including grass, wood, and agricultural and municipal wastes.	The combination of technological developments (particularly in enzymes) and the abundance of test facilities points to significant advances. Novel ways of using by-products from biorefinery operations will further increase activity. R&D advances should permit biorefineries to use all types of biomass. Even if not entirely successful in this, they will be able to adapt more easily to a wider range of biomass types.
Biofuels	Biofuels are derived from biomass and/or biological processes. Some biofuels, including sugar cane ethanol, use traditional production methods only. Modern biotech can be applied to biofuels for two purposes: *(1)* to develop new plant varieties with properties advantageous to fuel production, and *(2)* to develop production processes that facilitate the use of new forms of biomass or that improve conversion efficiencies.	Driven by government support and high energy costs, large quantities of biodiesel and bioethanol are produced based on fermentation and transesterification; they represent a small but notable share of transport fuels. Research is ongoing into lignocellulosic conversion and microbial production. These new technologies, if developed, could improve economic competitiveness and address challenges and concerns about the impact of biofuel production on the environment and food supply.	New plant varieties with product quality traits will increase production yields, but plants tailored to specific production processes are unlikely to appear. Production volumes will increase. Some of this could be based on cellulosic and microbial production, but much depends on technological advances and success in scaling up production.

The bioeconomy in 2015

Technology developments to 2015 will expand the number of economically competitive applications of biotechnology, strengthening the bioeconomy. Increasingly powerful and affordable platform technologies will continue to be used in all biotechnology applications. These will include rapidly developing fields such as bioinformatics, metabolic pathway engineering and synthetic biology.

New applications will lead to major increases in the uptake of biotechnology. Biological techniques and knowledge will be used in many more products. By 2015, nearly all pharmaceutical products, as well as most new varieties of large market crops, will be developed using biotechnology. Biotechnological processes will produce a growing percentage of chemicals and plastics.

Supply chain linkages between agriculture and industry will become more robust. New feedstock crops with quality characteristics adapted to the needs of biorefineries will reduce the production costs of biofuels and biochemicals. Soybean and maize varieties will be modified, respectively, to increase their content of oils and starches suitable for biofuels. This will be combined with new industrial processing techniques that increase energy yield and decrease waste. Health biotechnology is likely to follow its own trajectory, but industrial biotechnology will produce many of the precursors for pharmaceuticals and some biopharmaceuticals are likely to be produced in GM plants.

The intensity of these linkages across applications will hinge on the speed of technology development. For instance, if synbio develops more rapidly than expected, linkages between industrial and health biotechnologies could increase, with micro-organisms producing pharmaceuticals that are difficult to chemically synthesise. Conversely, rapid synbio development could decrease the integration between primary production and industry. Both products produced from biomass feedstock, or new products that were previously impossible to produce using biotechnology, could be manufactured by metabolically engineered or novel micro-organisms.

With the possible exception of agricultural biotechnology, many of the most useful socioeconomic benefits of the bioeconomy will remain elusive unless there are major technical breakthroughs. Health outcomes will improve, but advances are more than likely to be evolutionary rather than revolutionary. Industrial production will be less environmentally burdensome, but there won't be major advances towards an environmentally

sustainable future. In agriculture, new crop varieties on the brink of commercialisation could increase agricultural production by increasing yields, reducing water and fertiliser inputs, and opening up previously non-arable lands to cultivation – and this at a time when population, demand and environmental conditions are challenging current systems.

Technological developments are not the only factor that will influence the utility of biotechnologies and the future of the bioeconomy. Biotechnology R&D must be performed, paid for, and lead to commercially viable products and products. R&D is influenced by how markets and businesses are structured, intellectual property and research are distributed, human resources are trained, and products are distributed and sold. These variables, which are the focus of the following two chapters, will be decisive in determining the future of the bioeconomy.

Notes

1. To clarify the context for these developments, some aspects of the biotechnologies that were discussed in Chapter 3 are reintroduced here.
2. Due to differences in yields both within and across countries, the GM share of global hectares planted is only an approximate measure of the GM share of total production in tonnes.
3. An exception is FLASHKIT. These tests, developed by the firm Agdia, are ELISA-based and can be used in the field to detect viruses and some bacteria.
4. The EC's Diag Chip project aims to develop a chip that can recognise 275 pathogens (EU directive 77/93/EEC).
5. The average drug requires 7.5 years between the first clinical trial and market approval (DiMasi, Hansen and Grabowski, 2003). Therefore, most drugs that enter clinical trials in 2007 are likely to fail or reach the market by 2015. The clinical trial data cannot predict market success rates after 2015 because most future drug candidates will not have reached the first phase of clinical trials.
6. This estimate of the share of all new NMEs that are biopharmaceuticals may be lower than the share reported in some other studies. The reason for the difference is likely due to how biopharmaceuticals are defined. In

this estimate, small molecule NMEs are excluded as the definition of biopharmaceuticals and experimental biotechnological treatments given in Chapter 3 is used.

7. An identical analysis by the authors using the *Prescrire* data (Annex 3.A3) indicated a similar trend.

8. In 2005, the FDA released guidelines on what types of genomic information it will require (FDA, 2005) and in 2006 the FDA and EMEA agreed on a procedure to be jointly briefed following voluntary submission of genomic data (EMEA, 2006). Also, in February 2007 Health Canada produced a guidance document on the submission of pharmacogenomic information (Health Canada, 2007).

9. One study argues that pharmacogenetics will not reduce revenues, estimating that the net present value of a pharmacogenetics drug is approximately USD 85 million higher than that of a conventional drug (Research and Markets, 2006).

10. Authors' interview with Dr. Angela Flannery, AstraZeneca, 29 October 2007.

11. Genentech obtained approval for Herceptin in this way, but the method is not always successful. AstraZeneca adopted this approach to rescue its lung cancer drug candidate Iressa, but failed.

12. See in-pharmatechnologist.com, 2007.

13. The total annual venture capital investment in the United States in biotechnology between 2001 and 2003 was USD 9 526 million (OECD, 2006), almost all of which was probably invested in health biotechnology.

14. An earlier study by Festel *et al.* (2004) estimated that biotechnology's share of all sales of industrial chemicals would increase from 2.5% in 2001 to approximately 19% in 2010, higher than the USDA estimate of a maximum biotechnology share of 13.1% in 2010. The largest relative growth would be in fine chemicals, where biotechnology's share would increase from 16% in 2001 to 60% in 2010 (compared to the USDA maximum estimate of 25.6%). The study was less optimistic than the USDA for the bioprocess contribution to specialty chemicals, which was estimated to grow from 2% of output in 2001 to 20% in 2010. In comparison, the USDA's maximum estimate was 25.3%.

15. For instance, the USDA (2008) identified succinic acid and propanediol as potential candidates.

16. For instance, the biobased production of polyhydroxyalkanoates (PHA) polyesters is expected by the end of 2008, whereas they were reported as under development in 2005 (European Bioplastics, 2008).

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Chapter 5

Institutional and Social Drivers of the Bioeconomy

The emerging bioeconomy will be influenced by public research support, regulations, intellectual property rights, and social attitudes. In 2005, public R&D expenditures within the OECD area for all types of biotechnology were USD 28.7 billion, compared to 2003 R&D expenditures by the private sector of USD 21.5 billion. The public sector is a major player in health biotechnology and accounts for a notable share of research for primary production, with 20% of field trials for genetically modified (GM) crops between 1989 and 2007 conducted by universities or government research institutes. Data on public research support for industrial biotechnology are not available, with the exception of biofuels. Here, most support appears to go to pilot plants instead of to R&D.

Regulations to ensure the safety and efficacy of biotechnology products influence the types of research that are commercially viable and research costs. Pure regulatory costs are highest for GM crops (ranging from USD 0.4 million to USD 13.5 million per variety) and for the open release of GM micro-organisms (approximately USD 3 million per release). The European Union's de facto *moratorium on the commercial production of GM crops appears to have hampered GM research in Europe. In health, the future of regulation is not clear, with economic pressures and technical opportunities pushing the system in different directions. Intellectual property rights could be increasingly used to encourage knowledge sharing through collaborative mechanisms such as patent pools or research consortia. Social attitudes to biotechnology will continue to influence market opportunities, but public opinion can change, for instance when biotechnology products provide significant benefits for consumers or the environment.*

The development of biotechnology is influenced by three institutional drivers and one social driver: public support for biotechnological research and training of scientists, regulations, intellectual property, and public acceptance.

Public research

The public research sector, consisting of universities and research institutes, is a key driver of both health and agricultural biotechnology. It provides new scientific and technological discoveries with potential commercial applications and it trains highly skilled human resources such as scientists and engineers.

Furthermore, by allocating funds to specific research areas, the public sector can influence the direction of research. For example, due to concerns over bioterrorism, the United States government increased expenditures on civilian biodefense almost ten-fold from USD 576 million in 2001 to USD 5.4 billion in 2008. The number of research grants on bioweapon agents increased more than fifteen times, from 33 grants between 1996 and 2000 to 497 grants between 2001 and 2005 (CHC, 2005). This rapid increase in funding and grants could have encouraged researchers to switch from other applications of biotechnology to biodefense.

Public R&D expenditures for biotechnology

Public R&D expenditure data, although incomplete, point to the crucial role of the United States and of the public sector in total biotechnology R&D within the OECD area. Current data on R&D expenditures and trend data for new PhDs suggest that developing countries such as China, India and Brazil will play a growing role in future biotechnology R&D.

Public expenditures within the OECD area for all types of biotechnology R&D in 2005 were approximately USD 28.7 billion. Europe accounted for USD 4.1 billion, other OECD countries for USD 1.43 billion, and the United States for USD 23.2 billion.[1] The United States therefore provided 81% of the total public R&D expenditures on biotechnology by developed countries.

Total private sector R&D expenditures on biotechnology R&D within the OECD area totalled USD 21.5 billion in 2003, less than the estimated expenditures by the public sector in 2005. The United States accounted for 66.3% of private sector R&D on biotechnology (OECD, 2006a).

Without a change in policy, particularly by European governments, future public R&D expenditures for biotechnology will continue to be

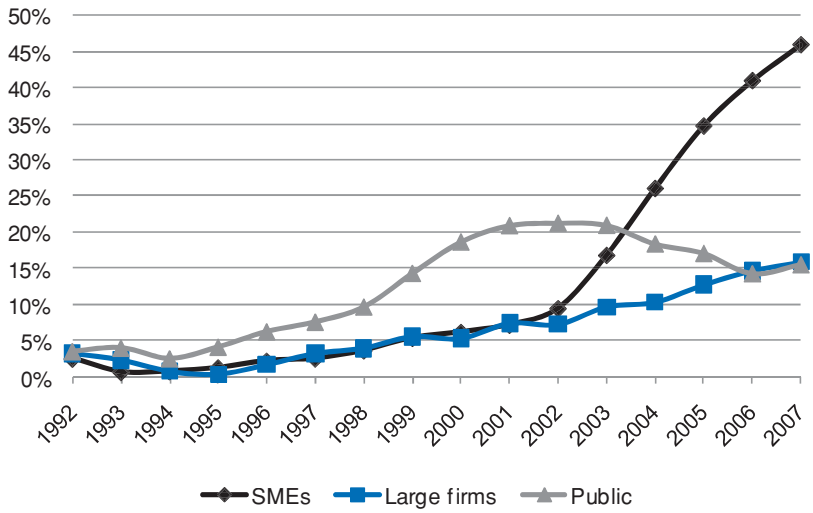
dominated by the United States, although large developing countries including Brazil, China and India are rapidly increasing their public research expenditures for agricultural biotechnology. The lead role of the United States, particularly for health biotechnology research, has led to tensions over who funds and who benefits from scientific research. American academics and policy advisors have often expressed concerns that other countries are "free riding" on American investment in health research (Tanne, 2003), for example by not paying their fare share of drug development costs.

Public research role and expenditure by application

The public sector is an important provider of biotechnology research for primary production in both developed and developing countries. In 2005, total public R&D expenditures in the United States on life sciences, excluding health research, were USD 3 billion, of which the vast majority was probably for primary production (NSF, 2008). In comparison, the combined annual public sector R&D expenditures for agricultural biotechnology in China, India and Brazil are expected to be approximately USD 1.2 billion over the next few years, of which USD 0.5 billion will be spent annually by Brazil, USD 120 million by China (of which USD 24 million is dedicated to GM rice) and USD 100 million by India (Reuters, 2007; James, 2007). In addition, international collaboration on agriculture plays an important role. For instance, the Consultative Group on International Agricultural Research (CGIAR), which aims to enhance primary production R&D efforts in developing countries, had a 2007 budget of over USD 500 million (CGIAR, 2007).

The value of public research for primary production can be illustrated by its share of overall GM research in the OECD area: 20.0% of 20 798 GM field trials between 1989 and 2007 were conducted by universities or research institutes. There is little difference in this share over time. Compared with private firms, the public research sector focused more on leading edge research for agronomic traits for yield and stress tolerance (see Figure 5.1). For example, between 1999 and 2001, 20% of the 569 trials conducted by the public sector were for agronomic traits, compared to 7% of all trials by large firms and SMEs. After 2003, public sector research shifted to new areas of leading edge research, while private firms, in part building on public sector discoveries, increased their investment in agronomic traits.

Figure 5.1. **Percentage of all field trials by type of applicant for agronomic traits (three-year moving average)**



Note: The figure shows the percentage of all trials by each type of organisation that were for agronomic traits. For example, 46% of all trials conducted by SMEs in 2007 were for agronomic traits, whereas only 15% of all trials conducted by large firms in 2007 were for agronomic traits.

Source: Authors, based on UNU-MERIT, 2008.

Public sector expenditures on health biotechnology are dominated by the United States, which spent an estimated USD 29.7 billion on all types of health-related R&D in 2005, or four times the estimated USD 7.5 billion (PPP) spent by the 25 countries of the European Union in the same year.[2] This includes research not linked to biotechnology. In contrast, there is little difference in total R&D expenditures by businesses active in the pharmaceutical sector, with 2003 expenditures by firms based in 13 main EU countries totalling USD 16.9 billion (PPP) compared to USD 15.9 billion in the United States that same year.[3] In per capita terms, private sector spending in the United States is slightly higher, at around USD 53, compared to USD 45 in the relevant EU countries.[4]

In addition to its contribution to R&D, the public sector has been the driving force behind a number of large collaborative research programmes that were essential to the advancement of health biotechnology. The most well known is the Human Genome Project, a public-private sector collaborative effort that sequenced the entire human genome two years

ahead of schedule in 2003, after 13 years of work. Other examples of public collaborative research programmes include the International HapMap Project to help researchers identify the genetic causes of diseases and drug reactions, and the Cancer Genome Anatomy Project (CGAP), which provides open access to genetic information related to cancer.

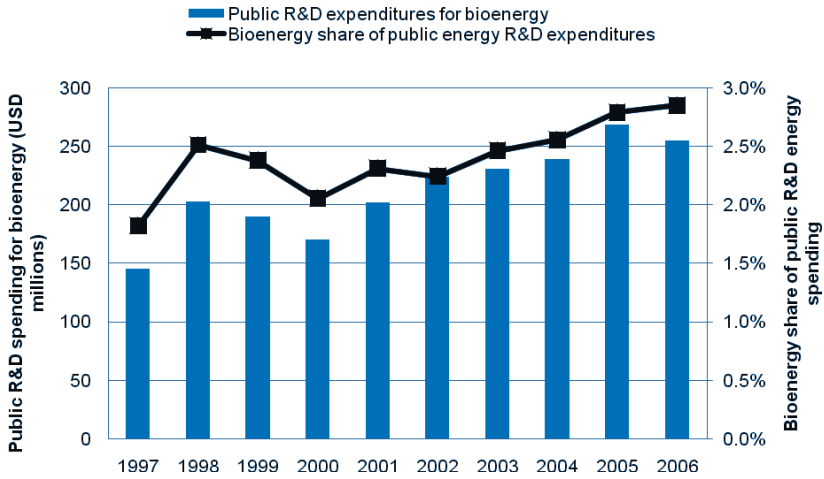
There are no data for public sector investment in all types of industrial biotechnology, but the International Energy Agency collects data on public sector investment in energy R&D. The amount of R&D support for biofuels is substantially lower than investments in health or primary production. As shown in Figure 5.2, the member states of the IEA spent just over USD 250 million in 2006 on bioenergy R&D. To put this in perspective, nuclear fission and fusion received more than 13 times and fossil fuels nearly 4 times more public R&D support than bioenergy (IEA, 2007).[5] Of note, the data in Figure 5.2 represent actual R&D expenditures. Government allotments for bioenergy R&D can be considerably higher. Including authorised but unallocated spending for federal grants, demonstration projects, and R&D for ethanol and biodiesel in the United States would increase support for biofuels research and development to an average of USD 360 million per year between 2006 and 2012 (Koplow, 2007).

In addition to funding R&D, governments can encourage the development of industrial biotechnology by providing specialised equipment to firms. For example, the Department of Energy in the United States allows industrial firms to use its state-of-the-art bioprocessing pilot plant at its National Bioenergy Center (NBC). This gives firms access to world-class equipment such as fermenters, filtration systems and centrifuges without the expense of developing their own pilot plant (DOE, 2003).

Skilled human resources and training

The future trajectory of the bioeconomy will depend on the supply of skilled human resources. This is most likely to affect R&D, where specialised skills are needed, as opposed to the sales, marketing and delivery of commercialised biotech products. In addition, the increasingly interdisciplinary nature of biotechnology will require experts from a range of science and engineering fields, including chemistry, physics, computer sciences, mathematics, and engineering, to work on the development of innovative new products. Consequently, the bioeconomy will evolve more rapidly in countries that can both produce highly trained scientists and attract top-notch researchers from around the world.

Figure 5.2. **Public R&D expenditures for bioenergy and the share of total energy R&D in IEA countries**



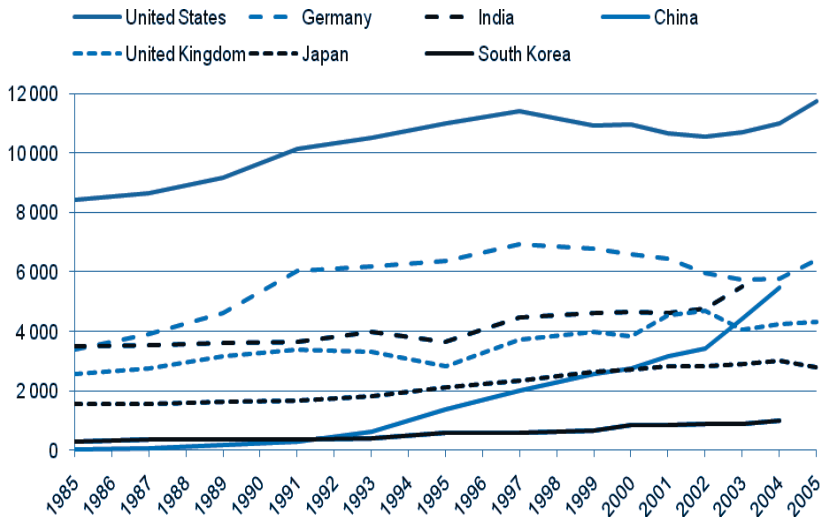
Notes: Includes public R&D energy expenditures for Canada, EU-15, Japan, New Zealand, Norway, Korea, Switzerland and the United States. R&D spending is in USD millions at 2006 prices using PPP.

Source: Authors, based on IEA, 2007.

One measure of the available human resources for biotechnology is the number of degrees awarded in biological or related sciences. Figure 5.3 shows the number of doctoral degrees awarded from 1985 to 2005 in physical, biological, and agricultural sciences for selected countries. Overall, the number increased 75%, from 19 826 to 34 641, and by a phenomenal 98.5% in China. China and India lag behind OECD countries in the percentage of their population with a relevant degree. Both countries have approximately four degrees per million residents while South Korea and Japan have around 20, the United States approximately 40, and Germany and the United Kingdom over 70 degrees per million inhabitants.

Figure 5.3. **Doctoral degrees awarded in the physical, biological and agricultural sciences**

Selected countries, 1985-2005



Notes: Physical sciences include earth, atmospheric, and ocean sciences. Data for doctoral degrees use International Standard Classification of Education (ISCED 97), level 6. Data do not include health fields.

Source: Authors, based on NSF, 2008.

The number of people with bachelor and master's degrees in fields related to the life sciences is also important to the development of the bioeconomy. Surveys in Finland and New Zealand found that more than 80% of people working in biotechnology R&D do not have doctoral degrees (OECD, 2006a). In the United States, the number of new bachelor and master's degrees in the agricultural and biological sciences combined increased by 65% and 50% between 1985 and 2005. Furthermore, there was a 144% increase in the number of doctoral degrees awarded in medical and other life sciences (NSF, 2008).[6]

The increase in the number of individuals with skills in biotechnology and related disciplines bodes well for the future of biotechnology R&D. The decline in the United States and Germany from 1997 to 2001 in the number of doctoral degrees is of concern, but this had little impact on the total number of new doctorates due to the large increase in China and steady increases in other countries. The rapid increase in the supply of human

resources and public R&D expenditures suggest that China will be an increasingly important centre for biotechnological innovation.

Regulation

Regulation and the predictability of the regulatory environment influence the direction of biotechnology research, the types of research that are commercially viable, and the costs of research and development. It mainly sets rules to establish the safety and effectiveness of biotechnology products. It also includes mandates, prohibitions and moratoria, such as the Bush Administration's prohibition on the use of federal funds for several types of embryonic stem cell research, or the refusal of several EU countries to approve GM crop varieties, resulting in a *de facto* European moratorium on growing GM crops within the European Union.

Most biotechnology research, biomaterials and equipment are only lightly regulated. However, in some cases controls on research are much more stringent for biosecurity reasons (see Box 5.1). For example, research involving dangerous pathogens has become more highly regulated in the United States after the 2001 anthrax attacks. A study on the impact of these regulations found that the additional start-up costs on research ranged from USD 1 million to USD 4 million, with annual maintenance costs thereafter ranging from USD 100 000 to up to USD 700 000 (OECD, 2005). These compliance costs could block research by small research institutes or firms, influencing the direction of research.

Many biotechnology products are regulated before commercialisation to protect humans, animals, plants and the environment. Research to establish environmental and consumer safety is required to meet regulations for biotherapeutics, animal therapeutics, GM plant varieties, and GM micro-organisms intended for open release (OECD, 1986). Products that are perceived as less potentially harmful to humans or the environment are less strictly regulated. These include *in vitro* diagnostics, non-GM biotech crops, and GM micro-organisms for use in a closed bioreactor. As a result, these products can typically be brought to market relatively quickly once R&D is complete.

Box 5.1. **Biosecurity**

Biotechnology research has the potential to contribute to positive socioeconomic outcomes in many unique ways. However, a small fraction of legitimate biotechnology research, especially involving dangerous pathogens, could be applied to nefarious activities. Biosecurity "measures to protect against the malicious use of pathogens, parts of them, or their toxins in direct or indirect acts against humans, livestock or crops" (OECD IFP, 2008) are therefore necessary.

Government, industry, and society have a stake in developing robust biosecurity systems that ensure public safety. Biosecurity came to the forefront of policy debates in late 2001 following the September 11th and subsequent anthrax attacks in the United States. The heightened security environment caused many governments to implement new regulation to mitigate risk and to dedicate significant resources to biosecurity measures. These regulations have increased operating costs for some laboratories.

Securing dangerous pathogens and other biological materials poses unique challenges that require non-conventional security mechanisms. Unlike nuclear and chemical materials, many biological materials are difficult or impossible to detect using current remote sensing technologies. The amount of biological material required to undertake an attack is much less than that of chemicals and access is much easier than for nuclear material. Biotechnology techniques are becoming more pervasive and user-friendly. Advanced equipment that was once only accessible to well-funded research laboratories is now relatively cheap and easily obtained. Furthermore, much legitimate biotechnology research, which could provide large socio-economic benefits, is inherently dual-use as it can be applied directly to malicious uses.

Novel policy approaches may be required to address biosecurity concerns. New measures to reduce the risk of further attacks range from UN Security Council declarations calling on all states to criminalise the use of biological weapons by non-state actors to the passage of the 2001 PATRIOT Act and the 2002 Public Health Security and Bioterrorism Preparedness and Response Act in the United States. While international fora, such as the Biological Weapons Convention (BWC), exist that focus on the risk posed by some biological materials, their slow consensual nature is not well suited to addressing unconventional risks posed by non-state actors. International discussions are underway to develop a common approach to securing dangerous pathogens and to mitigate the potential for misuse of research results – both intentional and unintentional. This will need to work in concert with increased international collaboration on biosurveillance, outbreak detection, development and distribution of medical countermeasures, and response to an incident (Ostfield, 2008). This will ultimately require the participation of all stakeholders (individual scientists, businesses, national governments, and international institutions) to develop a comprehensive biosecurity strategy that provides security while simultaneously allowing legitimate life sciences research to flourish.

Note: For instance see OECD, 2007a.

Table 5.1 provides estimates of the regulatory costs of bringing a biotechnology product to the market. Most of the estimates are for the United States. Almost all biotechnology firms are likely to apply for market approval for their products in this jurisdiction, since the United States is the largest market in the world for most biotechnology products, These estimates reflect the administrative and legal costs, plus the costs of conducting research that has more than a purely regulatory function. They do not include lost potential income due to the time required to obtain regulatory approval.[7]

Table 5.1. **Indicative regulatory costs to commercialise a biotechnology product**

USD thousands

Agriculture	
Plant	
GM crop[1]	435–13 460
MAS crop[2]	5–11
Animal	
Vaccine[3]	242-469
Therapeutic[4]	176–329
Diagnostic[3]	9-189
Health	
Therapeutics[5]	1 300
In vitro diagnostics[6]	150–600
Industry	
GM open release[7]	1 200–3 000
GM in closed loop	Unknown

Sources:

1. Authors, based on Just *et al.,* 2006. Lower estimates exclude all costs that could be associated with proving environmental or human safety, while higher estimates include such costs. All estimates exclude "facility & management overhead costs".

2. Figures from the German Bundessortenamt and converted from Euros to USD using the average of monthly exchange rates from June 2005 to September 2008 (1 EUR = USD 1.34).

3. Provided by the USDA Center for Veterinary Biologics. Estimates assume that the applicant already possesses an establishment license.

4. Fiscal year 2008 fees for the FDA from US Federal Register, 2007a.

5. Based on a new drug application requiring clinical data, product fees, and a rough estimate of the costs of production establishment inspections per drug, from US Federal Register 2007b.

6. Fiscal year 2008 fees, based on FDA, 2008.IVDs are classified as medical devices. Lower figure is for businesses with less than USD 100 million in sales.

7. Total costs to industry in first year, in 1995 USD, from EPA, 1997.

Regulation of health products covers the design of clinical trials and other research to establish safety and efficacy, but most of the costs involved are product research and development costs rather than regulatory costs. Establishing product safety in countries where liability rests with the manufacturer would be in the manufacturer's interest regardless of whether or not a regulatory agency required it. Proving efficacy would also be required to ensure that doctors were confident that their prescriptions would benefit their patients. Similarly, the cost of research to create a distinct, uniform and stable new plant variety is not counted as a regulatory cost. It is debatable whether or not safety costs should be included for GM crop varieties. Although seed firms would be held legally accountable for an environmental or safety incident – regardless of how the crop variety was developed – safety tests are not required for varieties developed using non-GM methods.

As shown in Table 5.1, regulatory costs vary enormously by sector and product type. Products that do not involve the open environmental release of a GM organism or *in vivo* medical interventions are much less costly than those that do. In agriculture, the regulatory cost of bringing a new GM plant variety to market ranges from USD 435 000 when safety costs are excluded to USD 13.5 million when safety costs are included. This is many times higher than the regulatory costs for a non-GM plant variety, which range from USD 5 000 to USD 11 000. Costs associated with a biotech-based animal therapeutic or vaccine are similar (in the range of USD 176 000 to USD 446 000) and costs associated with animal diagnostics are slightly less, ranging from USD 9 000 to USD 189 000.

In the United States, the regulatory cost for a human therapeutic is approximately USD 1.3 million, while the regulatory cost of an *in vitro* diagnostic ranges from USD 142 000 to USD 557 000. For both products, full or partial fee waivers can be granted to small firms or for orphan or high-priority drugs. The cost difference for therapeutics compared to diagnostics and many other medical devices is due to greater regulatory requirements for products that are intended for internal use, such as pharmaceuticals. Products that do not interact with living humans pose considerably fewer health hazards.[8]

Industrial biotechnologies are lightly regulated when they are destined for use in a closed loop bioreactor, or when non-GM biotech micro-organisms (*e.g.* developed using MAS or directed evolution) are to be used in an open environment. Regulation is much more stringent for GM micro-organisms for open release into the environment, such as for environmental remediation applications. In this case, many of the same regulatory requirements as for GM crops are applicable, and the regulatory costs are between USD 1.2 million and USD 3 million.

Effects of regulation on innovation

High regulatory costs can give a competitive advantage to large firms compared to small or medium sized firms. This is especially the case in agriculture, where the costs of bringing some products to market exceed the financial capacity of small firms. High regulatory costs can also block some types of innovation, especially when they have relatively small markets. Many environmental applications of industrial biotechnology, such as bioremediation, have small markets because the micro-organisms need to be adapted to local temperature, humidity, and soil conditions. For these cases, the relatively high regulatory costs could limit research to wild varieties of bacteria, or favour the use of gene shuffling or metabolic pathway engineering over the use of GM technology.

Regulation that effectively prohibits the use of a generic technology can have more damaging effects on innovation and the development of a bioeconomy. The *de facto* moratorium on growing GM plant varieties in Europe[9] is a case study of the power of regulation to alter long-term market structures and future business opportunities (see Box 5.2). The evidence suggests that the moratorium adversely affected the ability of European seed firms and the European public research sector to conduct research into GM technology. So far, this has not had a major negative effect on the global market share of European seed firms[10] – possibly because these firms have used MAS and other technologies to develop non-GM seed for the European market. They have also shifted most of their GM research and commercialisation activities outside Europe. However, growing demand for agricultural crops, combined with new crop varieties with attractive GM agronomic and product quality traits that are likely to reach the market by 2015 (see Chapter 4), could place European seed firms at an increasing competitive disadvantage.

A similar decline in agricultural biotechnology research occurred after several Australian states implemented a moratorium on GM plantings. The number of GM field trials conducted in Australia declined from 57 between 2001 and 2004 to 15 from 2005 to 2007 (Acil Tasman, 2008). An Australian federal government review concluded that the "moratoria were having negative effects on the agricultural and research sectors" (DHA, 2006).

For health applications of biotechnology, technical developments and high research costs create a different set of regulatory challenges, namely the need to balance risks and benefits with the costs of developing health treatments. Experience in the long-established field of drug regulation shows that the balance of risks and benefits can change abruptly as science develops and experience is gained, requiring adjustments to health regulations (Dukes, 2008).

Box 5.2. **Regulation and competitiveness: the *de facto* European moratorium on GM**

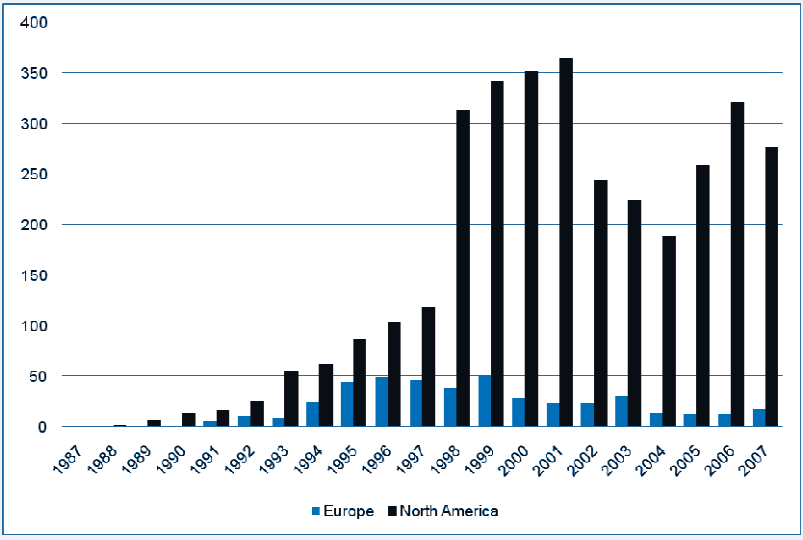
The European Union introduced a *de facto* moratorium on the commercial use of GM crops in 1999. Although this did not prohibit GM field trials, the commercial restrictions plus the high profile destruction of several GM field trials by anti-GM activists, caused a drop in European field trials and a possible decline in the ability of European seed firms to compete in this technology.

GM field trials in Europe declined from a peak of 280 trials in 1997 before the 1999 moratorium to 117 the year after the moratorium. The number further declined to below 80 trials per year between 2001 and 2006. Even before the moratorium, European seed firms reacted to public opposition to GM by conducting an increasing percentage of their field trials in Canada and the United States. The percentage of all GM field trials by European firms that were conducted outside of Europe rose steadily from 20% in 1992 to between 80% and 90% since 2001.

The European seed firms' strategy of moving research to the United States and Canada was not entirely successful in terms of keeping up with their competitors in GM technology. The comparative strength of these firms, as measured by their share of total OECD field trials, declined after 1999. Between 1993 and 1998 inclusive, European firms accounted for 32.3% of all OECD field trials by firms. After 1999 the European share dropped precipitously, and since 2001 has averaged 16.5% of all OECD GM trials.

GM research by the European public research sector was also adversely affected. The number of GM trials in Europe by public sector institutions fell from a high of 50 in 1999 to below 20 after 2004, as shown in the figure. In comparison, the number of GM trials by the public research sector in North America grew, exceeding 200 trials every year since 1998 with the exception of 2004.

GM field trials by public research organisations in Europe[1] and North America



1. Includes firms based in the European Union and Switzerland.
Source: Authors, based on UNU-MERIT, 2008.

An example is the type of regulatory requirements that could be in place in the future for regenerative medicine based on stem cell therapies and tissue engineering. One perspective is that these technologies should be regulated as pharmaceuticals, requiring the submission of full clinical trial data, while an alternative perspective is that they should be more lightly regulated as medical devices (Tait *et al.*, 2008). An argument in favour of lighter regulation is that regenerative medicine based on the patient's own tissues or cells would have a very low rate of adverse immune system reactions, reducing risks. This issue is unlikely to be resolved without further research.

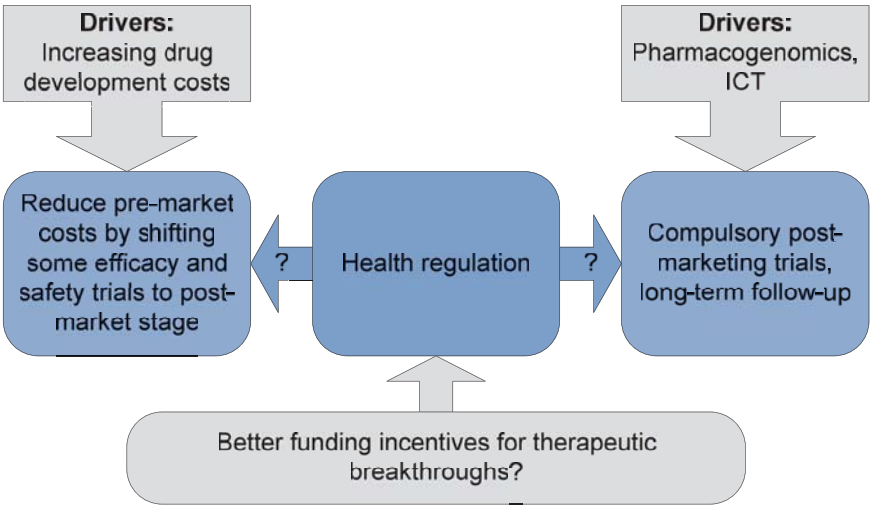
Health regulatory systems can adjust to new technologies. For example, while only a few pharmacogenetic products are on the market, regulatory systems have been responsive to the use of such data (OECD, forthcoming) – as seen with Herceptin, the first drug to require pharmacogenetic testing. The FDA in the United States first failed Herceptin because of a lack of effectiveness. After a post-clinical genetic evaluation was launched, Herceptin was found to be effective in a genetic subgroup of the clinical trial patients. Once these results were presented to the FDA, Herceptin received FDA Fast-Track designation and the drug was approved for the market in only four and a half months (PwC, 2005).

Despite little previous experience with pharmacogenetic submissions, the FDA was able to act quickly because of the flexibility of the regulatory system, which allows regulators to consider clear, albeit at the time new, evidence of efficacy. Regulation is continuing to evolve as the FDA and the European Medicines Agency (EMEA) work to harmonise rules for pharmacogenetic data submissions (FDA and EMEA, 2006).

In response to the long-term increase in the cost of developing a new drug, research is examining how to decrease costs, for instance through changes to regulatory requirements for safety and efficacy (Rawlins, 2004) or through the adoption of new technologies that reduce the time required to develop a new drug (Kaplan and Laing, 2004). One option under discussion is to reduce the level of evidence required to establish safety or efficacy before market approval is granted. Instead, some of this evidence could be obtained from clinical trials conducted after market approval (SustainAbility Ltd, 2007; DG Enterprise, 2007; Kaplan and Laing, 2004). However, as long as trials are conducted after market approval is granted, this would not reduce total drug development costs. The potential benefits derive from speeding up market entry, which would extend the patent life of a therapy. A second option under discussion is to revise the regulatory system to take advantage of the potential health benefits of new technologies and biomedical data. These include pharmacogenetics and the use of ICT to build databases that can link patient health records, including prescription

histories, with long-term health outcomes. The latter could be coupled with compulsory, long-term post-market research on the effects of medical interventions on health outcomes. Figure 5.4 summarises the possible futures for health regulation, driven by increasing costs on one side and emerging technologies on the other. Variations of both options could also be implemented in a revised system of health regulation.

Figure 5.4. **Multiple futures for health regulation**



A third factor that could influence regulation is a change in the incentive system for health innovations. Currently the system is criticised for providing too many incentives for firms to develop "me too" health products and insufficient incentives for therapeutically "innovative' products" (Morgan, Lopert and Greyson, 2008). Several options to improve incentives have been widely discussed, including prizes or a system where the price paid for new pharmaceuticals increases with its additional effectiveness compared to existing best practice.[11] In both cases, the price paid will partly depend on research after post-market approval, to ensure reliable data on the benefits of the treatment (Pogge, 2005; OECD, 2007c).

All of the potential regulatory futures under discussion partly require research into safety and efficacy *after* market approval is received for a pharmaceutical or other therapy. This will require additional research to determine the stringency of the pre- and post-market requirements for safety and efficacy and how to fund long-term follow-up research.

Intellectual property rights

Intellectual property rights of relevance to the bioeconomy include patents, trademarks, copyright, and trade secrecy. Patents provide a key incentive for investment in innovation in most biotechnology applications. Laws and patent office guidelines have had to evolve along with the biotechnology sector in order to accommodate the technology, a key example being the European directive 98/44/EC that explicitly allows patents on the applications of genetic sequences. Such intellectual property has frequently been controversial because of fears that research will become more difficult or patient access or quality of care will be adversely affected (Hopkins *et al.*, 2006, 2007). In the future biotechnology firms, and the public sector institutions, upon which they depend for much of their technology, will continue to use a mix of different intellectual property rights. In order to avoid further concerns around concentration and potential adverse effects, the importance of supplementary and complementary mechanisms in inducing innovation and dissemination are likely to be of increasing interest. Supplementary mechanisms include research prizes, public sector grants for research, philanthropy, and policies to support markets. Complementary mechanisms include innovative uses of existing intellectual property systems to induce innovation and foster collaboration. These mechanisms include open source and open science initiatives, patent pooling and patent clearing houses, licensing practices that encourage the development of knowledge markets, and licensing practices that enable freedom to operate for humanitarian reasons and for basic research in the public sector (Herder and Gold, 2008).

In primary production, obtaining the right to use one of a small number of key enabling technologies for gene transfer can be time consuming and expensive, due to the number of firms and institutions that own patents for these technologies and the cost of obtaining a license.[12] Collaborative mechanisms for sharing intellectual property, such as Cambia's open source Transbacter technology for gene transfer among plants, could thus prove increasingly attractive to SMEs and agricultural research institutes, particularly in developing countries.

In health biotechnology, some collaborations between pharmaceutical companies, biotechnology firms and public research organisations aim to reduce the cost of identifying new drug targets and validating biomarkers. The success of these types of collaborations depends on developing strategies to manage access to proprietary knowledge and to share the benefits of discoveries from its use. The Biomarker Consortium, established in October 2006, is an example of a public-private research collaboration. Guidelines ensure that pre-existing intellectual property can be shared when

required for research into biomarkers. Inventions from consortium research projects can be patented as long as all members of the research team receive a non-exclusive licence at no cost and non-members can obtain a non-exclusive licence for a fee.[13]

Patents are not as important for industrial biotechnology as they are for health applications. This is because of the importance of tacit knowledge to process engineering and the need to optimise enzymes for customised production processes that are frequently protected by secrecy (Podtschaske and Mannhardt, 2008). The optimisation of a micro-organism is conducted either by the firm that owns the production process or by an SME under contract to the owner. This work partly relies on confidentiality agreements, although SMEs and larger firms active in industrial biotechnology use intellectual property rights to protect proprietary methods such as gene shuffling for optimising organisms. Patents are possibly of greatest value to enzyme manufacturers, where they are used to protect screening technologies for new enzymes, technologies to generate molecular diversity, modified micro-organisms such as bacteria or yeast that express the enzyme, and fermentation and purification processes.[14]

Social attitudes

An important influence on potential markets is the attitude of the public towards biotechnology products. Acceptance of biotechnology varies between health, agricultural and industrial applications, but also within applications. For instance, few people are opposed to the use of biotechnology in the development of therapeutics or vaccines; whereas stem cell research and genetic testing elicit a much wider range of opinions regarding the social, ethical (see Box 5.3), and economic implications of these technologies. In primary production, animal cloning is more negatively viewed by the public than GM crops.[15]

Public attitudes to biotechnology evolve over time in response to new discoveries and media coverage. For instance, in Europe, North America and Japan, the percentage of the population with a positive opinion of biotechnology declined in the late 1990s, when public debate surrounding GM crops was very active. Since 2000, the year in which there was extensive and positive media coverage of the human genome project, the share of the population with a positive opinion of biotechnology increased (Rigaud, 2008). Opinions also vary by country. In a 2005 survey of European attitudes to GM technology, 46% of respondents from the Czech Republic believed that GM should be encouraged, compared to only 21% of German respondents (Gaskell *et al.*, 2006).

Box 5.3. **Ethics and the bioeconomy**

Ethics concerns morality, or what is viewed by an individual or society as a good or a bad action. Ethics vary over time - what is widely accepted as good or bad behaviour can change - and between groups of people.

The ethical views of a population can influence the bioeconomy through its impact on regulations and other laws that affect research (what is permitted and the level of public support for research), markets (what people will buy and at what price), and business models (what business strategies are legally permitted). Opinion survey research within OECD countries suggests that public attitudes to biotechnology are influenced by a range of ethical views, including strong moral beliefs that some actions are inherently good or bad), utilitarian views, where a technology is accepted if its benefits are considerably greater than the amount of harm that it causes; and by concepts of fairness, in terms of who obtains the benefits from new technology.

Ethical controversies over biotechnology have involved human cloning, stem cell research using embryos, genetic screening, animal welfare, the confidentiality of genetic information, informed consent for the use of personal genetic data or tissue samples, bioprospecting, biodiversity, and environmental effects. Public attitudes are the most resistant to change when they are based on strong moral views, as is probably the case for human cloning. Surveys in the OECD area suggest that public attitudes to many other biotechnological controversies are strongly influenced by either utilitarian ethics, as in the case of GM crops or stem cell research, or concepts of fairness, as with confidentiality, informed consent, or bioprospecting. In both cases, ethical views can change, either because a technology is shown to have large benefits, or by agreements that ensure that benefits are widely distributed.

Source: Rigaud, 2008.

Public attitudes to biotechnology can also change very quickly, depending on perceived risks or benefits. As an example, the percentage of Australian adults with a favourable view of GM crops increased rapidly from 45% in 2005 to 73% in 2007. This was largely caused by an increase in public awareness of the potential for GM technology to provide improved crop varieties that can tolerate drought and salinity, both severe problems in Australia (Acil Tasman, 2008). European public opinion towards GM could also become more favourable if GM crops offered European consumers clear environmental or other advantages.

Both challenges and opportunities arise from this dynamic public response to biotechnology. Favourable public opinion could help build support for biotechnology while negative opinions could lay the foundation for stringent regulatory policies that adversely affect research and adoption. As noted in Box 5.2, the European Union's regulatory response to GM crops, driven by negative public attitudes, has reduced agricultural biotechnology R&D in Europe.

A frequent concern is that consumer resistance to GM plant foods, as in Europe, is reducing global demand for the use of biotechnology to develop improved agricultural crops. However, this is unlikely to significantly slow progress in the application of biotechnology to develop crop varieties, for three reasons. First, most of the market for the main GM crops to date is not for direct human consumption. In the OECD, only 10% of current demand for coarse grains (corn, barley, oats etc.) is for food. The other 90% is for animal feed and industrial feedstocks (OECD-FAO, 2008), which have been minimally affected by consumer resistance to GM. Second, the main GM crops are widely traded globally and also purchased by countries that do not permit GM crops to be grown domestically. The European Union, though restricting the use of GM plant varieties in domestic agriculture, imports large quantities of GM maize and GM soy products for animal feed from countries such as Argentina, Brazil and the United States that predominantly grow GM varieties of each of these two crops (OECD, 2006b). Third, many other biotechnologies that have not met consumer resistance are available for plant and animal breeding in addition to GM.

Notes

1. Estimates for the United States and Europe are from Enzing *et al.* (2007), who include as Europe the 25 member states of the European Union plus Iceland, Norway, Switzerland, Turkey and Croatia. Data for 2003 for other OECD countries were available for Korea, Canada and New Zealand. There were no data for Japan and Australia (OECD, 2006a).

2. Based on OECD data for Government Budget Outlays and Appropriations for Research and Development (GBOARD) (last accessed 21 January 2008). This includes general health R&D, medical research, preventive medicine, biomedical engineering and medicines, occupational medicine, nutrition, drug abuse and addiction, social medicine, hospital structure and organisation of medical care. The EU 25 results could be underestimated, possibly because of unrecorded expenditures in the health services sector.

3. Data on business expenditures are from the OECD's ANBERD database and are in USD purchasing power parities (PPP). The most recent available data are for 2003. The results cover the EU 13, which includes the 15 member states of the EU in 2003 except for Austria and Luxembourg. Pharmaceutical sector R&D expenditures in the 12 countries that joined the EU after 2003 are probably very low. Data are only available for Poland (USD 88 million PPP) and the Czech Republic (USD 40 million PPP).

4. This calculation uses 2005 populations from the UN (2006) of 300 million for the United States and 378 million for the 13 relevant EU countries.

5. The bioenergy share of all public expenditures on energy R&D has been increasing, however – from 2% in 2000 to 2.9% in 2006.

6. See Appendix Charts 2-27, 2-29, and 2-31 of NSF, 2008.

7. Lost income can be substantial for patented products that command a price premium, such as pharmaceuticals or GM plant varieties because the time required to pass regulatory requirements will reduce the effective lifetime of the patent.

8. However, concerns about the quality of diagnostic test results exist and have led to guidelines on best practices to improve the quality of genetic tests (OECD, 2007b).

9. Opposition to GM technology, dating to the mid-1980s, has resulted in restrictions or effective prohibitions on commercial plantings of GM crop varieties in several OECD and non-OECD countries. In Australia, planting GM rapeseed was effectively banned until the end of 2007 due to a moratorium imposed by several state governments. In Switzerland, a 2005 referendum led to a five-year moratorium on the cultivation of GM crops and the import of GM animals. Plantings of GM crops in the European Union have been seriously restricted through a *de facto* moratorium in many of the member states since 1999, and tight restrictions on GM plantings in the few states that have approved commercial plantings, such as France, Germany and Spain.

10. The global market share of European seed firms in the top ten by seed sales (including both GM and non-GM seeds) increased slightly, from 19.6% in 2000 to 21% in 2006. Five European seed firms were in the top ten in terms of sales in 2000: Syngenta, Limagrain, Advanta, KWS, and Aventis. Their combined sales totalled USD 2.552 billion, out of an estimated global seed market of USD 13 billion in 2000 (RAFI, 2001; ETC Group, 2007).

11. Aspects of the latter system already exist in orphan drug legislation and in the pricing decisions of national and private healthcare organisations.

12. The *agrobacterium* technology for transferring genetic material into plants is surrounded by a "patent thicket", with patents numbering in the hundreds (Cambia, 2007).

13. See *www.biomarkersconsortium.org/images/stories/docs/ip_policies.pdf*.

14. See the company profile for Novozymes, *www.mediconvalley.com/profiles/49*.

15. Nearly two-thirds of Americans surveyed stated that they were uncomfortable with animal cloning as opposed to 46% for GM crops (The Mellman Group, 2006). In Australia, a survey concluded that while 64.1% of respondents saw cloning plants as acceptable, only 35.9% responded similarly regarding cloned animals (Biotechnology Australia, 2005).

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Chapter 6

The Business of the Emerging Bioeconomy

Social, economic and technological factors will create new business opportunities for biotechnology, requiring new types of business models. The main business models to date have been the small, dedicated biotechnology firm (DBF) that specialises in research and sells knowledge to large firms, and the large integrated firm that performs R&D and manufactures and distributes products. This structure characterises the health sector. In primary production, gene modification technology has created economies of scope and scale that have driven rapid corporate concentration. Only a few DBFs have been active in industrial biotechnology, as profitability depends on the ability to scale up production. This requires specialised engineering knowledge and large capital investment.

This chapter identifies two business models that could emerge in the future: collaborative models for sharing knowledge and reducing research costs, and integrator models to create and maintain markets. Collaborative models are relevant to all application areas. Their adoption, combined with new business opportunities for non-food biomass crops, could revitalise DBFs in primary production and in industry. Integrator models could develop in health biotechnology to manage the complexity of predictive and preventive medicine, based on biomarkers, pharmacogenetics, shrinking markets for individual drugs, and the analysis of complex health databases.

The ability of private firms to develop profitable business models that can recover the research, production, distribution and marketing costs for biotechnological products and processes will strongly influence the shape of the emerging bioeconomy. A "business model" refers to how firms do business – how they use their capabilities and resources to produce and profit from selling biotechnology goods and services in the market.

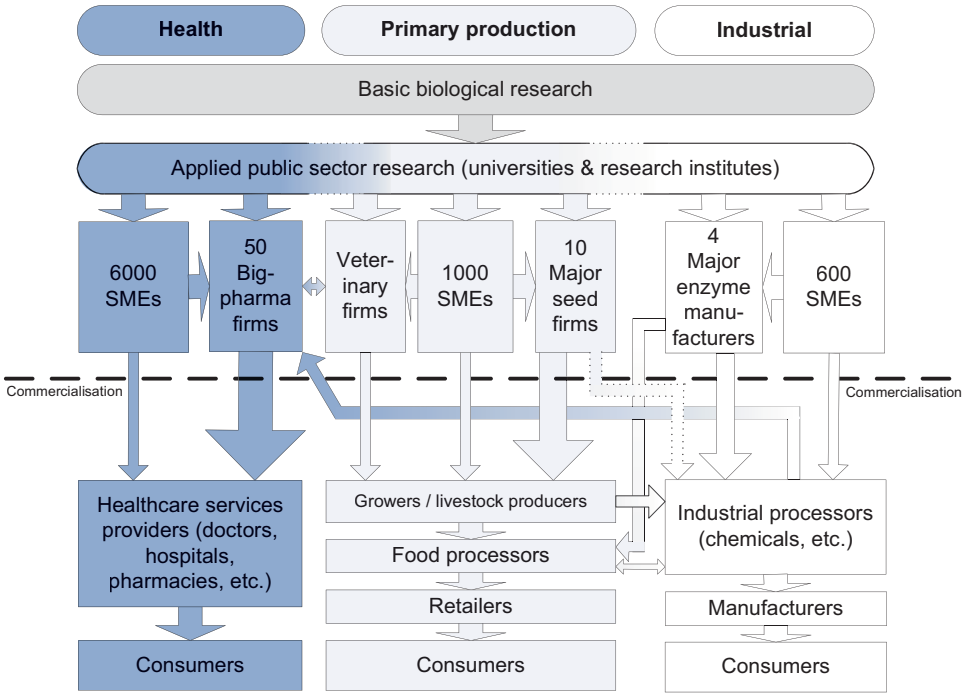
Two types of business models have dominated biotechnology since the late 1970s – small and medium sized enterprises (SMEs) that concentrate on biotechnology research (commonly referred to as "dedicated" biotechnology firms or DBFs) and large, vertically integrated firms (McKelvey, 2008). These two models will continue to play a role up to 2030. However, they will need to evolve further if they are to fully exploit future challenges and opportunities from technological developments, as discussed in Chapter 4, or the changes in institutions that support the bioeconomy, as discussed in Chapter 5. This chapter evaluates the current industrial structure of biotechnology and the types of business models that might develop in the future.

Current business models for biotechnology

The value-added chain for biotechnology extends from basic research to the end-consumer, as shown in Figure 6.1. The horizontal dashed line marks the commercialisation boundary. Firms and institutions above the line perform R&D to produce biotechnology products and processes. Firms, institutions, and consumers below the line primarily purchase biotechnology services and products, either for use in their own production processes or as final consumers. These include healthcare service firms, food processing companies, and chemical manufacturers. A few of these firms also conduct biotechnology research.

The DBF is often referred to as the "classical" business model. DBFs concentrate on developing the commercial potential of scientific discoveries and technological inventions that are often made by researchers in universities and hospitals. Many DBFs require years or decades to develop a discovery into a marketable product and lack the resources to manufacture, distribute, and market their inventions. Their business model depends on obtaining financing from venture capital firms, an initial public offering (IPO) on the stock market, selling licences to specialised knowledge to large firms, or conducting research for larger firms under contract or as part of a joint venture.

Figure 6.1. **Value-added market structure in biotechnology**



Notes: Estimates of the number of SMEs are based on data in OECD, 2006a. For simplicity, feedback loops from post-commercialisation to research, and between firms active in research and the public research sector, are omitted.

The second dominant business model, the large vertically integrated firm, is involved in all or most of the activities to develop and market a new biotechnology product or process, including R&D, production, distribution and marketing. They earn revenue from selling biotechnology products such as pharmaceuticals, crop varieties and industrial enzymes. In addition to developing their own products, large vertically integrated firms provide a market for the discoveries of DBFs. In a few cases, DBFs such as Amgen and Genentech in pharmaceuticals were able to grow into large vertically integrated firms.

The structure of the pre-commercialisation value-added chain is particularly complex for health biotechnology, with an estimated 6 000 SMEs within OECD countries, most of which are DBFs. These firms are active in drug development, platform technologies such as gene sequencing, gene synthesis, drug screening and bioinformatics; or in medical devices, bioengineering, drug delivery technology, and other technical specialties.

Once a new pharmaceutical or medical device has been approved by regulatory authorities, the route to the market is short. Healthcare products mostly reach final consumers via healthcare providers, such as doctors and hospitals. Products produced using industrial biotechnologies also follow a relatively simple path to consumers. The most complex post-commercialisation structure is for primary production. As an example, new seed or animal varieties are sold to growers, who then sell their output to food or industrial processors. Food processors then distribute products to retailers, who finally market the product to consumers.

Figure 6.1 identifies several linkages across applications. Basic biological research on genomes and complex cell processes leads to discoveries with commercial potential by research groups in universities, research institutes and firms. These discoveries can be of value to all sectors, or only relevant to a specific application. For example, research by agricultural scientists on genetic and phenotypic markers in plants and animals is of little relevance to other applications, whereas a technology to manipulate genes can be used with little or no modification in plants, animals or micro-organisms. Health biotechnology firms have research links and subsidiaries in veterinary medicine, of relevance to primary production. Industrial biotechnology firms provide chemical precursors and other products such as vitamins for the health sector. Seed firms can develop new plant varieties that are optimised for industrial processes. Strong linkages also occur between primary production and industrial biotechnology following commercialisation. This is mainly due to the use of biomass in some industrial processes.

The commercialisation of biotechnology products and processes in all three applications is dominated by large integrated firms that span research, manufacturing and marketing. However, very few of these firms integrate downstream with the firms that use biotechnology products, with the exception of some of the industrial firms. This could change. Several developments discussed below are creating opportunities for new business models that span both the production and use of biotechnology.

To date, business opportunities for the classical DBF model have been much greater in health, which explains why there are approximately ten times as many SMEs in the OECD area active in health as there are in industry. Furthermore, many of the approximately 600 SMEs in industry and 1 000 SMEs in primary production only engage in a few biotechnology activities. Health biotechnology also dominates the R&D activities of large integrated firms. The top five health biotechnology firms spent USD 6 333 million on R&D in 2006, compared with the USD 1 650 million spent by the top five firms active in primary production and the USD 275 million spent by the top five in industrial biotechnology. The R&D expenditure of

the top R&D performer for industrial biotechnology, Novozymes, is only 3.7% of the R&D expenditures of Genentech, the top performer for health biotechnology.[1]

The two dominant business models form a symbiotic relationship. The DBFs provide large firms with services and with a portfolio of alliances to access potentially valuable technologies. In return, small firms are able to access near-term revenue, gain credibility, and access complementary assets such as sales and distribution functions via their larger partners. This division of labour reflects the increasing technical complexity and breadth of the life sciences. Even the largest companies cannot master, by themselves, all relevant technologies nor undertake all R&D necessary to sustain their businesses (Hopkins *et al*., 2007). Although the depth and future viability of this symbiotic relationship, particularly the role of DBFs, varies across applications, this relationship is one of the most notable features of the bioeconomy. This is likely to persist as long as the large firms are unable to keep up with the pace of technological developments.

Current market structure by application

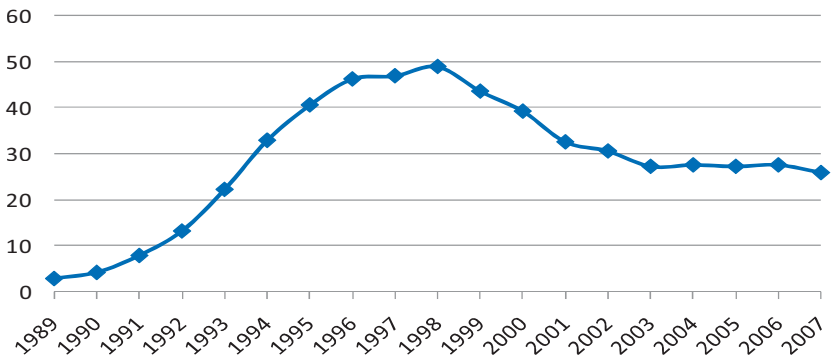
In primary production, DBFs have played a declining role in the OECD in agricultural biotechnology due to the concentration of capabilities in a shrinking number of firms since the mid-1990s.[2] Many SMEs active in the seed sector were acquired by larger firms or merged with other SMEs (Joly and Lemarie, 1998; Oehmke and Wolf, 2003; Marco and Rausser, 2008), while large firms also went through multiple mergers and acquisitions (see Box 6.1). The result is a marked fall in the number of SMEs active in GM field trials (a measure of capabilities in plant biotechnology) after 1998, as shown in Figure 6.2. In total, only 41 SMEs were active in one or more field trials within the OECD area between 2005 and 2007. Over the same period, the share of GM field trials conducted by the top five leading firms increased from 53.0% of all trials between 1995 and 1997 to 79.6% of all trials conducted between 2005 and 2007 (see Table 6.1).

Box 6.1. **Mergers and acquisitions in the seed sector**

Mergers and acquisitions (M&A) in the seed sector have contributed to intensifying concentration in the sector. The case of Bayer CropScience, one of the world's largest seed firms, provides an instructive example. The seed divisions of Hoechst and Schering merged in 1994 to form the large seed firm AgrEvo, which then purchased Plant Genetic Systems, a Belgian agricultural biotechnology firm, in 1996. In 2000 AgrEvo merged with Rhone-Poulenc Agro to form Aventis, which was later purchased by Bayer to form Bayer CropScience in 2002. Since 2002, the company has acquired all or part of six other companies involved in primary production.

Source: Bayer CropScience, 2007a.

Figure 6.2. **Number of SMEs with one or more GM field trials in the OECD**[1]



1. SMEs are small and medium-sized firms, generally with less than 250 employees. The results are three-year moving averages.

Source: Authors, based on UNU-MERIT, 2008.

Table 6.1. **Percentage of all GM field trials by the leading firms**[1]

	1995-1997 2 746 field trials	2005-2007 3 207 field trials
Top firm (Monsanto)	22.0	47.2
Top 5 firms[2]	53.0	79.6
Top 10 firms	69.0	90.9
Top 20 firms	82.7	96.1
Top 25 firms	86.4	97.6

1. As measured by number of field trials conducted.

2. The top five firms in 2005-07 were Monsanto, Targeted Growth, DuPont-Pioneer Hibred, Bayer CropScience, and Syngenta.

Source: Authors, based on UNU-MERIT, 2008.

Technological and economic factors have favoured large vertically integrated firms in primary production. GM technology, for instance, can be used to insert a useful set of genes into multiple varieties of the same crop species, as well as into different crop species. This creates a strong incentive for large firms to acquire smaller seed firms to access their stocks of elite germplasm that are tailored for specific local or regional growing conditions. In addition, the R&D costs of identifying commercially useful genes and the regulatory costs can be spread over a larger market. Monsanto, for instance, introduced genes for resistance to glyphosate

herbicides into cotton, soybeans, canola, maize and wheat and has repeated this process for the Bt gene that confers resistance to many lepidopteran insect pests.[3] It also undertook a series of acquisitions to access germplasm in each of these major crop species. Due to the economies of scale provided by GM technology, large firms are likely to continue dominating the crop-breeding sector in developed countries, particularly for large market crops.

Interviews with approximately 20 DBFs active in agricultural biotechnology in Europe, North America and Oceania highlight the difficulties faced by small firms (Blank, 2008). Most of the DBFs interviewed had the capability to develop GM crop varieties, but were rarely able to bring GM crop varieties to the market themselves. Most of them lacked at least two of three essential inputs: money, particularly to cover regulatory and R&D costs; a marketing infrastructure that includes contacts with a customer base and a delivery system to link the firm to its customers; and elite high-yielding germplasm, which is particularly important in countries that have a patent-based system for plant varieties.

The interviews show that the most common business model for research-intensive SMEs in primary production is to license technology – such as a suite of genes to improve yield or drought tolerance – to one of the large firms, or to be bought out by a large firm (Blank, 2008). These are the same options that characterise the classical business model in health, but firms active in developing food crops have far fewer opportunities for selling their knowledge due to an oligopolistic market with very few buyers.[4]

A different set of technological and market conditions favours some types of large vertically integrated firms in industrial biotechnology. The market for biotechnological products such as enzymes includes thousands of firms around the world and is served by over 100 firms that produce enzymes. However, enzyme production is very concentrated. Four firms, three of which are based in Denmark, account for over 80% of global sales: Novozymes, Danisco (including Genencor), Chr. Hansen, and DSM.[5] In addition, at least 1 000 companies world-wide use biotransformation processes for the production of bulk and specialty chemicals (Reiss *et al.,* 2007). In some of these market segments the profitability of chemical firms depends on their engineering knowledge and ability to scale up production. This creates a barrier to small biotechnology firms that lack the engineering expertise or capital to build large-scale production plants.

The basic business structure of health biotechnology has not changed since the late 1970s. The commercialisation of pharmaceuticals is dominated by large vertically integrated firms, with DBFs providing services and

developing therapies up to a proof of concept (for pharmaceuticals, this often requires the successful completion of Phase II clinical trials).

The ample availability of low-cost capital has enabled small DBFs to survive, and in some cases bring a product all the way to market. Although many health DBFs are acquired by large firms, the continual entry of new start-ups in the field has prevented an increase in concentration. For example, the share of total R&D spent by the top ten firms in pharmaceuticals and health biotechnology has remained stable, at 64.3% in 2002 and 64.0% in 2006. As shown in Table 6.2, the number of firms that have developed biopharmaceuticals or experimental biotechnology therapies that have reached clinical trials has increased over this period, from 69 firms in 2002 to 80 in 2006.

Table 6.2. **Concentration of R&D in pharmaceuticals and health biotechnology**

	2002	2006
Share of total R&D expenditures in pharmaceuticals and health biotechnology by top 10 firms[1]	64.3%	64.0%
Number of firms conducting clinical trials of all types of therapies[2]	253	365
Number of firms conducting clinical trials of biopharmaceuticals or experimental biotechnology therapies[2]	69	80

1. Derived from the share of total R&D expenditures by the top ten global firms in pharmaceuticals and health biotechnology. Total R&D expenditures worldwide were USD 44.8 billion in 2002, rising to USD 60.6 billion in 2006. R&D expenditures of the top ten pharmaceutical and health biotechnology firms were USD 28.8 billion in 2002, increasing to USD 38.7 billion in 2006. Figures converted from Euros to USD using the average of monthly exchange rates from June 2005 to September 2008 (1 EUR = USD 1.34).

2. Based on an OECD analysis of the number of firms included in the Pharmaproject database (Informa, 2008) that have one or more pharmaceutical or biopharmaceutical NMEs in Phase I, II, or III clinical trials or pre-registration. The results for all pharmaceuticals include formulations, which are excluded for biopharmaceuticals.

Source: Authors, based on R&D data from the 2006 EU R&D Scoreboard of the 1 000 largest EU and 1 000 largest non-EU firms by R&D expenditures (EC, 2007).

The market for *in vitro* diagnostics (IVD) for humans is more concentrated, however. The top 15 IVD firms in terms of sales represent an estimated 77.8% (USD 24.6 billion) of the global IVD sales of USD 31.5 billion in 2005.[6] The top three firms account for 40% and the top five firms nearly 54% of the global total. While the data do not differentiate between biotech and non-biotech IVDs, the situation is assumed to be similar in both areas.

In the near future, the largest opportunities for DBFs will remain in the health sector, where they are nurtured by high levels of public R&D spending (see Chapter 5) and where there are opportunities for licensing knowledge and technology to large vertically integrated firms. In primary production, there are ongoing opportunities for DBFs to develop and sell innovative products in markets that do not favour large vertically integrated firms, such as for small market crops, livestock breeding and aquaculture. Otherwise, large vertically integrated firms are likely to continue to dominate primary production. Similar conditions apply in industrial biotechnology, with opportunities for DBFs that can provide services such as metabolic pathway engineering or directed evolution to large firms.

Emerging business models in biotechnology

Two emerging business models could play an increasingly important role. They are collaborative models for sharing knowledge and reducing research costs (see Box 6.2) and system integrator models to create and maintain markets. Both models currently exist in some form, but over time they could be responsible for a larger percentage of both research and outputs. The collaborative model is relevant to all applications. System integrators can function both within an application field – such as between healthcare providers and pharmaceutical firms – and across two applications, such as between agricultural and industrial biotechnology.

Collaborative models partly shift earned revenue from licences for knowledge to the sales of final products. Given the importance of licence revenues to the classical business model, one question is why any DBF would be interested in participating in a collaborative model.

The advantages of collaboration are greater network involvement in problem solving and testing, a reduction in transaction costs to acquire new knowledge, and a reduction in licensing costs when firms can access knowledge produced by the collaborative network at low or no cost. These advantages can accelerate technological progress and reduce R&D costs. This is not a panacea, however, as the effectiveness of collaborative models will vary by application. Long-term private sector research may not be viable in some biotechnology applications without the ability to earn revenue from licensing intermediary knowledge. Knowledge markets and brokers could help reduce transaction costs for licensing by increasing the visibility of both the demand for and supply of specialised knowledge.

Box 6.2. **Collaborative business models**

There are many types of collaborative models that encourage firms to contribute resources to fund research and thus share the benefits of research discoveries. In a research consortium, several firms pool resources to fund pre-competitive research and provide the results to other consortium members at low or no cost, depending on their level of contribution to the research. These results are usually protected by intellectual property, with a no-cost licence for all consortium members. In some cases non-members of the consortium can license the intellectual property for a fee.

Another option is patent pooling. Here, firms conduct research separately but make their patent rights available to other members of the pool at no cost. Each firm must contribute to the patent pool to be able to use the patent rights of other firms. An example of this is the non-profit organisation Cambia, which manages a type of patent pool that provides a protected "commons" of research tools for agricultural biotechnology, including a technique for gene transfer that circumvents proprietary methods. Firms and organisations that use the technologies must agree to contribute follow-on improvements in the research tools to the pool of available technologies (Cambia, n.d.). Open source models make all knowledge available to the greater public at no cost, but users that build on the knowledge must reciprocate by making their results freely available under an identical open source licence.

Collaborative business models such as a consortium can also earn a profit, but many types of collaborations are set up as non-profit organisations or include participants from both the public and private sector. To date, most produce research and inventions, with the commercialisation of products and processes left to their members.

Source: Herder and Gold, 2008; McKelvey, 2008.

The system integrator business model coordinates different actors, either for research or along a value chain. The integrator can be a public organisation, a private firm,[7] or a non-profit organisation. An example of the latter is the Bill and Melinda Gates Foundation, which plays an integrator role in some areas of health research.

The key role of an integrator is to create functions or markets that would have difficulty developing without a coordinating agent. For instance, a biorefinery could fail because the available biomass is unsuited for industrial processing. Clearly defined standards for the processing characteristics of biomass could solve the problem by encouraging agricultural biotechnology firms to develop crops that meet the standards. When these conditions are absent, a system integrator can solve the problem by coordinating different actors along the value chain.

The following sections discuss the implications of future challenges and opportunities for business models within each of the three main applications of biotechnology, plus the possible convergence of primary production and industrial biotechnology. Three types of factors come into play here: economic factors such as demand and costs; technical factors due to emerging and competing technologies; and social and institutional factors, including public research, regulations, intellectual property and public acceptance.

Primary production

The application of biotechnology to primary production is an evolving success story. Even with minimal policy intervention, the application of biotechnology to improve and manage food, feed and fibre crops is likely to increase substantially to 2030, driven by rising incomes, populations, and increased agronomic stresses from climate change. In addition, the expectation of a long-term increase in the cost of fossil fuels from a decline in the supply of low-cost sources of petroleum; an increase in demand for energy; and restrictions on the production of greenhouse gases (GHGs) should create a growing market for biomass, including non-food crops such as grasses and trees, as a feedstock for biofuels, chemicals and plastics. Other potential biotechnology markets include the use of plants to produce valuable chemicals such as biopharmaceuticals and the production of nutraceuticals from plant and animal sources. All of these trends are likely to increase investment in primary production technologies.

Some technological improvements in primary production may not require biotechnology over the short-term future. Firms can avoid the use of biotechnology completely through conventional plant or animal breeding. When phenotypic screening for valuable traits is possible through visual inspection, conventional breeding can be cost effective compared with MAS and other biotechnology techniques (Dreher *et al.*, 2003). However, the advantages of phenotypic screening alone should decline over time as the cost of biotechnological methods falls in response to the expiry of key patents, greater familiarity with the technology, and improved marker libraries for plant and animal species.

Some of the main challenges for primary production are social and institutional factors, including public opposition to biotechnology, a lack of supportive regulation, and barriers to the use of biotechnology in developing countries. First, public opposition to GM food crops or GM or cloned animals is unlikely to halt the use of biotechnology, but it may drive firms to alter the *type* of biotechnology that they use. Second, the potential market for biomass is likely to be strongly dependent up to 2030 on regulatory

policies to shift economies towards zero- or low-carbon energy sources. Third, much of the future growth of primary production will be in developing countries. These countries could increase their capacity to use biotechnology in order to develop improved food, feed and fibre crops that are adapted to local growing conditions.

What effect will these opportunities and challenges have on emerging business models for primary production?

The development of markets for biomass is creating new business opportunities for small agricultural DBFs. Large vertically integrated firms do not control elite germplasm varieties of fast-growing grasses or trees and the regulatory costs for these crops are lower than the costs for food crops.[8] Both of these factors create an opening for DBFs to compete with large firms by reducing the development costs for non-food biomass crops. Several agricultural DBFs, including Athenix, Arcadia Biosciences, Edenspace and Targeted Growth, are exploiting discoveries made outside primary production and applying them to the development of biomass crops. Another favourable development for DBFs is the expiration, in the near future, of key patents for genetic transformation tools, which will reduce research costs.

These new market opportunities suggest that agricultural DBFs will increasingly avoid the large market crops that are dominated by large firms, particularly maize, soybeans, cotton and rapeseed. This conclusion is supported by an analysis of GM field trials. Compared to large firms, a much higher percentage of the GM field trials conducted by SMEs has been for non-major crops, reaching a peak of 70% of all field trials by SMEs in 2003 and exceeding 50% of trials in 2007. For comparison, the relative interest of large firms in non-major crops has been declining over time, accounting for only 17% of all field trials conducted by them in 2007 compared to a peak of 40% in 2000.[9]

Both research consortia and collaborative models are another option for agricultural biotechnology. The complexity of the post-commercialisation value chain in this application (see Figure 6.1) creates opportunities for firms that use biotechnology products to collaborate on upstream research while competing on downstream products. Current examples include ArboGen, active in developing new tree varieties and supported by a consortium of three forestry firms, and Biogemma, supported by a consortium of five European seed firms. The three firms behind ArborGen compete in forestry products, with all benefiting from improved tree varieties. Biogemma has GM expertise but it also conducts research on genomics and crop plant traits that can be commercialised through non-GM biotechnology (Biogemma, n.d.).

Many public research institutes, as in New Zealand and Australia, develop crop varieties for local growing conditions. They often collaborate with private firms to develop a variety to the proof of concept stage, before licensing the technology to firms for commercialisation. These types of crops do not attract the interest of large seed firms because the market is often too small to provide an adequate return on research costs.

The business model of large multinational firms that currently dominate the development of new food crop varieties in the OECD should continue to be successful. This model is likely to be supplemented by both private-private and public-private collaboration. The greatest competition for these firms could come from rapid increases in the technological capabilities of developing countries such as China, India and Brazil. Indeed, all of these countries have major agricultural biotechnology programmes. Given the importance of agriculture to their economies – either as a source of income or to feed increasingly wealthy populations – these countries are likely to view biotechnology for primary production as a strategic asset and could use government investment in public research to support the capabilities of national firms. Some of these firms should be internationally competitive in markets for food, feed and fibre crops well before 2030. These firms could also provide new markets for the discoveries of DBFs.

Health

The classical business model in health biotechnology faces ongoing problems in maintaining economic viability (Pisano, 2006).[10] Health DBFs have required frequent injections of capital from venture capitalists and large pharmaceutical firms. The problem is that the research-intensive business model for health biotechnology has not delivered on its promise to increase productivity in the sector, measured in terms of the number of new drugs reaching the market per USD billion in R&D expenditures (Hopkins *et al.,* 2007). This is a possible reason why the profitability of the classical business model in health is of concern, although health biotechnology is likely to be profitable once large pharmaceutical firms, which typically provide the path to market for DBF products, are included.

One concern is that the cost of capital for health DBFs could increase in the future. The long-term cumulative losses of health DBFs, a future rise in the cost of capital in response to greater investment opportunities in developing countries, and lingering effects from the 2007-09 credit crisis could encourage financiers to shift investment to potentially more profitable and less risky areas of biotechnology with shorter product lead times, such as clean energy or medical devices. This would have a pronounced impact on evolving business models. Health DBFs, consequently, could

increasingly abandon long-term, risky research on new therapeutics to focus on medical devices and drug delivery systems with shorter product development times. This could favour smaller, more agile R&D specialists that seek product markets rather than providing services (McKelvey, 2008). A decline in financial support for DBFs could be balanced by increased public sector investment in "translational research", *i.e.* research to bring new therapies closer to the commercialisation stage before they are picked up by the private sector. [11]

The prices that health biotechnology firms can charge for new therapies is also under pressure as public healthcare systems and private insurers try to contain costs. Between now and 2030, healthcare expenditure as a percentage of GDP in both OECD and non-OECD countries is expected to increase significantly. While much of this is attributable to long-term care for a growing elderly population, another factor is the cost associated with new technologies.[12] Recognition of that fact will increase the pressure to contain the costs of new diagnostics and treatments produced by health biotechnology firms. Several technological developments hold the promise of substantial cost reductions in drug development – *e.g.* molecular pathway engineering to synthesise complex drug molecules such as artemisinin, new methods such as RNAi for identifying drug targets, and the use of stem cells to replace animal models in toxicology studies.

Other technological developments are creating new opportunities for existing business models, but also major challenges. Regenerative medicine, pharmacogenetics, and predictive and preventive medicine will shrink markets for individual drugs, but the pharmacogenetics could also reduce the share of new molecules that fail in clinical trials, reducing drug development costs. On the other hand, predictive and preventive medicine could be hugely expensive to develop, due to the cost of long-term trials to validate thousands of potential biomarkers (see Box 6.3).

Many social and institutional challenges will also arise. The ability to create and analyse large databases of genetic, phenotypic, prescribing, and health outcome information will be essential to predictive and preventive medicine. The construction of these databases will require solutions to confidentiality issues and the question of whether patients will be required to release information on risk factors to insurers. Support for head-to-head clinical trials to identify the most effective treatment regimes and the inevitable discovery of adverse drug reactions or outcomes from analysing large databases will increase risks for pharmaceutical firms by making it difficult to predict future sales. At the same time, these approaches could also identify unknown health benefits, creating new markets.

Box 6.3. **Identification and validation of biomarkers**

Validated biomarkers to chart disease progression are essential for preventive medicine. The validation process requires extensive research to establish that a biomarker is an accurate predictor of the presence of disease, the risk of developing a disease, or the effectiveness of a therapy to treat the disease.

Estimates of the number of potential blood protein biomarkers are in the thousands. Laboratory scientists will need to identify candidate biomarkers and to standardise analytical procedures. Both scientists and clinicians will need to link biomarkers to pharmacological effects, estimate dose ranges, and determine the efficacy of different treatments. The validation phase will require integrating clinical data on biomarkers with medical practice in order to collect blood and tissue samples relevant for clinical and prognostic purposes. Consequently, identification and validation will require the involvement of experts from different fields and public organisations or healthcare providers that can obtain the consent of patients to provide tissue and blood samples.

There are several options for paying for and coordinating this complex process. One is for private or public healthcare providers to coordinate research using an open source software model. If the process is amenable to a modular product system, guidelines and standards could be established to permit the sharing of information across different steps. Just such a modular approach was used in the human genome project and for global databases such as GenBank. The FDA Critical Path Initiative has developed standards for the voluntary submission of pharmacogenetic information and a tool called ArrayTrack, to manage, analyse and interpret multiple types of data. These initiatives run on voluntary contributions – therefore, like open source software systems, they need to attract a critical mass of participants to produce useful results.

Another alternative is for biomarkers to be developed and validated in a research consortium on a for-profit basis, with biomarkers protected by intellectual property rights. This is similar to the Biomarker Consortium established by the National Institutes of Health (NIH) in the United States, with the participation of over a dozen pharmaceutical firms. Since there are potentially thousands of biomarkers, establishment of the Biomarkers Consortium does not prevent the development of other models to identify and validate biomarkers.

Source: Biomarker Consortium, 2007; McKelvey, 2008; OECD, 2008.

The complexity of the challenges and opportunities for health biotechnology could have wrenching implications for the current business model of large vertically integrated pharmaceutical firms, based on using the revenues from a few blockbuster drugs (with annual sales of over USD 1 billion) to cover high R&D costs. Smaller markets for many health therapies could seriously disrupt this business model. In recognition of this fact, several large pharmaceutical firms are moving into new fields. For

example, in 2008, Pfizer announced the launch of a new research unit for regenerative medicine (NYT, 2008). Given that regenerative medicine often uses a patient's own (autologous) cells to reduce the risk of rejection, this is unlikely to fit current business models in the pharmaceutical sector. Other large pharmaceutical firms are following suit by reducing their emphasis on blockbuster products and instead turning to smaller markets for targeted therapies (Alltucker, 2008). Another alternative business model is for large pharmaceutical firms to reduce costs by dramatically improving the efficiency of supply chains for clinical trials, production and marketing (McKelvey, 2008).

The promise of predictive and preventive medicine is better health benefits. Individuals could be offered individually tailored combinations of pharmaceuticals and healthcare services, including exercise and diet regimes (DHHS, 2008). This will require massive public and private investment into pharmacogenetics, systems biology, bioinformatics, long-term clinical trials and analysis of health records, as well as new public-private agreements to access large-scale data and biological material and genetic information.

Preventive medicine will create business opportunities for the aforementioned integrators or coordinators to manage the analysis of large databases. Millions of SNPs (single nucleotide polymorphisms) must be identified and analysed, along with phenotypic and environmental data, to determine the effect of these factors on response to treatment.

The push towards individually tailored healthcare will require new methods of coordinating healthcare systems. Medical practitioners, even more than today, will contribute to long-term ongoing research to establish the efficacy of preventive medicine. A shift to predictive and preventive medical care is likely to require large upfront investment by healthcare services, with most savings occurring years later in time. This transition will not be possible without the support of healthcare personnel and funding agencies.

In many countries pharmaceutical firms do not sell directly to healthcare providers. In countries with private sector healthcare providers, an integrator could create a market for predictive and preventive medicine by providing reduced health insurance premiums to individuals in return for their agreement to provide personal data on their phenotype, genotype, prescribing history, and outcomes. Kaiser Permanente, a health services firm in the United States, is an early leader in this area, already using patient data to identify adverse drug outcomes. An extension of this model could involve the collaboration of pharmaceutical firms. In return for offering lower cost drugs to the healthcare provider, pharmaceutical firms would receive access to patient data and the right to retain and analyse biological material.

The next step would be a single systems integrator in countries with private healthcare systems. The integrator would link pharmacogenetic knowledge, information on patient outcomes, and information on the effectiveness of different therapies in order to develop, co-ordinate and deliver new combinations of health goods and services. The elderly population, for example, could benefit from sophisticated IT-based monitoring systems to identify the side effects of multiple medications and calculate dosages for specific medical conditions. Tait *et al.* (2008) suggest that a systems integrator could create a market for predictive and preventive medicine by co-ordinating the development of new products – pharmaceuticals, tissue-based and regenerative therapies, diagnostics and devices – with personalised delivery of healthcare services. Although no single product would earn blockbuster profits, the firm would earn revenue from a diverse range of drugs and therapies and from healthcare services. This would be a radical departure from current business models, where there is usually a distinct separation between firms that develop technology and firms or public organisations that deliver healthcare services.

New collaborative models could also improve R&D efficiency by weeding out drugs that are unlikely to succeed or by rescuing drugs that have already failed in clinical trials. Pharmaceutical firms collect extensive data on failed drugs that they do not make publicly available because the information could be commercially valuable to their competitors. While this is an effective business strategy for each individual firm, it drives up costs for all firms and for the healthcare system by preventing the sharing of data on what does and does not work. A shift in business models towards greater collaboration and data sharing to develop predictive and preventive medicine could encourage firms to set up a consortium to share confidential data on molecular compounds and toxicology (Herder and Gold, 2008).

A variation on this model for early stage research was explored by Goldman Sachs. In this model, capital is targeted at specific drug development projects, rather than at the firms themselves. The investments would group together similar drugs from various firms that are in the early stages of clinical trials, to pool resources and reduce duplication (Jack, 2008).

Regenerative medicine based on tissue engineering and stem cells could create new treatments that would cure chronic, incurable diseases such as diabetes, dementia and arthritis. Where effective, this would replace and consequently destroy the market for pharmaceuticals to treat these chronic diseases.

Regenerative medicine can be based on embryonic stem cells or on the patient's own (autologous) cells. Embryonic stem cells can be used to

develop therapies for treating multiple patients. The use of autologous cells, however, has a major medical advantage: it avoids tissue rejection by the patient's immune system. For both embryonic and autologous stem cells, the market for regenerative medicine will require personalised clinical care plus the involvement of a laboratory with the expertise to culture new tissue.[13] The use of autologous stem cells, in particular, will require close collaboration between laboratories that develop new tissue and clinics that obtain the autologous cells and surgically implant new tissue into the patient.

Business models for regenerative medicine will need to manage a mix of intellectual property rights. The chemicals and genetic techniques to control the differentiation stem cells into the required tissue type are patentable, but surgical methods to complement tissue culture are not patentable in most jurisdictions, with the United States a notable exception. Even there, it is legally difficult for a patent owner of a surgical method to enforce the right to exclude others from using it. The patentability of stem cells varies between embryonic and autologous cells and between jurisdictions. Embryonic stem cells can be patented in the United States (Rohrbaugh, 2006), but not in Europe. The patentability of autologous stem cells is still unclear.

Regenerative medicine does not fit easily with current pharmaceutical business models. When autologous stem cells are used, there is no standardised, patented product to sell. Both types of stem cells require both clinical and laboratory services. The closest business model might be the private cosmetic surgery clinic. This could create opportunities for mid-sized clinical firms that license tissue engineering services, partially protected by trade secrecy, from specialised laboratories.

Industry

Some uses of industrial biotechnology, such as enzymes or bioreactor production systems for fine chemicals, are economically competitive without new business models or institutional support. Conversely, biofuels, bioplastics and other types of biochemicals face technological and institutional challenges. The main technological challenges are the cost and difficulty of scaling up bioproduction from small-scale systems that provide proof of concept to large-scale plants that can economically produce thousands or millions of tons of output per year. Other challenges include ensuring an adequate, long-term and reliable feedstock supply at a reasonable price. Institutional support is also required, including policies that raise the relative price of fossil fuel feedstock and environmental regulations or mandates that create markets for the use of biofuels and other

outputs of industrial biotechnology.[14] There are also vast opportunities for industrial biotechnology, including the global market for liquid transport fuels of 43 million barrels per day in 2006 (expected to increase to over 60 million barrels per day in 2030).[15]

Interviews with both DBFs and large firms active in industrial biotechnology suggest that DBFs such as Amyris will play an ongoing role by using synbio, directed evolution, or metabolic pathway engineering to develop customised enzymes and micro-organisms for chemical production (Podtschaske and Mannhardt, 2008). As these products are almost always intermediaries in complex production systems, DBFs must collaborate with or license their knowledge services to large firms. In most applications of industrial biotechnology, a lack of capital and engineering expertise for large-scale production and distribution systems hinders DBFs from developing into large integrated firms. To succeed, industrial biotechnology DBFs need access to scaled-up production facilities and infrastructures to develop and test their products. Consequently, they must collaborate closely with large industrial firms or rely on government subsidies for pilot testing biological processes.

The concept of a biorefinery that can use different types of biomass inputs to flexibly produce different products has elements of a new business model. The most common type of biorefinery produces biofuels, but with the possible exception of those in Brazil, most biofuel refineries currently require direct or indirect subsidies, such as mandates on the percentage of transport fuel consumption met by bioethanol. Research into biorefineries for food chemicals also partly depends on government support through co-financing. The vegetal-based chemistry programme at the Roquette biorefinery in Lestrem, France, for example, has 47% of its research costs funded by the French government (Rupp-Dahlem, 2007).

The main challenges in the near term for biorefineries are logistical. Biorefineries need to be located close to sources of biomass because of high transport costs. This could limit the optimum size of a single biorefinery, producing a network of mid-sized biorefineries in regions of high biomass availability. One option is that mid-sized biorefineries could be owned by consortia consisting of a DBF that provides the knowledge and expertise for advanced biotechnological processes and a large firm that provides production engineering capabilities. The plausibility of this type of business model is supported by several strategic alliances in 2008 between small enzyme supplier firms and large chemical firms and between ethanol producers, DBFs that provide biotechnological expertise, and large agribusiness firms.

In the longer term, the biorefinery business model will be challenged by technological developments in metabolic pathway engineering and synthetic biology. These two technologies have the potential to develop micro-organisms capable of producing a number of products, including carbon-based fuels and chemicals, with very little biomass feedstock. These production systems would draw energy from the sun and carbon from the atmosphere. If successful, the economic future of biorefineries could be limited to the production of high-weight and low-value products, such as biofuels, in regions with ample supplies of low-cost biomass.

Developments in metabolic pathway engineering and other forms of synthetic biology could shift industrial biotechnology from a science to an engineering-based discipline. This would expand the business opportunities of DBFs that can provide customised R&D services for designing microbes to large industrial firms.

Environmental performance standards based on a robust methodology for life cycle analysis (LCA) (see Box 6.4) could be a major driver for industrial biotechnologies that reduce harmful environmental effects, or for energy that produces less GHGs across the entire production chain. To make a difference, these standards may need to be backed by government regulation, but it is also possible for a consortium of firms with enough market power to establish a *de facto* LCA performance standard for biofuels or biochemicals. The adoption of such performance standards could provide business opportunities for firms able to brand themselves as "green".

Integration between primary production and industry

The main opportunity for integrators in agricultural and industrial biotechnology is to span both the production of biomass feedstocks and their use in industrial processing. A possible business model would link biorefineries, seed firms and growers, through either ownership or a collaborative model. For example, a large seed/biorefinery firm could develop plant varieties that are optimised for its bioprocessing operations. The varieties could be grown by independent farmers under contract. This is likely to be most easily realisable in large industrial conglomerates that are active in both areas. For example, the Dow Chemical Company, the owner of Dow AgroSciences, is also active in developing biorefineries. It could use its ownership of Dow AgroSciences to develop crop varieties suited to its industrial processing operations.[16]

Box 6.4. **Life cycle analysis (LCA)**

Life cycle analysis, or assessment, is a method for calculating the total environmental impacts of a product over its full life cycle. These include environmental impacts from the production of material inputs, product manufacture, distribution and transport, intended use, and after use disposal. LCA methods are described in the International Organization for Standardization's environmental management standards ISO 14040 and ISO 14044,[1] although they are primarily best-practice guidelines.

The greatest interest in LCA for biotechnological products is for primary production and industrial applications, such as the use of biomass to produce biofuels, chemicals and polymers.

LCA consists of four stages: *(1)* defining the goal and scope of the assessment, *(2)* taking an inventory of all processes, inputs and outputs from producing and using the product, *(3)* assessing all environmental impacts, and *(4)* interpreting the results. The first stage requires defining a functional unit of a product and identifying the boundaries of the assessment. For example, a LCA for liquid transportation fuels would need to define a unit of liquid fuel of equivalent energy, rather than a volume of liquid, due to differing energy densities in an equivalent volume of fuel. ISO guidelines recommend that the inventory stage should include the environmental impacts of all inputs, such as material production, transport, and capital investment in infrastructure or manufacturing plants, but in some cases capital goods or minor inputs are excluded. The ISO guidelines recommend including land use effects in the assessment stage for environmental impacts. The interpretation stage links different types of outputs, such as CO_2 and methane production, to an endpoint of interest, such as equivalent units of GHG production.

An important purpose of LCA is to determine the full environmental impacts of different types of products for the same function. Examples include a LCA of bioplastics compared to plastics manufactured from petroleum, or a LCA comparison of different transport systems using biofuels, petroleum, or electricity. Transport system impacts could include GHG production (including the additional effect of changes in land use), noise, particulate air emissions, and pesticide and fertiliser use for the production of biofuel feedstocks.

The complexity of LCA can be reduced by using customised software packages and specialised databases. The latter, such as Ecoinvent, provide information on the environmental impacts of hundreds of products, including the impacts of crop species such as wheat and rapeseed grown in different countries.

1. See *www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=38498*.

Source: Product Ecology Consultants, 2008; Jungbluth, 2008; Ecoinvent, 2008.

Conclusions

Figure 6.3 charts the relationships between emerging business models, which complements Figure 6.1 on current business models. The specific biotechnology application is not shown in Figure 6.3 because the emerging collaborative and integrator models are relevant for all applications.

How knowledge is shared and coordinated is one of the main factors that influence the emerging business models. Open source, collaborative and consortium business models can reduce costs through sharing knowledge – even when knowledge is patented, as with research consortia. DBFs can also participate in collaborative business models, although, in some cases, this might conflict with business models based on licensing intellectual property rights to large vertically integrated firms or system integrators.

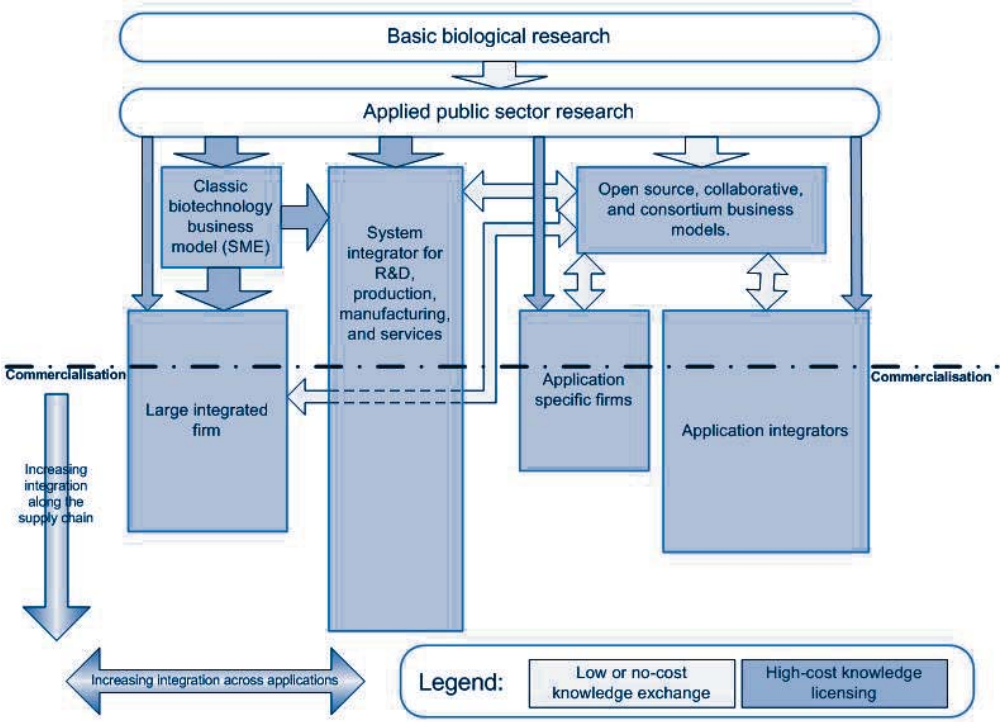
The system integrator spans the research and post commercialisation phases. In health, this type of business model could include both the commercialisation of products and the provision of health services, which explains the long vertical length of this business model in Figure 6.3.

Integrative business models that combine product development and services would be a radically new model for healthcare. This model could be essential for the rapid development of regenerative medicine, based on the need to combine customised products and clinical practice. Predictive and preventive medicine might also require an integrative model that includes the provision of services to patients and a mechanism for providing firms that develop therapies with data on treatment outcomes.

The wide horizontal dimension of application integrators represents business models that span two or more application fields, such as industrial and primary production biotechnology. This business model could face competition from either the use of standards or synthetic biology. In the former case, well-defined specifications (standards) for the processing characteristics of plant biomass varieties could replace the need for an integrator. In the second case, synthetic biology could be used to develop made-to-measure micro-organisms that produce chemicals without the need for biomass feedstock.

The size of the emerging bioeconomy will depend on whether or not the business models adopted are appropriate and profitable. The next chapter uses scenario analysis to look at the development of the bioeconomy to 2030 and the types of business models that might prosper, given plausible economic, technological and social developments over the next 20 years.

Figure 6.3. **Emerging business models in biotechnology**



Note: For simplicity, feedback loops from post-commercialisation to research and between firms active in research and the public research sector are omitted.

Notes

1. For details on the leading R&D performing biotechnology firms by application, see Annex Table 6.A1.1. The six largest pharmaceutical firms (Pfizer, GSK, Sanofi-Aventis, Roche, Novartis and Merck) had R&D expenditures of USD 25.9 billion in 2006, but an unknown and possibly large share of their expenditures may not have involved biotechnology. With the exception of Novozymes, biotechnology research expenditures can only be roughly estimated for industrial firms.

2. Concentration is also high in primary production for some veterinary products. Of the diagnostics that have been licensed by the USDA Center for Veterinary Biologics, eight firms produce 80.6% of the licensed products, with two firms producing more than half of all animal diagnostics (57.5%) (USDA, 2007). Three firms produce all of the fourteen biologics licensed in the United States for fish, and one firm (Novartis Animal Health) is responsible for ten of these products (USDA, 2008).

3. GM wheat has not yet been approved for commercial use.

4. In a few interviews conducted by the OECD, one manager of an SME active in crop breeding commented that well before 2030 there were likely to be only "three major firms to which we can license our products: Monsanto, a merger between Syngenta and Pioneer Hi-bred, and the Chinese government". A more sanguine respondent noted that "the three to five biggest firms will remain dominant".

5. In 2007, Novozymes had a world market share of 45-50% of industrial enzymes (24% of the food enzyme market) (Novozymes, 2008). Danisco/Genencor was second, based on 2006 data, with 30% (Fletcher, 2007).

6. Data on the IVD sales of the top 15 firms are from Medical Product Outsourcing (2006). Data on the global IVD market are from TriMark Publications (2007).

7. A few large firms in pharmaceuticals already act as integrators, although they often focus on adding value to their own products, rather than playing the role of an integrator on a wider scale. As an example, GSK has entered into alliances over the past decade to realise the potential of pharmacogenetics for its small molecule drug pipeline (Hopkins *et al.*, 2007).

8. For example, tests for possible food allergies are not required for non-food crops.

9. Figures based on an analysis of the UNU-MERIT GM Field Trial Database.

10. According to Pisano (2006), the aggregated profit of American DBFs in the health sector (limited to publicly-traded DBFs) is close to zero, with profit equal to all revenues from product sales, licensing agreements, R&D services, etc. minus all expenditures. If the most profitable company Amgen is excluded, or private companies included, the aggregate profit turns into a loss.

11. Many OECD government agencies are experimenting with ways of improving translational research in health, including the Dutch Center for

Translational Molecular Medicine (*www.ctmm.nl*) and the National Institutes of Health in the United States (*http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp*). Of note, the "translational" model is common in agricultural biotechnology, due to decades of government support for agriculture through land grant colleges in the United States and publicly funded agricultural research institutes in many different countries.

12. OECD (2006b) projections show that "non-demographic factors (including effects from technology and relative prices) play a significant role in upwards pressure on [future] long-term care expenditures and are the most important driver of the increase in [other] health-care expenditure".

13. An example is the 2008 windpipe transplant in which the patient's own stem cells were used to create new cells to line a windpipe scaffold (Roberts, 2008).

14. The recent report on biofuels by the Royal Society (2008) evaluates the effectiveness of the current policy regime in promoting environmental benefits.

15. The market for transport fuels varies with the price of oil, but at USD 50 per barrel, the current global market is worth USD 785 billion per year.

16. An integrated model is not always adopted even when feasible. Land O'Lakes and Cargill, the two largest feed producers in the United States (Hendrickson and Heffernan, 2007), had large seed businesses, but neither integrated their seed business in a production chain to supply their feed production. Cargill sold its seed division to Mycogen (a fully owned subsidiary of Dow AgroSciences) in 2001. As a farmer's cooperative, Land O'Lakes maintains its seed division as part of its services for its owners and sells seeds for alfalfa, corn, soybeans, canola, grain sorghum, wheat, sugar beets and turf grasses. But there is no indication that the cooperative specifically uses the products of its farmers in its processing operations.

Annex 6.A1

R&D Expenditures by Leading Firms Active in Biotechnology

Table 6.A1.1. **Estimated 2006 R&D expenditures of relevance to biotechnology by leading companies in each application**

USD million

Primary production		Health[5]		Industry[7]	
Company (country)	Biotech R&D[1]	Company (Country)	Biotech R&D[1]	Company (Country)	Biotech R&D[1]
Syngenta (Switzerland)	510	Pfizer (United States)	7 770	Novozymes (Denmark)	95
Monsanto (United States)	470	GlaxoSmithKline (United Kingdom)	4 350	BASF (Germany)	55
Bayer CropScience[2] (Germany)	310	Sanofi-Aventis (France)	3 750	DuPont (United States)	45
Du Pont Pioneer[3] (United States)	190	Roche (Switzerland)	3 450	AKZO Nobel (Netherlands)	40
BASF[3] (Germany)	170	Novartis (Switzerland)	3 450	Dow (United States)	40
LimaGrain[4] (France)	85	Merck (United States)	3 100	DSM (Netherlands)	15
KWS SAAT (Germany)	65	Genentech[6] (United States)	2 600	Kyowa Hakko Kogyo (Japan)	9
Dow Agrosciences[3] (United States)	55	Amgen (United States)	2 150	Ciba (Switzerland)	6
	-	Novo Nordisk (Denmark)	715	Wacker Chemie (Germany)	6
	-	Biogen Idec (United States)	460	BHP Billiton (United Kingdom)	2
Total	1 855[8]		31 795		313

1. Figures converted from Euros to US dollars using the average of monthly exchange rates from June 2005 to September 2008 (1 EUR = USD 1.34).

2. R&D expenditures are for 2007 (Bayer CropScience, 2007b).

3. Firm also active in agrochemicals. The share of its R&D expenditures in biotechnology has been estimated by multiplying its R&D expenditure data in the EU R&D Scoreboard by its share of 2007 sales in agriculture.

4. Limagrain, n.d.

5. The first six health firms spend a significant but unknown share of their total R&D on research that does not involve biotechnology. The R&D expenditures of the remaining four firms (Genentech, Amgen, Novo Nordisk, and Biogen Idec) are predominantly biotech related. The next largest pharmaceutical firm by R&D expenditures is Genzyme, with R&D expenditures of USD 405 million, almost all of which would be for biotechnology.

6. R&D expenditures are for 2007 (Genentech, 2007).

7. All industrial companies except Novozymes are not core biotechnology firms. The estimate for industrial biotechnology R&D is therefore much weaker than for primary production or health. As data are unavailable, 5% of the R&D expenditures of the remaining nine firms are estimated to be industrial biotech. It is also possible that major firm processing firms such as Nestle, Danone and Unilever spend more on biotechnology R&D than the chemical firms and mining firms in this list.

8. Biotechnology R&D for primary production is possibly even lower, with an alternative 2004 estimate of USD 708 million for the ten largest primary production firms of BASF, Bayer CropScience, Dow AgroSciences, DuPont, FMC, Monsanto, Makhteshim Agan, Nufarm, Sumito Chemical, and Syngenta (Phillips McDougall, 2005).

Source: Authors, based on EC, 2007, unless otherwise noted.

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Chapter 7

The Bioeconomy of 2030

What is the bioeconomy of 2030 likely to look like? This chapter describes a "probable" bioeconomy in 2030 and develops two fictional scenarios that explore the interaction of different factors on possible futures. The "probable" bioeconomy builds on the types of products that are likely to reach the market by 2015. Within the OECD region, biotechnology could contribute to 2.7% of GDP in 2030, with the largest economic contribution of biotechnology in industry and in primary production. The economic contribution of biotechnology could be even greater in developing countries, due to the importance of these two sectors to their economies.

The scenarios assume an increasingly multi-polar world, with no single country or region dominating world affairs. They include plausible events that could influence the emerging bioeconomy. The results highlight the importance of good governance, including international cooperation, and technological competitiveness in influencing the future. Complex scientific challenges and poorly designed regulations could reduce the ability of industrial biotechnologies to compete with other alternatives. For instance, rapid reductions in the cost of renewable electricity combined with technical breakthroughs in battery technology could result in electrical vehicles out-competing biofuel transport systems. Public attitudes could result in some biotechnologies not reaching their potential. An example is predictive and preventive medicine, where the advance of this technology could be limited by public resistance to poorly planned and intrusive healthcare systems.

Introduction

So far, this report has identified the types of biotechnological processes in use and the products on the market today (Chapter 3) and likely to appear by 2015 (Chapter 4). Chapter 5 looked at the role of regulation, intellectual property rights, and public attitudes in the emerging bioeconomy. Chapter 6 examined emerging business models that could solve some of the bottlenecks and take advantage of new opportunities.

This chapter goes further, using two methods to evaluate what the bioeconomy of 2030 might look like. The first method adopts a "business as usual" approach, identifying biotechnologies that could reach the market by 2030 and estimating the potential size of the bioeconomy. The second method uses scenario analysis to explore the factors that could lead to very different bioeconomies by 2030.

The probable bioeconomy in 2030

How likely are different biotechnologies to be commercially successful by 2030? Two key factors, identified through the scenario exercises described below, are the rate at which biotechnological research produces successful innovations, and changes to regulatory and institutional policies. For both factors, this estimate of the probable bioeconomy adopts a conservative perspective. First, the estimate assumes that long time periods are required to develop a discovery into a commercially viable application, as supported by the historical record for biotechnologies (see Chapter 1). Second, the estimate assumes that most changes to regulatory and institutional policies are likely to be adaptive. Policy changes that require deep or disruptive economic changes are much more difficult to implement and consequently less likely.

Table 7.1 lists (in no particular order) the types of biotechnologies that are likely to be available by 2030. For these biotechnologies, the probability of solving scientific and technological problems is high, they are likely to be commercially viable, and regulatory and institutional conditions are already supportive in several major markets. Many of these biotechnologies are already commercially viable in some form or close to commercialisation.

Table 7.1. **Biotechnologies with a high probability of reaching the market by 2030**

Primary production	Health	Industry
Widespread use of MAS in plant, livestock, fish and shellfish breeding.	Many new pharmaceuticals and vaccines, based in part on biotechnological knowledge, receiving marketing approval each year.	Improved enzymes for a growing range of applications in the chemical sector.
GM varieties of major crops and trees with improved starch, oil, and lignin content to improve industrial processing and conversion yields.	Greater use of pharmacogenetics in clinical trials and in prescribing practice, with a fall in the percentage of patients eligible for treatment with a given therapeutic.	Improved micro-organisms that can produce an increasing number of chemical products in one step, some of which build on genes identified through bioprospecting.
GM plants and animals for producing pharmaceuticals and other valuable compounds.	Improved safety and efficacy of therapeutic treatments due to linking pharmacogenetic data, prescribing data, and long-term health outcomes.	Biosensors for real-time monitoring of environmental pollutants and biometrics for identifying people.
Improved varieties of major food and feed crops with higher yield, pest resistance and stress tolerance developed through GM, MAS, intragenics or cisgenesis.	Extensive screening for multiple genetic risk factors for common diseases such as arthritis where genetics is a contributing cause.	High energy-density biofuels produced from sugar cane and cellulosic sources of biomass.
More diagnostics for genetic traits and diseases of livestock, fish and shellfish.	Improved drug delivery systems from convergence between biotechnology and nanotechnology.	Greater market share for biomaterials such as bioplastics, especially in niche areas where they provide some advantage.
Cloning of high-value animal breeding stock.	New nutraceuticals, some of which will be produced by GM micro-organisms and others from plant or marine extracts.	
Major staple crops of developing countries enhanced with vitamins or trace nutrients, using GM technology.	Low-cost genetic testing of risk factors for chronic diseases such as arthritis, Type II diabetes, heart disease, and some cancers.	
	Regenerative medicine provides better management of diabetes and replacement or repair of some types of damaged tissue.	

Primary production

In primary production, biotechnology is already widely used to develop diagnostics for plant and animal diseases and to develop new varieties of trees, crop plants, livestock animals and aquaculture species with valuable traits. Applications to breeding include not only GM, but also many other biotechnologies such as gene shuffling, intragenics and marker assisted selection (MAS). The use of biotechnology in primary production is therefore likely to be pervasive by 2030 for the production of plant and animal food sources and for plant sources of feed and fibre. The separation

of agriculture into biotechnology and non-biotechnology disciplines will be obsolete, due to the rapid adoption of biotechnology to develop better diagnostics and improved varieties of farmed plants and animals.

Three uses of biotechnology for primary production face economic or social barriers: animal cloning, the use of GM technology for small market crops, and the use of GM to develop functional foods. By 2030, the most probable use of animal cloning is to produce high-value animal breeding stock and compounds such as pharmaceuticals. The main barrier to greater use of cloning is likely to be public opposition to cloned meat. The application of GM to small market crops does not face large technical barriers, but it could be constrained by regulatory costs and an ongoing focus by the small number of multinational seed firms on large market crops. GM functional foods for developed countries also face cost constraints compared to cheaper alternatives such as fortifying food. The most probable use of biotechnology for functional foods is in developing countries, where breeding programmes for major staple crops could use biotechnology to increase levels of essential minerals and vitamins.

Health

In health, almost all research to develop or apply new diagnostics and pharmaceuticals will use biotechnology, for instance to identify drug targets, improve drug delivery, or tailor prescribing practices to the genetic characteristics of patients. The exception will be generic drugs that were developed before 2015, although even here prescribing practices will be increasingly influenced by pharmacogenetics. Testing for serious genetic diseases will be widespread and inexpensive. Testing for genetic profiles that increase the risk of chronic diseases such as arthritis, Type II diabetes, heart disease, and some cancers will also be inexpensive, but the use of these tests in medical practice could be restricted to higher-risk older populations or to individuals that already show other risk factors for these diseases.

Both pharmacogenetics and analysis of linked medical records will improve the safety and efficacy of therapeutic treatments. The latter will allow researchers to link prescriptions, behavioural factors and genetic data to long-term health outcomes. This will significantly improve public health by identifying adverse drug reactions, unwanted drug interactions, and other factors that both negatively and positively influence health outcomes. It will also reduce the potential market for therapies that are only effective or safe for specific sub-groups, and it could lead to more drug withdrawals after market approval. Several hundred genetic biomarkers could be validated for use in drug prescribing.

The promise of both regenerative medicine and predictive and preventive medicine will only be partly realised. Although many of the necessary technologies and research discoveries for these two biotechnologies are under development, there are still many technical, economic and social challenges that need to be solved. Nonetheless, several types of regenerative medicine will be available by 2030, such as to treat diabetes or to repair damaged tissue. The replacement of complex organs such as the heart, lung or liver is likely to lie further off in the future.

Industry

The use of biotechnological processes in industry is increasing rapidly and will likely continue to increase up to 2030, but there are several possible outcomes. The future use of biotechnology to produce bulk chemicals, polymers and fuel is uncertain, partly because economic competitiveness will depend on government investment to create markets. Industrial biotechnology will moreover need to compete with alternative technologies, from other technological fields. As an example, biofuels will compete with alternative sustainable sources of power, including wave, geothermal, wind, solar and nuclear energy, and with fossil fuels combined with carbon capture and storage. Biofuels have an inherent advantage for transport applications because they are the only renewable source of liquid fuel and because some types of biofuels do not require substantial changes to existing transportation infrastructures. Nevertheless, technical breakthroughs in battery technology and in the generation of renewable electricity could give the edge to electric vehicles powered by solar energy or other sources of electricity.

The most probable industrial uses of biotechnology in 2030 are to produce enzymes for a range of industrial processes; one-step synthesis of high-value chemicals and plastics using micro-organisms in bioreactors; and the production of high energy-density biofuels from sugar cane and cellulosic crops. Large-scale commercial production of bulk chemicals or biofuels from micro-organisms or algae, without the use of biomass, is less certain by 2030, due to considerable technical difficulties in scaling up production to commercially competitive levels.

Integration

The level of integration of the bioeconomy in 2030 will be influenced by the competitiveness of biotechnological solutions compared to other technologies. A major unknown is the future of biomass production, cultivation and use. If biomass provides an economically and environmentally sustainable feedstock for chemical and fuel production,

there will be extensive integration between primary production and industrial biotechnology. Conversely, if other technologies – including synthetic biology – prove superior, the level of integration will be reduced. It is highly likely that there will be some degree of integration, however, as biorefineries should be competitive in humid tropical and sub-tropical regions with high rates of plant production, which includes the south-eastern United States.

In 2030 the bioeconomy will be integrated with alternative sustainable technologies for reducing resource constraints and environmental problems, as part of a global shift towards greater social and economic sustainability. Life cycle analysis will be widely used to identify the most environmentally sustainable products and methods for manufacturing products. Some chemicals might be produced using petroleum or natural gas feedstocks, while others might be more efficiently produced using biomass. Energy production will be based on a mix of renewables, with the specific mix dependent on local resource assets.

A shift to developing countries

The increase in the global population to 8.3 billion by 2030 will increase demand for food, feed, energy, fertiliser and clean water. A large share of the production and consumption of biotechnological industrial and primary products by 2030 will be in developing countries such as Brazil, India, China and South Africa, due to growing populations and incomes.

Several of these countries are also likely to be world centres for biotechnological research, based on an ample supply of highly skilled researchers, particularly in China. The increasing role of developing countries in biotechnology will influence the location of skilled human resources, R&D, markets, competition and trade.

For all applications of biotechnology, firms will increasingly adopt a global strategy to take advantage of research capabilities, technological advances and markets in both developed and developing countries.

The economic impact of the bioeconomy

An estimate of the impact of biotechnology in OECD countries or on the global economy in 2030 would require trend data for each class of biotechnology products and processes as well as estimates of how the product mix might change over time – for example, by how much will the relative size of the market for biopolymers increase in 2030 compared to the market for basic food staples? This task would require a report of its own.

However, a rough estimate of the future economic impact of the bioeconomy can be made by assuming that the economic share of each major application will remain approximately equal to what is observed today. For example, primary production accounted for 1.77% of total gross value added (GVA) in the European Union in 2005 and is assumed to account for a similar share of GVA in 2030.

A first step in this exercise is given in Table 7.2, which shows the maximum possible economic impact of biotechnology in the three main application fields. This would be achieved if *all* economic activities in the three key sectors involved biotechnology: pharmaceutical manufacturing (the main health application), primary production, and industrial sectors where biotechnology can be applied. Under this assumption, the maximum contribution of biotechnology to gross value added (GVA) in the EU-25 and the United States would be 5.6% and 5.8%, respectively. These sectors account for over 4% of employment in the EU-25 and 2.5% in the United States.

Of course, biotechnology is unlikely to contribute to this level of economic activity by 2030, although it may approach this limit at a later date. Many industrial processes will continue to rely on existing technologies in 2030, with biotechnology possibly contributing to 35% of all chemical production in 2030 within the OECD area.[1] Biotechnology will contribute to the development and production of almost all new pharmaceuticals in 2030, but generics that predate the biotechnology revolution will account for part of the pharmaceutical market. In 2005, generics accounted for between 10% and 40% of the pharmaceutical markets in European countries (Perry, 2006). The contribution of non-biotechnological generics should decline over time, so a generous estimate is that they would account for 20% of pharmaceutical GVA in 2030, with biotechnology accounting for 80%. In primary production, biotechnology will not be widely used in boreal forests, but it could contribute to half of agricultural production and almost all of aquaculture and plantation forestry, for a total contribution of approximately 50% of primary production output. Given these shares, a rough estimate is that the potential contribution of biotechnology to GVA by sector in the OECD plus a few other European countries, based on current shares and GVA levels by application, would total USD 1 062 trillion: USD 259 billion in health, USD 381 billion in primary production, and USD 422 billion in industry. This equals approximately 2.7% of total GVA in these countries.[2]

Table 7.2. **Maximum potential contribution of biotechnology to gross value added and employment**

	GDP[1] (USD billions)	Share of gross value added (%)			Total employment (thousands)[6]	Share of total employment (%)		
		(Health) Pharmaceuticals [2]	Primary production[3]	Industrial sectors where biotech has some application[4,5]		Pharmaceuticals[2]	Primary production[3]	Industrial sectors where biotech has some application[4,5]
EU-25	16 379	0.66	1.77	3.13	171 247	0.31	1.87	1.96
United States	13 790	1.24	1.83	2.71	141 216	0.23	1.04	1.25
Australia	890	0.27	3.08	3.83	8 741	0.13	2.06	1.41
Canada	1 406	0.36	2.21	3.99	15 314	0.19	2.65	-
Iceland	20	-	9.34	1.52	0.159	-	6.88	-
Japan	5 103	0.62	1.34	1.94	52 935	0.21	0.82	1.73
Korea	982	-	3.78	4.91	21 557	-	8.82	-
Mexico	886	0.73	3.79	6.23	-	-	-	-
New Zealand	124	-	9.19	-	1 443	-	0.65	-
Norway	369	0.23	1.46	-	2 310	-	3.60	-
Switzerland	414	-	1.36	-	-	-	-	-

Sources:
1. 2007 GDP in official exchange rates from the CIA Factbook.
2. EUKLEMS Project Database for the EU-25, the United States, Australia, and Japan, data from 2005; OECD Structural Analysis Database (STAN) for all other countries for 2004 except Canada (2002 for value added and 2003 for employment), Mexico (2003 for value added) and Norway (2002 for value added). The two databases are not fully comparable. There are no data for Turkey.
3. EUKLEMS Project Database for the EU-25, the United States, Australia, and Japan, data from 2005; OECD STAN for all other countries for 2003 except Canada and New Zealand (2001 for value added and 2003 for employment), Iceland (2002 for value added and 2003 for employment), and Switzerland (2002 for value added). The two databases are not fully comparable.
4. EUKLEMS Project Database for the EU-25, the United States, Australia, and Japan, data from 2005; OECD STAN for all other countries for 2004 except Canada (2001), Iceland (2002), and Japan, Korea, and Mexico (2003). The two databases are not fully comparable.
5. Relevant sectors with biotech applications: metal mining (1314), textiles (17), pulp & paper (21), chemicals excluding pharmaceuticals (24) and instruments (3345). The NACE code for each sector is given in parentheses. Data not available for Canada (instruments), Iceland (mining), and Mexico (textiles and pulp & paper).
6. EUKLEMS Project Database for the EU-25, the United States, Australia, and Japan, data from 2005; OECD STAN for all other countries, data from 2003 except Australia (2001). The two databases are not fully comparable.

These figures underestimate the potential for biotechnology in 2030, as they exclude biofuels, new applications that are not currently imaginable, and impacts that are difficult to measure in monetary terms. Such impacts include the effect of health biotechnology on the length and quality of life, and the environmental benefits of agricultural and industrial biotechnologies. Furthermore, they do not take into account increases in the GVA of each application – such as an increase in agricultural output in response to increasing demand for biomass as an industrial feedstock.

A striking implication of these rough estimates is that the economic contribution of biotechnology is potentially greatest in industrial applications, with 39% of the total potential GVA from biotechnology, followed by primary production with 36% of the total and health applications at 25% of the total. This estimate conflicts sharply with an OECD estimate of the distribution of R&D expenditures by businesses in 2003, as shown in Table 7.3. The lion's share of private sector R&D investment, 87%, went to health applications in 2003, with only 2% of biotechnology R&D expenditures spent on industrial applications.

Table 7.3. **Current R&D expenditures versus future markets for biotechnology by application**

	Share of total OECD business expenditures on biotech R&D in 2003	Estimated potential share of total biotechnology gross value added (GVA)[1] in the OECD area[2] for 2030
Health	87%	25%
Primary production	4%	36%
Industry	2%	39%
Other	7%	-
	100%	100%

1. See Table 7.2 and the accompanying text for the estimated potential share of biotech GVA by application.

2. OECD member countries plus several EU-25 countries that are not members of the OECD. Due to a lack of data, Turkey is not included.

Source: OECD (2006) for the distribution of biotech R&D expenditures.

These results suggest that private sector investments in biotechnology R&D are not in line with the potential market opportunities for biotechnology by application. This could partly reflect higher R&D productivity in primary production and industrial biotechnology compared to health biotechnology, but a lack of incentives, supporting regulations, skilled researchers, or complementary investment in public sector R&D could also play a role. A change in private sector priorities could already be

under way, however, as shown by a recent increase in investment in clean energy (Dellenbach, 2008).

Biotechnology could account for an even higher share of GDP in developing countries, due to the greater importance to GDP of primary and industrial production compared to OECD countries. In contrast, the share of GDP from the use of biotechnology to develop and manufacture pharmaceuticals and medical devices is likely to be greater in developed countries, due to the concentration of advanced research capabilities and markets in the OECD area. Most new health technologies will also be too expensive for much of the world's population. This will limit the benefits of many health biotechnology products in 2030 to a population of 1 billion in the developed countries, where per capita incomes are sufficient, and possibly another 500 million to 1 billion affluent individuals in developing countries.

Scenarios for the bioeconomy of 2030

The probable bioeconomy of 2030 that is described above is based on "business as usual" conditions. Yet, the bioeconomy of 2030 could vary substantially from this baseline, depending on unforeseeable events plus the interaction of technological, economic and political choices.

Two scenarios, included in Annex 7.A1 to this chapter, investigate how different drivers and events *might* shape the future of the bioeconomy, both within OECD countries and worldwide. It should be noted that scenarios are not capable of either predicting the future or creating a consensus over the most likely outcomes. Unlike the estimates in Chapter 2 on the global population, age structure and energy consumption in 2030, they are not extrapolations and consequently of no value for long-term economic or technological planning. Instead, the scenarios serve as a tool for thinking through the future implications of a range of political and private decisions.

The scenario exercise began with the construction of six scenarios: two each for primary production, industrial, and health biotechnology.[3] An analysis of these six scenarios showed that the two key influences on the future bioeconomy are the successful commercialisation of biotechnological products and processes (dependent on advances in science and technology and on the competitiveness of biotechnology compared to other technologies) and the quality of governance, defined as the system of regulations and policies that influence the development and use of biotechnology. The six scenarios were combined into the two composite scenarios provided in the annex: "Muddling Through" and "Uneven Development". In contrast to many scenario exercises, which tend to

provide either consistently positive or consistently negative outcomes,[4] these two scenarios include a mix of both positive and negative outcomes. The "Muddling Through" scenario, however, leads to more positive outcomes than the "Uneven Development" scenario.

Both scenarios build on the estimates in Chapter 2 of the drivers of the bioeconomy and the short-term predictions in Chapter 4 on the types of biotechnologies that should reach the market by 2015. They assume an increasingly multi-polar world, with no single country or region dominating world affairs (Zoellick, 2008), and include plausible natural and political events that could influence the bioeconomy. In addition to the possible effects of the global financial crisis of 2007-2010 on the bioeconomy, these plausible events include environmental degradation, drought and poor weather, disease, and a case of bioterrorism. The scenarios do not include highly unlikely events such as a global pandemic resulting in many hundreds of millions of deaths. The reader is reminded that these two scenarios are entirely fictitious. They are written in the past tense as "histories" viewed from a 2030 perspective. The citations in the full scenarios are only provided to support the plausibility of some of the fictitious events.

A short summary of each scenario is given below, along with a discussion of the relevant policy lessons that can be drawn from them.

Scenario 1: "Muddling Through"

Between 2009 and 2013 research and business investment in biotechnological applications for primary production and industry continued to grow, in part due to an expected return to high commodity prices after the global financial crisis of 2007-10. In addition, governments supported biotechnology investment and research as part of economic growth initiatives. However, it was apparent after 2010 that the era of abundant cheap capital for investment in high-risk technology firms had ended. This particularly affected pharmaceutical start-ups, with investment shifting to less risky areas with shorter-term payoffs, such as medical devices, diagnostics, bioenergy, and agricultural biotechnology. The decline in cheap capital partly supported a search for new business models that could reduce costs through sharing knowledge.

Investment in predictive and preventive medicine continued, but the concept faced serious barriers from rising costs, with a growing public debate on where healthcare dollars should go – to low-cost lifestyle changes or to high-cost medical interventions. The former was partly supported by the response to an influenza pandemic in 2014, where public health actions such as quarantines and travel restrictions were more effective than new

antiviral drugs. The influenza crisis also strengthened the ability of international institutions such as the WHO to manage and address health threats. There was some progress in other regulatory conditions for health, such as an agreement between the Food and Drug Administration (FDA) in the United States and the European Medicines Agency on the validation of biomarkers. The FDA also introduced requirements for ongoing assessment of pharmaceuticals after market approval and the US government earmarked funds for clinical trials to compare the efficacy of different pharmaceuticals for treating a specific disease. Mid-sized public health jurisdictions developed comprehensive medical record systems that permitted researchers to investigate the long-term effects of pharmaceutical use and environmental factors on health outcomes. This research reinforced the benefits of a science-based versus "art-based" medical system, but success in changing doctor and patient behaviour was patchy.

Two consecutive years of extreme drought and high temperatures in the main grain growing regions of the world in 2016 and 2017 drove global grain supplies to a record low and prices to a record high. Serious starvation in the poorer parts of the world was narrowly avoided through the actions of the United Nations to obtain global agreement to restrict the use of grain as animal feed. The experience proved the worth of drought-resistant GM crops, causing Europe to end its GM moratorium. It also served as a wake-up call to take climate change seriously, leading to global agreement to phase in carbon taxes that were high enough to lead to notable reductions in GHG emissions. This led to increased energy conservation as well as an investment boom in low-carbon energy, including biofuels.

In 2019, several factors conspired to shift the incentive and funding systems for health research from patents and market pricing of patented drugs to a global prize-based system, where patents expired once market approval was obtained. All new drugs were therefore produced at generic prices. Firms were rewarded for drug discovery by financial "prizes" that varied with the health benefits of each drug. The pharmaceutical industry accepted the new system because it offered a solution to the long-term decline in profits due to shrinking market sizes for individual drugs (in part from the use of pharmacogenetics) and because an international levy system based on national per capita GDP created a large prize pool that could amply compensate risky investments in health research. National governments accepted the new system because it reduced healthcare costs, particularly in middle- and low-income countries. The prize system also increased investment in research for medical devices and regenerative medicine. Investment in the latter had suffered under the patent system because patents could not adequately protect therapies based on stem cells and tissue engineering.

The years between 2025 and 2030 marked the consolidation of the bioeconomy, with widespread adoption of biotechnological techniques in primary production. There were a few failures, such as the release of enormous reservoirs of carbon from the conversion of savannah and rainforest in South America and Africa to cropland. This was due to a lack of international agreement on life cycle standards for agricultural products, biochemicals and high-density biofuels. The latter were produced from sugar cane or fast-growing grasses and trees, particularly in tropical and sub-tropical regions. Biofuels from algae could have reduced the need for vast areas of new cropland, but technical problems delayed this option. The cost of producing biofuels from algae only began to become competitive towards 2030, but its future is unsure, due to ongoing competition from alternative sources of renewable energy.

The focus of healthcare research had partly shifted from pharmaceuticals to regenerative medicine, diagnostics and surgical techniques. Research in predictive and preventive medicine had led to many successes in the ability to prevent or delay some types of cancer. Genetic screening of embryos for inherited diseases and high risks for other serious diseases was common. However, the general public resisted predictive testing on children and adults when there were no effective therapies to treat the disease, if it developed. Under these conditions, predictive testing created more anxiety and misery than good. Medical practice was both increasingly automated and personalised, with treatment regimes based on software that analysed genetic and other diagnostic test results, medical histories, and behavioural and environmental data. The ability of doctors to ignore best practice treatment protocols had declined, due to greater enforcement in managed healthcare systems.

Policy relevance of the "Muddling Through" scenario

A combination of good governance and the high technological competitiveness of biotechnology across a range of applications resulted in the beneficial outcomes outlined above. Good international governance was promoted by positive co-operative experiences, such as a co-ordinated response to a major influenza crisis. That helped countries reach agreement in later years over other important issues such as food shortages and climate change. The trust that developed also facilitated international co-operation on a new incentive structure for healthcare applications. Contentious issues remained, however, and global consensus was still a challenge that required compromise by all actors.

Serious crises can create a window of opportunity for governments to implement disruptive or radical change. For instance, in this scenario, a co-

ordinated approach to climate change was only introduced after a major scare of global food shortages. An uncoordinated and poorly governed approach (not explored in this scenario), where each country pursues its own interests independently, could have been disastrous, with increasing trade frictions over scarce resources and rapid climate change.

Biotechnology thrived in this scenario where it was technologically competitive, although in some cases, such as for biofuels, supportive regulation played an important role. Economic factors also influenced competitiveness and a search for solutions. The decline in the profitability of the pharmaceutical sector created an opportunity to put in place a new incentive structure for health research. These changes supported greater investment in technologies, such as regenerative medicine, that provided a higher socioeconomic return. Several promising technologies, exemplified in the scenario by predictive and preventive medicine and algal biofuels, were less successful than hoped due to complex scientific challenges. Algal biofuels also faced continued competition from alternative sources of clean energy, with no clear technical winner at the end of the scenario. In the case of preventive and predictive medicine, public resistance to intrusive healthcare limited its advance.

Scenario 2: "Uneven Development"

Between 2009 and 2014, agricultural biotechnology, controlled by five major firms, continued to build on past successes, with a steady stream of improved varieties of GM maize, wheat, rice and soybeans. Europe did not permit GM crops, but biofuel production in both the United States and Europe thrived. Mandates on the biofuel content of transport fuels favoured existing investments in crop-based biofuel production over cellulosic biofuels. In combination with technical difficulties, low subsidies for cellulosic biofuel led to a fall in investment in this technology, with green investors shifting towards solar and geothermal energy sources. Pressure from NGOs led to an end to all biofuel subsidies in 2014 in Europe.

In health, two of the world's largest pharmaceutical firms, an ICT firm and a private healthcare provider in the United States formed a joint venture to take advantage of the FDA's requirements for compulsory post-marketing follow-up and the use of pharmacogenetic information in clinical trials. The healthcare provider offered the pharmaceutical firms access to its members and its extensive medical database system in return for reduced drug prices.

No agreement had been reached internationally on GHGs. Interest in climate change had declined markedly because temperatures had increased very little since 2007. Climate scientists had predicted that a long cycle in

the earth's orbit would only create a temporary delay in climate change for a decade, but their warnings were ignored.

In September 2016 terrorists released a synthetic bacteria in London that caused severe intestinal pain in thousands of people. No one died, but the potential for terrorists to create a lethal bacteria or virus sent shock waves throughout the OECD area. Governments immediately shifted their priorities towards domestic security, introducing severe security restrictions on research into both synthetic life forms and GM research. The high cost of meeting these restrictions caused many industrial and agricultural firms to abandon research projects in these fields. They also found it increasingly difficult to retain scientific staff who left to take up higher-paid positions in biosecurity research. Security concerns prompted OECD governments to promote conservation and speed up the implementation of alternative energy sources to imported fossil fuels, including the construction of nuclear power plants. In North America, GHG production continued to increase.

Biosecurity research had several beneficial effects. It resulted in cheap diagnostic arrays for animal, plant and human pests and diseases. Doctors could quickly determine if cold symptoms were caused by viruses or bacteria, reducing overprescribing of antibiotics and consequently the development of resistant strains of bacteria. Global databanks of plant and animal DNA, maintained as part of biosecurity, were used in the 2020s to prevent illegal trade in biomaterials.

The health sector was largely protected from the problems affecting agricultural and industrial biotechnology, due to more competitive salaries and US funding of research to quickly identify and treat new pathogens. The joint venture for health was shut down in 2020 and replaced by a merger between the partners, dominated by the ICT firm and the healthcare provider. The new business model was called a Networked Health Provider (NHP). The merger was driven by conflicts between the partners over the use of expensive drugs that were not particularly innovative and the unwillingness of the two pharmaceutical partners to move into regenerative medicine, which threatened some of their markets. The new firm was able to assemble new technology, build new types of expertise, and surmount regulatory barriers to innovation. The NHP model became very profitable, largely on the basis of adopting new medical devices and regenerative therapies, and was copied in India and China.

The fact that the main route to market for healthcare products was increasingly mediated by NHPs meant that small firms could develop a much wider range of healthcare products. Drug development no longer dominated health biotechnology, with almost half of private research invested in diagnostics and regenerative medicine.

The period between 2022 and 2030 was marked by a partial recovery in the use of biotechnology in primary production and industry. Brazil and a few other non-OECD countries had developed economically competitive biorefineries for high energy-density biofuels and for bioplastics by 2025, originally building on the expertise of European enzyme firms that moved part of their operations overseas to escape European and American restrictions on research.

Concern over GHGs and climate change grew into a serious global issue by 2027, due to seven consecutive years of accelerated climate change. This renewed interest in using GM and other biotechnologies to develop stress-resistant crop varieties. China and India were first movers in this area. Both industrial and agricultural firms lobbied OECD governments to relax some of the restrictions on the use of biotechnology.

The major success of the NHP health model created growing unease over the development of a highly visible two-tier healthcare system, with NHP members that could afford higher health premiums benefiting from better healthcare than individuals served by other healthcare providers. European and other countries with public healthcare systems were slow to adopt the NHP model and were therefore less successful in introducing an integrated system for providing healthcare. They also had to purchase many new therapies from NHPs at high prices. In response to a growing political debate over NHPs, several countries with publicly funded healthcare systems were threatening in 2030 to invoke the opt-out clauses of the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) in order to produce patented therapies at low cost.

Policy relevance of the "Uneven Development" scenario

Some of the problems described in this scenario are due to variations in the technological competitiveness of biotechnology, often exacerbated by poor political decisions such as insufficient support for promising technologies. Although the security measures introduced as a result of the bioterrorist attacks resulted in several beneficial innovations, they also stifled growth in agricultural and industrial biotechnology. The situation was made worse by the unintended effects of higher salaries in biosecurity. Carefully designed systemic policies to support both biosecurity and agricultural and industrial biotechnology could possibly have avoided some of these problems. Progress in health biotechnology was supported by a major organisational innovation that closely linked research into health therapies with the provision of health services. Yet the benefits were not widely shared. At the end of the scenario, growing tensions over access

could have led several countries to undermine the system of patent rights that provided the main incentive for investment in health research.

The scenario is further marked by the failure to respond to global problems such as the threat of climate change. Concern over the issue declined because of a decade with little increase in global temperatures. Recognition of the problem did not develop until late in the scenario, when climate change returned with a vengeance. The solutions were inadequate, addressing the symptoms of climate change rather than the cause. The main response was to develop crop varieties adapted to hotter and drier growing conditions, rather than reducing GHG production.

Conclusions

Biotechnology could contribute to approximately 2.7% of the gross value added of OECD countries in 2030 and perhaps more, depending on favourable technological developments and policies. Of possibly greater interest to policy, biotechnology can increase productivity and help address climate change, water stress, food scarcity, energy security, and disease. All of these challenges are included in the scenarios.

The descriptions in this chapter of the probable bioeconomy and the two scenarios of different futures show that many factors will influence the emerging bioeconomy. Some of the factors are fortuitous technological advances, both in biotechnology and in competing technologies. Other factors include the major challenges facing the world, such as food scarcity due to climate change and drought or disease pandemics among livestock.

Several of the events described in the scenarios create political crises that also open windows of opportunity. How governments react to financial crises, food scarcity or pandemics can shape the future development of the bioeconomy. The future is also influenced by international co-operation, especially with developing countries, and incentive structures for research and markets. Incentives influence the types of biotechnologies that are commercially viable and the distribution of its benefits. The structure of incentives can also support environmentally sustainable technologies over less benign alternatives – or *vice versa*.

Although the events described in the scenarios are completely fictitious, the lesson to be learned is the key role of good governance. This requires well-designed policies to support the current trajectory of the bioeconomy and flexible policies that can foresee and effectively respond to unpredictable crises. Policy options for the bioeconomy are examined in the following chapter.

Notes

1. The 35% estimate is obtained from linear extrapolation to 2030 of the USDA upper estimates of the biotechnology share of world chemical production in 2005, 2010, and 2025 (see Table 4.6 in Chapter 4). The lower USDA estimates would predict a 2030 biotechnology share of world chemical production of 27%. The upper estimate is used here for OECD countries, under the assumption that technical progress will be greater within the OECD countries than within developing countries.

2. These estimates are calculated from the data in Table 7.2 for each OECD country and assume that 80% of pharmaceutical production would be due to biotechnology, 50% of primary production, and 35% of industrial production in sectors where biotechnology has potential applications (see Note 5 to Table 7.2). Missing data, such as health GVA for New Zealand, are estimated from the nearest neighbour in terms of economic structure. Therefore, the GVA share for Japan is applied to Korea, Australian GVA shares to New Zealand, USGVA shares for pharmaceuticals to Switzerland, and EU GVA shares for industrial production to Switzerland and Norway.

3. Three reports develop the scenarios for health, primary production, and industry. See Tait *et al.*, 2008 for scenarios of health biotechnology; Murphy *et al.,* 2008 for scenarios of primary production biotechnology; and MacRae, 2007 for scenarios of industrial biotechnology. All scenarios can be downloaded from www.oecd.org/futures/bioeconomy.

4. Other scenarios of the bioeconomy that were evaluated for this report have end-dates between 2015 and 2056. See USDA, 2005; German Ministry of Education and Research, 2004; Bezold and Peck, 2005; EC, 2007; NZ MoRST, 2005; IBM, 2006; Neild and Pearson, 2005; WBCSD, 2000.

Annex 7.A1

Fictional Scenarios to 2030

Scenario 1 – Muddling Through

2010 to 2013: Gradual shifts

In 2010 investment in biotechnology research was dominated by health applications, which accounted for 85% of R&D expenditures. Agricultural biotechnology continued to build on past successes, with several new GM varieties of major crops reaching the market before 2012. These included improved product quality and drought tolerance traits for maize and soybeans. China began large-scale plantings of pest-resistant GM rice in 2011. Awareness of industrial biotechnology had increased as a result of the production of biofuels, which was a major market for GM enzymes.

The biofuels sector was experiencing biomass supply and market problems. Greater demand for biomass inputs had driven up the price of what was previously low-cost waste, while a glut in by-products from biofuel production drove down the price of what were previously profitable sources of income. The increased costs of biomass also increased the cost of producing biopolymers.

The substantial increase in prices for agricultural commodities and petroleum before 2008 had begun a gradual shift in the structure of the biotechnology industry. These commodity prices fell steeply after 2008 due to an increase in the supply of grains and a reduction in the growth of demand for petroleum due to the global financial crisis of 2007-2010, but prices still remained above the average of the 1990s. Investors expected the prices of agricultural commodities and petroleum to increase after 2010 due to a long-term increase in demand, leading to a sustained increase in investment in agricultural biotechnology and in energy. This was supported by government investment by several OECD and developing countries in R&D and infrastructure for primary production and industrial biotechnology, as part of economic growth initiatives in response to the global financial crisis. Venture capitalists invested in small firms working on cellulosic sources of biomass, such as low-lignin grasses. Large seed firms expanded their research programmes to develop crops with enhanced quality traits that would reduce biomass processing costs and increase conversion yields for biofuels and valuable chemicals. Research also increased in new and more efficient uses for plant and animal wastes for energy production.

The refusal of several European governments to permit plantings of GM grain crops faced increasing opposition from the European livestock industry, which was paying high prices to import GM feed from the United States and South America. However, European consumers

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remained hostile to GM. There was a general assumption by European policy analysts that public opinion would not change until consumers directly benefited from GM products, for instance from healthier GM foods. It was unlikely that consumers would benefit from a fall in prices, with almost all of the cost savings from GM going to seed firms and farmers. In contrast to the situation in Europe, Australian public opinion had turned strongly in favour of GM, due to fears over food security as a result of the long drought during the 2000s. By 2012 Australia had become a major grower of GM rapeseed, drought-resistant barley and other grains for animal feed.

The use of biotechnology in the health sector was rising rapidly. Biotechnologies such as RNA interference were widely used in drug discovery for both small- and large-molecule drugs. Over half of the clinical trials conducted included some pharmacogenetic data from patients; firms were seeking to reduce the prevalence of adverse drug reactions and experimented with identifying sub-groups of patients that responded well to therapy, particularly in cancer treatment. New diagnostics for genetic risk factors, targeting increasing numbers of genes, were continually appearing on the market, while the cost of genetic testing was falling steeply every year.

The concept of predictive and preventive medicine attracted increasing interest from pharmaceutical firms, venture capitalists and health policy analysts, but progress continued at a slow pace. The concept required patients who were very likely to develop a specific disease, due to a genetic predisposition or environmental factors, to take steps to prevent the disease from developing. Depending on the disease, this could require a change in lifestyle, diet, or medical treatment well before the development of symptoms. Diagnostic tests for risk factors for many chronic diseases – such as cancer, heart disease, arthritis and Type II diabetes – formed much of the predictive component of preventive medicine, but most of these tests could only detect relatively low risks. There were few predictive tests to determine if genetic or environmental factors were actually leading to specific diseases, rather than simply increasing theoretical risks. These predictive tests required validated blood protein and other markers that could detect a developing disease well before the appearance of symptoms.

Healthcare experts interested in predictive and preventive medicine were aware of the difficulties in getting patients to actively participate in changing their lifestyles. This problem was even greater when behavioural changes were suggested to patients long before the appearance of any symptoms. Research on smoking cessation programmes and dietary changes to control cholesterol levels had shown significant benefits (Kay-Tee *et al.*, 2008).This demonstrated that individuals, if sufficiently motivated, would alter their behaviour when faced with long-term risks. But the same research also showed how difficult it was to change long-term habits, and that any changes occurred slowly. Furthermore, research showed that people disliked prevention that required self-monitoring, as it increased anxiety and consequently reduced their quality of life (Gulliford, 2008).

Although the potential contribution of biotechnology to healthcare was widely appreciated, neither politicians, nor the CEOs of health product firms, nor public or private healthcare service managers knew how to solve the main problems of rising healthcare delivery costs, declining research productivity, and an apparent worsening of the cost/benefit ratio for new technologies. Many biopharmaceuticals, marketed at prices of over USD 50 000 per year, only

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made small improvements to the median survival of patients.[1] These results also intensified a debate over whether or not more public funding should go into low-cost lifestyle changes compared to high-cost medical interventions.

A major hurdle was how to pay for the identification and validation of over 2 000 potential biomarkers. To break this impasse, ten major pharmaceutical firms and non-profit research organisations had established a research consortium in the mid 2000s to identify and validate biomarkers. Additional members had joined over the years.

Validation required years of careful clinical trials and the ability to link long-term patient outcomes with biomarkers and treatments. In 2009 the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA) in the United States agreed on mutually recognised standards for validating biomarkers, an essential step towards supporting research in this area. The standardisation built on earlier collaborative work between the EMEA and the FDA on harmonising the submission of pharmacogenetic data during clinical trials.

The FDA adopted a life cycle approach to evaluating the risk of pharmaceuticals that went well beyond market approval. It considerably strengthened its post-market follow-up requirements to identify long-term safety concerns and introduced mandatory registration of all clinical trial results. To complement these efforts, the National Institutes of Health (NIH) in the United States earmarked USD 500 million per year for comparative trials of different pharmaceuticals or other surgical treatments for the same medical condition.

2014 to 2025: The transition years

The Cambodian influenza pandemic of 2014 reinforced the need for a global public health surveillance system under the World Health Organization (WHO). Although the pandemic was the worst global flu outbreak since 1918, the experience gained ten years earlier during the SARS outbreak of 2003 proved invaluable in significantly limiting the scale of the pandemic to 20 million deaths worldwide – a much lower death rate than in 1918, when 40 million people died out of a much smaller global population (Smith, 2006). The use of antiviral medicines had only a limited effect on the pandemic. Most lives were saved due to public health actions such as quarantines and travel restrictions. The total economic costs of the pandemic were severe, estimated at 3% of global GDP. Many scientists were relieved that the pandemic had not occurred several years later. There had been talk of reducing the global health surveillance system as a way of reducing the costs of the overstretched United Nations budget.

As a result of the Cambodian flu pandemic, UN member countries agreed to a large increase in the UN's WHO surveillance budget and began discussions to establish a fund to support research into developing new antibiotics in order to address continued concerns over antibiotic-resistant strains of bacteria. Several years later, the United Nations also obtained earmarked funding to replace traditional poultry and livestock breeding methods in South East Asia with modern methods that substantially reduced contact between people and animals. The goal was to reduce the risk of transmission of zoonoses, such as influenza viruses, from animals to humans (Smith and Alvarez, 2008).

By 2013 it was widely recognised that the 25-year glut of cheap capital that had supported venture capitalist investment in long-term, high-risk technology projects had ended by 2010.[2]

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A major cause was increased opportunities for profitable short- and medium-term investments in developing countries, particularly after the global financial crisis of 2007-2010, which led to a large decline in petrodollars and Asian trade surplus funds invested in the United States. Investment in high technology followed higher rates of return in energy technology – part of a global boom in low-GHG energy sources – and in agricultural biotechnology due to high sustained prices for food and feed commodities. It became comparatively more difficult for small biotechnology firms in pharmaceuticals to raise capital. An increasing share of a dwindling supply of venture capital investments in health went to medical devices and diagnostics with shorter development times than pharmaceutical projects.

High prices for agricultural commodities had increased the rate of conversion of pasture and forest lands to crop production, particularly in South America, Indonesia, and parts of Africa with abundant rainfall (Bruinsma, 2003). The cost of growing grains in Africa was now competitive with world prices. By 2014 the "food versus fuel" debated had quieted down, with 15% of crop production going to biofuels; these used sugar cane and GM grain varieties that had been modified to reduce processing costs and increase fuel yields.

The success of the open source Biobrick Foundation in identifying genetic "building blocks" for chemical production raised interest in developing business models based on knowledge sharing and public/private research consortia. Several small industrial biotechnology firms were established in order to build on the results of the Biobrick movement. They developed customised micro-organisms that could produce valuable chemicals without the need for a large sequence of chemical synthesis steps. These organisms were sold to large chemical firms, a few of which had the capacity to develop designer micro-organisms in-house. Patent pooling and research consortia among public sector research institutes and small agricultural biotechnology firms in developing countries and in smaller developed economies such as New Zealand, Australia and Korea opened up new business models and attracted significant investment.

In 2014 the World Business Council on Sustainable Development held a conference to discuss an incentive system based on prizes for medical research (Love and Hubbard, 2007). Interest in a prize system had been gradually growing since a World Business Council meeting on the topic in 2001. The success of alternative business models such as patent pools and the Biobrick Foundation had also increased interest in looking for new types of incentive systems for research. Another factor in calling the conference was concern over falling market sizes for individual drugs from the increasing use of pharmacogenetics. The conference did not reach agreement over a prize incentive system. However, it did provide a forum for discussion between large and small pharmaceutical and medical device firms and public and private health service providers over incentives for health innovation. The WHO agreed to sponsor another meeting three years later in 2017.

Earlier enthusiasm for GM functional foods in developed countries waned, after market research established that the majority of consumers were unwilling to pay premium prices for nutrient-enriched staple foods. In contrast, smaller markets for specialty nutraceuticals boomed, in part due to public interest in preventive diets for cancer and other chronic diseases. An example was increased interest in producing Omega-3 fatty acids in GM algae. The main market for functional foods was in Africa, where agricultural research organisations used

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biotechnology to develop cassava, maize and sorghum varieties with enhanced levels of essential minerals and vitamins.

Due to high feed prices for livestock, in 2014 all member states of the European Union accepted a proposal by the European Commission to allow farmers to grow crop varieties developed using intragenics,[3] but several major countries maintained their opposition to transgenic GM crops. The acceptance of intragenics improved conditions for seed firms as they could now use GM technology to transfer genes from wild strains of a species to elite cultivated varieties. In the same year, international agreement on the safety requirements for GM crops also reduced regulatory costs. This improved the ability of SMEs to develop gene constructs for small market crops such as vegetables.

The traceability systems developed at the turn of the century in response to the Bovine Spongiform Encephalopathy (BSE) crisis in the United Kingdom led to the development of advanced tracking systems for agricultural products. Microchips and accompanying scanners provided information on the health and movements of each animal from birth to death. These applications were used widely in developed countries and increasingly adopted in developing countries in order to maintain or access markets. In some cases, increased application of security and traceability measures was facilitated by World Trade Organization (WTO) agreements (such as those requiring export countries to maintain full records on livestock for export).

Biotech advances in food safety, such as microchip diagnostics that turned colour in the presence of bacterial contamination, allowed the WTO's *Sanitary and Phytosanitary Measures* and *Technical Barriers to Trade* agreements to continue to function effectively. These technologies were adopted by developing countries, such as China and Indonesia, that had experienced several severe cases of food contamination. Effective food safety technologies, improved tracking and tracing technology, and improved sanitation in food processing factories led to a drastic reduction in the number of contaminated food events.

The Malthusian years

Two consecutive years of extreme drought and high temperatures in the major grain growing regions of the world between 2016 and 2017, plus extreme weather events in many other regions, drove global supplies of the main food and feed crops of maize, rice, sorghum, soybeans and wheat to a record low. This caused an explosion in food prices, to a level that was painful even for developed countries. The problem was exacerbated by low global grain reserves for over a decade and the devastation of wheat crops in Europe and the Ukraine by a new strain of wheat rust fungus that originated in the Punjab region of Pakistan and India.

The "Malthusian years", as they were quickly called by journalists, fuelled further investment in agricultural biotechnology and in cellulosic fermentation for the production of biofuels. Average daily calories consumed in developed countries fell by 5%, followed by a dip in the percentage of the population that was obese and a decline in the number of new cases of Type II diabetes. Widespread starvation in poorer countries was only avoided by the actions of the United Nations to reach global agreement to curtail the use of grain and oilseeds for meat production and biofuels.

Fictional Scenarios to 2030

The Malthusian years also ended the European moratorium on GM crops. Opposition had been declining for years in the face of increasing awareness of the environmental benefits of GM in terms of reduced pesticide use and improved stress tolerance. Researchers had estimated that the Malthusian years would have been much worse without the widespread adoption of improved GM varieties of drought- and heat-tolerant maize and soybeans that had been introduced to the market in 2015 in the Americas, India and China.

Overwhelming data to support the theory of climate change had failed to convince developed and developing countries to take the phenomenon seriously, and previous agreements lacked enforcement mechanisms. GHG production in almost all major emitting countries had continued to increase every year. The experience of the Malthusian years spurred global acceptance of a binding agreement in 2019 to drastically increase carbon taxes, over ten years, to USD 500 per tonne. International Energy Agency (IEA) and OECD economists had estimated that a carbon price below this level would never encourage the sweeping social changes and private investments required to address climate change.

An immediate effect of the carbon tax was a jump in investment in energy conservation. Although conspicuous high-energy consumption had already become socially unacceptable, much waste still existed. The increase in carbon taxes also created an investment boom in low-carbon energy technologies.

Several large American and Brazilian agricultural and industrial firms invested in joint ventures to develop fast-growing perennial crops for cellulosic fermentation. Although the process remained more expensive than using starch plants such as maize, new technology was developed that could cheaply remove water from biomass, significantly decreasing transportation costs.

Another welcome technical breakthrough in Brazil resulted in the efficient large-scale production of high energy-density liquid biofuels from sugar cane. These biofuels had several important advantages over bioethanol. The energy density per litre was very close to that of gasoline, versus 69% for ethanol; they could be used in ordinary engines; and they did not attract water. This meant that they could be cheaply exported from Brazil in bulk tankers and shipped through existing pipelines.

Several publicly funded health jurisdictions covering populations of approximately 4-5 million people had established comprehensive medical records systems. These linked lifelong records on therapeutic treatments, genetics and environmental behaviours such as exercise, diet and housing with long-term health outcomes. The complexity of the informatics system for comprehensive healthcare favoured small to mid-sized health services. An early leader in the United States was the private health services firm Kaiser Permanente, with 9 million patients. Research by these health providers created a wealth of information on adverse drug reactions, the success of different health therapies, and both positive and negative interactions between different therapies. The early results increased medical knowledge of the most effective interventions for a range of chronic diseases. This helped to reinforce the benefits of a "science-based" medical system as opposed to an "art-based" system that left many treatment decisions to individual doctors. In these jurisdictions healthcare delivery was increasingly linked to the development of mandatory treatment protocols. However, success in

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introducing evidence-based medicine was patchy. Doctors resisted restrictions on their ability to make decisions "best adapted to the individual". The public interpreted some of the guidelines as forcing patients to take the cheapest available option rather than the "best" option.

The profitability of the pharmaceutical sector was declining, due to the use of pharmacogenetics and evidence-based treatment regimes that had significantly reduced the market size for many drugs. Higher incomes in China and India had created double digit growth in pharmaceutical markets that partially compensated for the smaller markets in developed countries (Pharma Futures, 2007). China was already the world's seventh largest market for pharmaceuticals by 2010, while both China and India had the world's largest number of patients with diabetes and obesity before the Malthusian years. However, the affluent middle class in India and China was not large enough to fully compensate for the reduced size of individual drug markets in developed countries. In 2018, average incomes in India and China were approximately USD 1 800 and USD 3 500, respectively.[4] These lower median incomes meant that national health priorities focused on low-cost public health solutions.

High manufacturing costs for biopharmaceuticals required firms to charge high prices for this class of drugs. Synthetic biology provided opportunities for lower cost production, but still required expensive bioreactors. After 2014, production costs for most biopharmaceuticals fell by between 60% and 90%, with extensive production of biopharmaceuticals from GM plants raised in greenhouses. These were protected through state-of-the-art security systems to prevent counterfeit drug production based on the theft of GM seeds.

The Chinese and Indian governments had both established regulatory agencies modelled on the FDA rules. This was due to their strong interest in supporting internationally competitive domestic pharmaceutical firms that could sell products in the two major markets of the United States and the European Union. A Chinese biotech "triangle" with strengths in agricultural, pharmaceutical and industrial applications had developed in three coastal states (Zhejiang, Shanghai and Jiangsu), built around universities, agricultural field stations, manufacturing plants and medical hospitals in Shanghai, Nanjing and Hangzhou. Average per capita GDP in the three states exceeded USD 12 500 in 2015.[5] Comparatively high living standards, proximity to the Shanghai International Airport, a well-developed infrastructure, good schools, internationally competitive salaries in the biotech sector and attractive recreational areas nearby meant that the Chinese biotech triangle was successful in attracting both Chinese and non-Chinese star researchers working in OECD countries. A major advantage of the biotech triangle was expertise in platform technologies of relevance to each of the three main application fields.

The shift to MeDFAs

In 2018 a mid-sized biopharmaceutical firm obtained market permission in the United States and the European Union for Amespira, a biopharmaceutical for the most common type of lung cancer. The drug was the first significant breakthrough in lung cancer treatment, extending survival by a median of nine months compared to existing best practice treatment regimes.

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However, the manufacturer priced Amespira at USD 200 000 per year, making it the most expensive drug in history other than a few drugs for very rare diseases. Many public and private insurers refused to pay for it. In the United States, the annual bill for Amespira to treat all new lung cancer cases was estimated at 10% of all expenditures on prescription drugs. Several Latin American and Asian countries used the public emergency and compulsory licensing provisions of TRIPs to manufacture biosimilar versions of Amespira for domestic use.

The case created intense public discussion within developed countries. Amespira was only covered by a few private healthcare plans for tertiary-level employees, who had very low smoking rates and hence low rates of lung cancer. Other patients had to either use their personal savings or do without. The glaring disparity in healthcare availability for a familiar disease flew in the face of people's sense of justice. The problem was particularly acute in Japan, due to the government's policy of not reimbursing "advanced" innovative new technologies. The manufacturer of Amespira mounted an unsuccessful public relations campaign insinuating that private individuals should cover the costs themselves, since no one could claim that they did not know that smoking caused lung cancer. The firm even offered to provide Amespira at a 75% discount for lifelong non-smokers.

The Amespira controversy gave political support to the case for using cash prizes as an incentive for medical innovation rather than patents. A number of other developments made the pharmaceutical sector much more receptive to the idea than it had been in 2014. The first was smaller drug markets and the near-disappearance of the blockbuster drug business model. One effect of these developments was a continual decline in the supply of funds to finance the next round of innovation. The second was the difficulty smaller biotech firms were encountering in raising venture capital. Third, large pharmaceutical firms were increasingly obtaining new drugs from small firms and earning a larger percentage of their revenues from generics. That meant that they had the expertise to manage complex royalty agreements and they were less reliant on profits from patented drugs. A fourth reason was associated with production problems. The increasing use of plants to produce complex pharmaceuticals had created several high-profile counterfeit cases, based on stolen seeds, which had reduced the revenue of a few major pharmaceutical firms.

A fifth reason was of particular interest to many American politicians. A cash prize system, with contributions based on national GDP, would end the free rider problem in drug development. Americans had complained for years that the high cost of drugs in the United States compared to other developed countries meant that Americans were subsidising medical innovation for the rest of the world. All proposals for the prize incentive system were based on a small levy on national GDP. This was designed to provide a prize pool equal to twice the global annual expenditures for R&D on pharmaceuticals and medical devices, or approximately USD 160 billion. The high potential payouts of this pool provided a sufficient profit incentive for long-term and risky investment. Even though the levy was tied to the UN World Development Index – so that wealthier countries paid a higher levy rate than poorer countries – the levy for the United States was 0.25% of GDP, which was one-third less than its private sector expenditures on medical R&D. American firms would also be able to compete on an equal basis with all other firms in the world for an annual fund four times greater than their current R&D levels.

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The WHO, with the encouragement of many health NGOs, took responsibility for obtaining international agreement on the details of the Global Medical Discovery Finance Awards (MeDFA) Treaty. Firms quickly started to talk of one "MeDFA" as a unit of currency, worth USD 1 million. Many of the basic ideas had been worked out in the 2000s[6] and in the two international conferences in 2014 and 2017. The final agreement was reached comparatively rapidly in 2019, due to the much-improved international negotiating environment on health since the Cambodian flu pandemic of 2014.

The MeDFA Treaty solved problems of parallel imports, denial of access to medical innovations based on high costs, and the free rider problem. Patents were still permitted under the agreement, but once a medical innovation received marketing approval in a major market, the patent expired and the innovation could be produced by generic manufacturers. The production of biopharmaceuticals in plants made this particularly easy and drove down drug costs substantially. Patents were mainly used to apportion payouts among different firms that contributed to the innovation. The size of the award, paid out over ten years, included both a minimum amount and a sliding scale based on improvements in quality-adjusted life years (QALYs). A minimum award was essential to provide a research incentive for rare diseases. A certain percentage of the total annual award was also set aside for problems that were difficult to measure in QALYs, such as improved drug delivery systems, surveillance systems, and therapies for potential pandemics or for bioterrorism.

Building on the international discussions in 2014, the MeDFA Treaty also earmarked 3% of the annual prize for new antibiotics. Improved public health in the developing world, hospital sanitation, and restrictions on prescribing antibiotics in developed countries had contained the growing threat from antibiotic resistant bacteria – but the public health community was convinced that it was only a matter of time before antibiotic resistance led to an untreatable and serious global pandemic.

The main problem with the MeDFA system, familiar to many small biotech firms, was how to pay for research without a revenue stream. Large pharmaceutical firms largely stepped in as both financiers and co-ordinators. Since payouts were apportioned on the basis of contribution, there was a strong incentive to collaborate rather than getting involved in expensive and redundant races to be the first to bring an innovation to the market.

The MeDFA system caused several major changes in medical innovation. As it was open to firms in all countries participating in the treaty (which included almost all UN member states), it encouraged greater medical research outside the main centres of pharmaceutical innovation of the United States, Europe, Japan, China and India. Second, many of the awards for the first five years were given to small medical device firms, particularly those active in stem cells and tissue engineering. The previous patent system had failed many of these firms. The dominant method was to use stem cells derived from the patient. These cells were treated and cultured, with the resulting tissue surgically inserted into the patient. The process was labour-intensive, but more problematically it was easy to keep secret and hence avoid paying patent royalties. Patients from developed countries would seek low-cost royalty-free treatment in clinics in Brazil or India for new teeth, cartilage, or pancreas islet of Langerhans cells for diabetes. The incentive provided by MeDFA awards strongly encouraged more research on stem cells and

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tissue engineering. In contrast to a patent incentive system, MeDFAs also provided greater incentives to find a cure for chronic diseases.

2025 to 2030: Consolidation of the bioeconomy

Climate change, pollution, and population pressure on water and land resources reduced the quality of water supplies in many developing countries by 2030. This led to a higher incidence of some infectious diseases and greater dislocation of populations, which in turn led to an increase in TB. Global warming increased the possible geographical range of malaria, dengue fever and other diseases (Tong and Soskolne, 2007). Public health actions, including rigorous inspection of cargo to identify vector insects, prevented the spread of these diseases to developed countries. The cost of public health actions were kept low due to the development of automated non-invasive DNA probes to identify pathogens and vectors in people and cargo. The decline of new influenza epidemics from the automation of animal husbandry in South East Asia produced major health benefits.

Molecular biology advances such as viral coat protein technologies provided protection from viruses found in wheat, rice and potatoes. As a large percentage of the major and minor crops used in agriculture had known DNA profiles, some minor crops also benefited from virus reduction technologies. Additionally, the ability to transfer multiple genes through artificial chromosomes (Houben *et al.*, 2008) conferred resistance to both agronomic stresses such as heat, drought and salinity and to nematode, insect and fungal infections that had increased in frequency in the main global food crops (soybeans, maize, rice, wheat, and potatoes). As these resistance traits diverted plant resources from producing larger grains, beans or tubers, yields were enhanced when the resistance genes were turned "off". Farmers used automated biosensors and diagnostics to identify increasing agronomic stresses or pest infestations. Faced with a threat, farmers could use chemical sprays to selectively "switch on" specific resistance traits. These molecular biology and genetics advances enabled the agricultural sector to increase yields in the face of a range of stresses.

Increasing incomes in China, India and South East Asia had led to a large increase in demand for animal protein, particularly fish, meat and dairy products. This was exacerbated by the global decline of most wild fish stocks, which meant animal protein needed to replace part of the demand for protein that had formerly been met with oceanic fish. The loss of cheap sources of wild fish, particularly the collapse of the Alaskan pollock fishery in 2014, had also temporarily reduced aquaculture production for carnivorous fish species – such as salmon, tuna, cod, trout and prawns – that required fish protein. Several companies had invested in biotechnology research to produce fish proteins in GM algae, but it was not until 2019 that algal fish protein was available in sufficient quantity and at a low enough price to again support widespread aquaculture for carnivorous fish species.

The decline of fish stocks, although predicted as far back as the 1950s, was due to a continual failure to reach an enforceable international agreement to control overfishing. Careful genetic "fingerprinting" and tracking of remnant wild populations of tuna, cod, whiting, herring, salmon, sardines, pollock, haddock and other species were used to try to recover several fisheries.

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The concerns in the Malthusian years over the security of supply for food, feed, and biomass for biofuels and industrial feedstocks had diminished, partly due to new agricultural biotechnologies for high-yielding food crops and dedicated energy crops such as GM grasses and eucalyptus varieties. The other reason was a substantial increase in agricultural land in South America and Africa. The international community had failed in its efforts to set rigorous life cycle standards for the carbon production and source of origin of both agricultural products and biofuels; consequently, high demand for grain for livestock and feedstocks for biofuels escalated the conversion of vast swathes of tropical savannah and rainforest to agricultural and biofuel crops. Unfortunately this released enormous reservoirs of carbon, damaging efforts to control global warming.

Global prosperity depended on strengthened trading rules under the WTO. Neither of the two major Asian powers, China and India, was able to produce enough food and feed to supply its own domestic needs. Both were major importers of food, feed, and biofuels from South America, Africa and North America, and exporters of high-value-added manufactured products. To reduce political tensions, the Food and Agriculture Organization (FAO) was given a mandate to maintain high global food reserves. It was widely believed that a repeat of the disaster of the Malthusian years could result in war without adequate global food reserves and free trade in agricultural commodities.

High energy-density biofuels were produced either from cane species or from cellulosic fermentation of low-lignin GM varieties of fast-growing grasses and trees. Biofuel production in temperate areas was mostly produced from GM grasses grown on marginal lands in Russia, Mongolia and the northern plains of the United States and Canada. Biofuel was also produced from trees in a few temperate countries, such as New Zealand, with ample low-cost, renewable forest plantations. Otherwise, the economics of production strongly favoured sub-tropical and tropical regions with ample rainfall, where biofuel production was ten times higher per hectare from tropical eucalyptus plantations than from trees in temperate zones such as Europe.

Sophisticated biorefineries, concentrated in the warm high-rainfall areas of South America, Africa, South East Asia and the Southern United States, produced little waste and could flexibly switch outputs in response to market prices. In addition to biofuel, many refineries could produce high-value oleochemicals and biolubricants for the chemical and manufacturing sectors and bioplastics sought by the automotive and manufacturing industries. Several high-value complex chemicals were produced by micro-organisms, developed using synthetic biology.

Four US-Brazilian agro-industrial conglomerates were responsible for 70% of global production of biofuels and biochemicals. To ensure supply and reduce costs, these firms maintained extensive GM cane and tree plantations to feed their biorefineries. Biofuels supplied 6% of global energy demand and were almost entirely used for transport. The major low-carbon energy sources for electricity generation were from nuclear, solar, geothermal, tidal and wind power.

The Middle East was a centre of research for the production of hydrogen fuel, algal fuels and synthetic biology. The cost of algal biofuels had been falling rapidly, due to a technical breakthrough that prevented bacterial infestation of unicellular algal biofuel farms.

Fictional Scenarios to 2030

Several energy consulting firms estimated that hydrogen and algal fuels could be cheaper than biofuels produced from cane or wood by 2032. In response, the four US-Brazilian conglomerates were investing heavily in biotechnology research to improve the competitiveness of high energy-density fuels from cane sugar and cellulosic crops.

Biofuel production was insufficient to meet all transportation needs. Consequently, transportation varied according to the opportunities within each region. Electrified public transport systems predominated in cities. Lightweight private vehicles built of composite biopolymers could run on an electrical charge for short distances or on a range of biofuels for longer distances. Due to high carbon taxes, petroleum use in 2030 was limited to feedstock material for bulk chemicals, air transport, and the production of electricity in combination with carbon capture systems.

Energy conservation and a gradual redesign of the structure of cities to accommodate higher densities encouraged more exercise from public transit use, bicycling and walking. A small reduction in food consumption due to higher relative food costs and increased exercise as part of daily life reversed the obesity epidemic that was a major health concern in 2010. Public opposition in developed countries to higher health premiums for risky personal behaviours had also declined over time. Both private and public health insurance premiums included reductions for indicators of healthy lifestyles, such as weight, blood pressure and diet. These were verified by annual check-ups with family doctors.

By 2030, comprehensive medical records systems had been gradually introduced in most health jurisdictions. These records were analysed to identify optimal treatment therapies and genetic risk factors for many chronic diseases. MeDFA provided a functioning incentive system that had helped to improve research efficiency by encouraging collaboration. The lack of patents after market entry meant that all products funded by MeDFA were produced as generics, reducing the cost of medical technology. Consequently, the populations of many developing countries could afford recent innovations in pharmaceuticals, diagnostics and medical devices.

It was no longer possible to speak of separate health biotechnology and pharmaceutical sectors. Biotechnological knowledge was used in all new drug development and in the development of many medical devices. However, the focus of healthcare research had partly shifted from pharmaceuticals to regenerative medicine, diagnostics and surgical techniques. Several debilitating chronic diseases such as cardiovascular problems, diabetes and arthritis were treated with tissue regeneration based on stem cells. The discovery of biomarkers for some early-stage cancers and bionanotech imaging technologies to detect them before metastasis (the major cause of cancer mortality) had opened up new opportunities for treatment through microsurgery and drug delivery systems based on nanotechnology.

Biomarkers for early-stage cancers improved survival substantially, but they were expensive because screening had to occur on a population scale. This substantially increased diagnostic costs, as 100 individuals would need to be screened each year after age 40 to detect one early-stage cancer. Part of the cost of screening and regenerative medicine was balanced by a fall in costs for chronic care. Small savings were also made from genetic screening of embryos for inherited diseases and serious risk factors. This led to a precipitous drop in the number of

babies born with such diseases (Campbell, 2008), many of which had required costly long-term medical treatment. However, costs started to creep up as the public began to use genetic screening to detect minor "flaws" or risk factors for chronic disease. There were heated public debates over the types of genetic factors that would justify aborting an embryo.

The main drivers for a continuation of high healthcare costs were the increase in neurodegenerative disease due to ageing population structures in Europe, China and Japan, and the research and application costs for predictive and preventive medicine. Neurodegenerative disease was viewed as the new cancer – greatly feared and with no effective cure in sight, despite billions of dollars spent on public and private R&D to find treatments.

Predictive and preventive medicine had created some notable successes in addition to the identification of biomarkers for early-stage cancer. Doctors were able to identify a risk of developing rheumatoid arthritis and several other autoimmune diseases, and to delay onset by an estimated average of ten years. For other diseases, testing for genetic risk factors and biomarker diagnostics could predict the onset of disease several years before the appearance of symptoms, but there were no effective therapies to prevent the disease from developing.

A five-year national experiment between 2024 and 2028 with predictive and preventive medicine in Denmark identified serious problems with the concept. With the exception of screening for cancer and rheumatoid arthritis after age 50, the experiment was judged to have caused almost as much misery as good. Knowing that one was at risk for serious chronic disease later in life created anxiety and depression among a large percentage of the population. Due to the probabilistic nature of risk factors, more people received screening or preventive treatment than benefited, driving up costs.

Danish parents quickly refused to let their children be tested for anything but serious treatable diseases that would appear within two years. Research showed that people were seeking quality of life and peace of mind. The overly enthusiastic application of predictive medicine appeared to have seriously reduced both. Older people particularly feared a loss of independence, so learning about a high probability of developing a debilitating neurodegenerative disease frequently caused serious depression and a lack of motivation.

The Danish experiment sparked intensive discussion internationally. Ethicists asked if the limits of medical intervention in healthcare had now been reached, since most people did not want to know if they faced serious health problems in the future. Scientists noted that with time, successful preventive therapies would be found for many of the diseases for which prevention was nonexistent or only partly successful. Public health researchers responded that part of the effectiveness of preventive medicine to date for cardiovascular disease and several cancers had been due to changes to diet, exercise, sleep, and an active social life – factors that had been known about for decades. Furthermore, a doctor could easily detect these types of major risk factors without the use of advanced medical technology.

The results of the Danish experiment led to new regulations for predictive and preventive medicine in many countries. Doctors were only permitted to test for diseases that could be cured or significantly delayed. Tests for diseases that could not be treated, or where early diagnosis made no difference to outcomes, were prohibited in most countries, except for research.

Fictional Scenarios to 2030

Predictive and preventive medicine had been expected in 2010 to automate healthcare. The role of the family doctor would be changed, from one who practices the "art" of medicine to a technician who identified individually optimised and evidence-based therapies, using software that analysed genetic and other diagnostic test results, medical histories, and behavioural and environmental data. By 2030, all of these systems were in place. The ability of doctors to ignore mandatory treatment protocols had declined, due to greater enforcement in managed healthcare systems and a change in medical school curricula. Doctors had not been turned entirely into technicians, however, as they played a key role in encouraging and supporting lifestyle changes.

Many people were living longer healthier lives due to improvements in healthcare and lifestyles. The retirement age in most OECD countries had been increased in step with increasing longevity: it averaged 69 years in 2030, preventing the expected pension crisis. As had been expected in 2010, information technology products and disease management systems increasingly permitted the elderly to live at home longer. This provided some healthcare savings, given the high cost of long-term in-patient healthcare. Some aspects of home care, such as automated health surveillance systems, were poorly accepted at first because patients saw it as an intrusion on their sense of independence (Dinesen *et al.*, 2008). With time, and remarketing as virtual "Health Buddies", they were widely accepted.

Pollution of fresh water supplies and oceans remained a serious problem. Coastal China, Eastern India, and the Gulf of Mexico were among the most polluted bodies of water on earth. Both India and China were investing in bioremediation techniques, improved agricultural systems and water conservation technologies to increase fresh water supplies and clean up polluted oceans. GM marine plants were used to revitalise marine areas that had become "dead zones" through industrial pollution and agricultural runoff. The marine plants were mechanically collected as a source of biomass for chemical biorefineries.

Scenario 2 – Uneven Development

2009 to 2014: Mixed progress

Regulatory systems posed significant constraints and costs on innovation systems, particularly in health and primary production. The cost of meeting regulatory requirements reduced the ability of small health or agricultural firms to invest in innovation. Small firms needed to both own valuable patents and receive financial support from either venture capital or large firms. One problem was increasing corporate concentration, which reduced the number of large firms – particularly in agricultural applications that were interested in buying new technology. This was a significant barrier when new technology threatened an existing technology owned by one of the major firms.

One effect was slow technical progress in agricultural biotechnology to develop cellulosic fermentation processes that jeopardised existing investments in starch based biofuels. The production of bioethanol from maize in the United States had doubled between 2007 and 2012, while European production of biofuels accounted for 15% of EU crop production by 2013.

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Agricultural biotechnology for food and feed crops, controlled by five major global firms, was nevertheless a success. Food and feed production increased in South America, India and China due to new GM varieties of maize, wheat, rice and soybeans. However, European countries continued to place obstacles in the way of growing GM crops. That led to a major conflict with European livestock producers, who were paying increasingly higher prices for animal feed. This was partly caused by the high share of European crop production diverted to mandated biofuels, and partly due to a number of crop imports rejected at the border because of trace amounts of non-approved GM crops. The biofuel policy was highly controversial, with environmental NGOs arguing that European biofuel policy was contributing to rather than reducing global GHG production. A major cause was the destruction of tropical rainforests to create farmland for biofuel and other crops.

Agro-industrial firms in both Europe and North America had responded to biofuel mandates by investing in expensive infrastructure for crop-based biofuel production. They successfully lobbied governments to maintain mandates that favoured these biofuels. Slow progress in cellulosic fermentation research, combined with the low price support for cellulosic fuels in the United States and Europe, meant that cellulosic biorefineries were likely to be unprofitable for the foreseeable future. As a result, "green" investors in cellulosic biofuels shifted their investment portfolios to other energy sources, particularly solar, geothermal, and petroleum exploration.

In early 2014, under pressure from NGOs, the European Parliament ended all mandates for biofuels, although another explanation was a lack of public support for GHG initiatives after five years of below-average temperatures. A few months later the European Parliament accepted a plan to construct a network of nuclear power plants to supply 80% of the European Union's electricity. The announcement caused a sudden drop in petroleum and natural gas prices, due to expectations of a large future drop in imports from Russia. Agricultural commodity prices, in contrast, only dipped slightly after the end of the European Union biofuel mandate because of increased global demand for food and feed. As a consequence, the use of agricultural starches as a feedstock in Europe for industrial chemicals and polymers was replaced with petroleum feedstock.

A major development in health biotechnology occurred in early 2015, when two of the world's largest pharmaceutical companies and a major ICT firm formed a joint venture, TripleC, with the largest private healthcare provider in the United States, Consolidated Community Carers (CCC), serving 100 million people.[7] The venture had been initiated by CCC, which saw a major business opportunity in the FDA's requirements for compulsory post-marketing follow-up and pharmacogenetic information in clinical trials. The healthcare provider offered the two pharmaceutical firms full access to its members for clinical trials and use of its extensive medical records system, developed by the ICT firm. The medical records tracked patients as long as they were a member of CCC and contained information on prescribing histories, health outcomes, environmental risk factors such as diet and exercise and, increasingly, genetic information and biomarkers. In return, CCC demanded a 25% reduction off the lowest price agreement in the United States for drugs produced by the two pharmaceutical firms. An additional benefit, which was the main interest of CCC, was to be able to provide the highest level of care in the United States, and consequently charge an

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insurance premium over its competitors. The ICT firm was interested because of the potential market for automated diagnostic and home healthcare products.

As part of the agreement, CCC retained control over the types of pharmaceuticals, regenerative therapies and diagnostics that the two pharmaceutical firms would test on its members. This was to prevent the pharmaceutical firms from increasing costs to CCC by testing drugs with minor benefits over existing therapies. In addition, CCC would only be able to charge an insurance premium if it could offer better health outcomes compared to its competitors. It therefore had a strong economic incentive to encourage its two pharmaceutical partners to conduct research into therapeutically innovative therapies.

2015 to 2022: Turbulence

Overall, the world economy had experienced moderate economic development after the end of the global financial crisis in 2010, with rapid growth in China and India. Demand for energy, mineral resources and agricultural commodities returned to growth rates that were above the long-term trend. No agreement had been reached internationally on GHGs. Public interest in climate change had declined because temperatures had increased very little since 2007. Global scientists had warned in 2008 that this was only a temporary anomaly caused by a long cycle in the earth's orbit, and that it would end by 2020. This would be followed by a rapid increase in temperatures if GHG production was not reduced. This warning was believed in some capitals and ignored in most. Production of biofuels continued in the United States because of subsidies that were justified by energy security, and bioethanol continued to be profitable in Brazil without subsidies. Elsewhere there interest in biofuels and other low carbon energy sources declined.

On 11 September 2016 terrorists attacked three American oil refineries in Louisiana, Mississippi, and Texas, temporarily paralysing oil production in the United States. A fourth attack the next day in London released a suspected toxin that affected thousands of people with severe intestinal pains. None of the attacks caused any deaths. The cause of the intestinal illness was discovered within a few weeks to have been a synthetic bacterium, probably produced in a lab in the Western United States. Both events sent shock waves through the United States and Europe – partly because they were unexpected, since there had been no major terrorist attacks for years.

Governments were far more concerned about the attack on London than the oil refinery bombings. The use of a synthetic pathogen raised horrifying possibilities of what might be achievable with synthetic biology, and concerns that the comparatively harmless bacteria used in London was a signal of much worse to come.

These events caused an immediate shift in government priorities towards domestic security. All developed countries immediately introduced severe security restrictions on research into both synthetic life forms and GM. The high costs of meeting the security regulations caused most small firms active in agricultural and industrial biotechnology to abandon GM research. Between 2017 and 2025, the United States poured funds into biosecurity research to detect trace pathogens in agricultural commodities, water, and imported goods. The high salaries and research opportunities in biosecurity caused bioscientists who were previously active in

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industrial and agricultural firms to move to biosecurity research. Although developing countries, including Brazil, India and China, also introduced increased biosecurity measures, these were less stringent. Biotechnological research in the three countries was also dominated by government laboratories, where it was easy to implement improved security measures.

Concern over the ability of terrorists or pathogens to cross borders reduced international trade, particularly in agricultural commodities. The possibility of a deep economic depression in Canada and Mexico, both heavily dependent on trade with the United States, caused the two countries to agree to a NAFTA energy security zone. The goal – zero petroleum imports by 2025 – was met by a mix of energy conservation measures, expanded production from the Athabasca tar sands in Canada, and biofuel production.

Renewable biomaterials such as biodegradable oils, plastics, and industrial inputs received minimal attention in most developed countries. Governments were too distracted by fundamental concerns over security, and industrial firms faced serious difficulties in hiring bioscientists and in conducting biomaterials research. Interest in sustainable environmental practices and products remained at very low levels.

Research into biosecurity had several commercially valuable benefits. The development of water conservation and purification technologies for the purposes of domestic water security and industry development had positive impacts on agricultural production in several countries where droughts were common, including Australia, the United States, and Spain. New biosecurity technologies based on nanotechnology, biosensing, and molecular and genetic diagnostics benefited pest control programmes in agriculture, particularly for animals, but also for crops. A major benefit was the development of sensors that could instantly identify hundreds of varieties of microbes. These were widely used by doctors and in hospitals to identify sub-types of bacteria that were resistant to specific antibiotics and to determine if common ailments were caused by viruses or bacteria. These sensors turned into a front-line defence against the growing problem of antibiotic-resistant bacteria.

In contrast to these benefits, genetic modification of crops crawled forward in the United States under stringent new security regulations and a lack of bioscientists. Most agricultural researchers in academia concentrated on biosecurity. Only a few large firms remained active in GM crop development, and they concentrated on pest resistance. The production of pharmaceuticals or industrial chemicals in GM plants was prohibited in the United States and in Europe because of concerns that the technology might be used illegally by terrorists to produce poisons.

Consumers in developed and security-conscious nations looked for "local food" labels showing the distance travelled by a food commodity on its package. "Food miles" were displayed the distance food travelled from the time of its production until it reached the consumer. Although originally developed to assess the environmental impact of food, it was now used to assess its security, assuming that every unit of distance travelled increased its chances of being tampered with.

Patents for industrial, agricultural and security biotechnologies became increasingly expensive to maintain as the United States and European countries used the security clauses of the TRIPS agreement to block patents that could reveal any information of value to terrorists.

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China and India provided patent protection, but it was difficult to enforce. The loss of effective patent protection was another contributor to the failure of biotech solutions in agriculture and industry.

The health sector was largely protected from the problems affecting the agricultural and industrial sectors, due to more competitive salaries. Furthermore, the US government increased funding for health research in the identification and treatment of new infectious pathogens.

In 2020, the TripleC joint venture had been shut down by its participating partners. It was replaced with a merger between CCC and the ICT firm and a friendly takeover by these two partners of the two pharmaceutical firms. The decision to move to an integrated firm was partly driven by frictions between CCC and the ICT firm on the one side, and the two pharmaceutical firms on the other, over the development of expensive drugs that were not particularly innovative. There were also disagreements over the use of regenerative medicine, which had been an increasing success but which threatened some of the markets of the pharmaceutical partners. The merged company was led by the CEOs of CCC and the ICT firm. The new TripleC was able to assemble new technology, build new types of expertise, surmount regulatory barriers to innovation and develop its new competition model. It had become very profitable, although so far largely on the basis of adopting new medical devices and regenerative therapies.

After the announcement of the merger, demand for membership in TripleC soared, due to expectations of significantly better healthcare services compared to competitors. This permitted TripleC to raise insurance premiums further. Due to logistical costs the business model was based on an upper limit of 100 million members, so there was no incentive to expand. Furthermore, the model depended in part on cherry-picking the healthiest Americans to reduce medical costs. The US Congress had banned health providers from requesting genetic information from potential patients. TripleC, however, was able to effectively screen its membership for the most expensive chronic diseases through routine medical check-ups and membership agreements to maintain weight within reasonable levels and follow age-adjusted exercise programmes. The firm avoided legislation in several states that prohibited insurers from refusing coverage by moving its head offices to Arizona.

Once accepted, new members underwent genetic screening to identify potential risk factors for chronic disease. This information was used both to design compulsory individual lifestyle programmes and in therapeutic research programmes.

The model in the United States was successfully copied in India and China, countries with poorly developed public healthcare systems and a burgeoning number of private sector healthcare firms. China's main healthcare firm was created out of a merger between a healthcare provider and several firms active in regenerative medicine, while the Indian firm followed the American example and was based on a merger between a pharmaceutical firm, healthcare provider, and an ICT firm. These firms and their business models were called Networked Health Providers (NHPs). The NHPs were leaders in translational medicine. With a large membership base and their own hospitals, they offered academics excellent facilities and access to their information databases.

Fictional Scenarios to 2030

While the profit base of any individual pharmaceutical in the portfolio of a NHP company was not comparable to that of a blockbuster drug, the co-ordination of a range of drugs and therapies proved to be a viable business model. The structure was also more effective than public agencies such as NICE in the United Kingdom in controlling excessive drug costs.

The fact that the main route to market for healthcare products was increasingly mediated and brokered via the NHPs meant that small health biotechnology firms could succeed financially with a much wider range of innovation strategies than was the case in 2015. Drug development no longer dominated health biotechnology; there was an equal focus on diagnostics and regenerative medicine. The fruits of public and private investment in life sciences began to emerge in new and often unexpected ways, stimulated by new types of partnership bringing together companies and individuals with biochemical, chemical, IT, physics and engineering expertise. NHPs sold therapies to each other, to public health systems, and to other private healthcare firms.

The NHPs benefited from an FDA requirement for pharmacogenetics to be used in clinical trials. The technology helped to identify ineffective drugs at an early stage of clinical trials, saving money. However, pharmacogenetics also led to a significant increase in the number of new innovative drugs on the market, stimulating a new round of basic research into new drug targets.

2022 to 2030: Partial recovery

In 2022 biotechnology was widely used in health and in biosecurity, but its application to industry and primary production was limited in developed countries. This was due to the high cost of meeting biosecurity rules, a lack of technological breakthroughs despite early promises and expectations, and a shortage of scientific researchers interested in either of these two applications. The European Union still banned GM crops. Science students were more interested in new challenges in nuclear, geothermal and solar research.

There were some successes. Brazil had developed economically competitive biorefineries for both biobutanol and bioplastics by 2025. Brazil benefited from the expertise of European enzyme companies that had moved most of their research operations to Brazil, China and India after the European and American restrictions on research into synthetic biology and GM organisms in late 2016. Researchers in India and South Africa had developed photosynthetic protein arrays on metallic frameworks that could efficiently produce solar electricity.

Industrial bioprocessing was centred in Brazil and India. Bioplastics were the biggest success of industrial bioprocessing and replaced most of the petroleum-based plastics globally, especially in Asia. Production was cheap and based on GM plant and microbial processes. Production used closed loop systems that recycled waste into feedstock. Microbes were also used to recycle bioplastics and bioplastic-containing products. Any form of waste was regarded by Brazilian and Indian researchers as a challenge to develop a microbial solution to waste recycling. Metabolic pathway engineering had a large part in developing this aspect of industrial biotechnology. The method, combined with synthetic biology, was used to develop microbes that could extract valuable metals, including uranium, from seawater.

Fictional Scenarios to 2030

Sustainable economic development in 2022 was patchy. Some regions, such as Europe and China, had invested substantially in nuclear power, ostensibly to reduce GHGs but also for energy security. GHG production in the NAFTA countries had increased due to extensive exploitation of tar sands, but conservation, as part of an energy security strategy, had mitigated the worst effects. Brazil, South Africa and India were the most carbon-neutral major economies, due to biofuels in Brazil and solar energy in South Africa and India.

Concern over GHGs and climate change grew into a serious global issue again by 2027, due to seven consecutive years of accelerated global warming. The increase in high temperatures and drought renewed interest in using GM technology to develop stress-resistant crop varieties. There was persistent lobbying of governments to simplify biosecurity legislation. China and India were first movers in this area, since they were increasingly concerned about the effect of increasingly erratic grain harvests in South America and Africa, their major source of grain imports.

The large increase in intensive dairy production in both China and India had allowed brucellosis, and in particular TB, to become major diseases of concern. Intensive hog production in South East Asia also resulted in an influenza outbreak in 2023. All of these emerging pandemics, including African Swine Flu in Kenya, were rapidly identified and contained, using real-time diagnostics and rapid response recombinant vaccine production methods developed as part of biosecurity research. Recombinant vaccines for livestock diseases were widely used. Some of these vaccines were produced in large quantities by the governments of China, Thailand and Vietnam, and used to inoculate livestock herds and human populations in South East Asia.

Biotechnologies for defence and health security applications (such as nanotech and biosensing) received further investment to support food security and traceability applications. For example, nanotech and biosensing technologies merged to provide biosensors capable of identifying nanoparticles of a pathogen or contaminant in crop or livestock shipments. Other technologies included skin tag scanners that identified livestock varieties within seconds, and microchips and accompanying scanners that provided a detailed history of individual animals and food products.

Up until 2028, biotechnology R&D was more extensively used for livestock than for crops, with marker-assisted selection and cloning used to develop disease-resistant varieties of livestock. An important area of research was the genetic sequencing of commercially valuable plant and animal species and of agricultural pests. The main motivation was to permit the rapid development of treatments for future crop and livestock diseases.

Global databanks of plant and animal DNA were maintained by the FAO and the National Institutes of Health (NIH) in the United States as part of biosecurity. The knowledge was applied in the 2020s to prevent illegal trade in biological materials. Illegal logging of natural forests had been virtually stopped by FAO monitoring systems, using biosensors that could identify illegal wood varieties and other plant products.

Some developing countries, particularly in parts of Africa, continued to struggle with periodic outbreaks of serious disease in farm animal populations. The continual pressure for increased productivity to feed a burgeoning population, together with pressure on land and

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water resources, resulted in stressed animals and poor management. These factors made disease outbreaks more likely. However, the eradication of rinderpest and the availability of better disease control through improved diagnostics and vaccines meant that eastern and southern Africa could compete with South America for meat production. As with South America, most of the animal products were exported to Asia.

European countries with public health systems were slow to adopt an integrated health system due to concerns over potential conflicts from a closer working relationship between for-profit firms and public health services. Consequently, European pharmaceutical firms struggled with funding, although they were able to benefit from pharmacogenetics and RNA interference in drug discovery. In addition, all drug firms in developed countries suffered from restrictions on the use of GM technology and synthetic biology to produce drugs. This had blocked low-cost production of complex biological and chemical molecules, increasing costs. In some cases, drugs could only be produced economically in India, where these technologies were still permitted.

The major success of the health NHPs had created new problems and threats to their business model by 2030. NHPs benefited from being able to charge high premiums for superior health services. This had helped to create a highly visible two-tier health system in the United States, China, India, and even the United Kingdom, where the National Health Service had evolved into a public-private NHP hybrid. A large fraction of society that could not afford to join NHPs was covered by "second class" traditional healthcare providers. These organisations had to purchase many new therapies from NHPs at high prices. In response to an ongoing political debate over NHPs, several developing countries with publicly funded healthcare systems were threatening in 2030 to invoke the opt-out clauses of TRIPs to produce patented therapies at low cost, instead of purchasing them from NHPs.

Notes:

1. As an example, bevacizumab extended median survival for colorectal cancer by 1.8 months, from 10.7 months to 12.5 months (NCI, 2005).

2. This trend was already visible in 2007. See Grésillon, 2008.

3. Intragenics uses GM technology to transfer gene constructs between plants that can interbreed under natural conditions.

4. 2005 USD, unadjusted for purchasing power parity.

5. 2005 USD, unadjusted for purchasing power parity.

6. Many of the characteristics of the treaty are derived from Love and Hubbard, 2007.

7. This example, and its continued development below, is inspired by the health scenario elaborated by Tait *et al.*, 2008.

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Chapter 8

Policy Options for the Bioeconomy: The Way Ahead

The social and economic benefits of the bioeconomy will depend on good policy decisions. The required mix of policies is linked to the potential economic impacts of biotechnological innovations on the wider economy. Each type of innovation can have incremental, disruptive or radical effects. In many (but not all) cases incremental innovations fit well within existing economic and regulatory structures. Disruptive and radical innovations can lead to the demise of firms and industrial structures, creating greater policy challenges, but they can also result in large improvements in productivity. This chapter identifies policy options to address challenges in primary production, health and industrial biotechnology. It also looks at cross-cutting issues for intellectual property and for knowledge spillovers and integration, global challenges, and the need to develop policies over both the short and long term.

Primary production provides a diverse range of policy challenges. Examples include the need to simplify regulation, encourage the use of biotechnology to improve the nutritional content of staple crops in developing countries, ensure unhindered trade in agricultural commodities, and manage a decline in the economic viability of cool-climate forestry resources for low value commodities such as pulp and paper. The main challenges for health applications are to better align private incentives for developing health therapies with public health goals and to manage a transition to regenerative medicine and predictive and preventive medicine, both of which could disrupt current healthcare systems. Industrial biotechnology faces multiple futures due to competitive alternatives from both outside and within biotechnology. Policy needs to flexibly adapt to different outcomes and prevent "lock-in" to inferior technological solutions.

The "probable" bioeconomy of Chapter 7 is based on expected technological progress and current business models and policies. It should provide commercially valuable products and processes for primary production and industry and improved health therapies. Due to high costs, new health therapies will most likely be limited to high income countries and to better-off individuals in other countries.

However, the bioeconomy could provide much greater socio-economic benefits than those described in the "probable" bioeconomy estimate of Chapter 7. For example, in the field of health, safe and effective therapies could delay the onset of chronic disease and fall within the financial means of a large share of the global population. In a world of growing demand for natural resources, biotechnology could dramatically increase the production of food, animal feed, fibre and energy, reduce the environmental costs of increasing production, mitigate some of the harmful effects of climate change, and reduce greenhouse gas emissions.

Achieving the full promise of the bioeconomy by 2030 requires a policy framework that can address technological, economic and institutional challenges. Some of the solutions will require adjustments to policies that support public and private research and collaboration, training of scientists, capital markets, appropriate intellectual property rights, competitive product markets, regulation to minimise risk, and a dialogue with the public on the benefits of biotechnology.[1] Other areas of biotechnology will not develop their full potential without major policy interventions and new policy mechanisms.

Why should governments provide long-term policy support for an emerging bioeconomy? The main rationale is the large potential of biotechnology to create new markets and to improve productivity, health and environmental sustainability. There is also an ethical imperative to support the bioeconomy. As noted in a 1999 report by the Nuffield Council on Bioethics,[2] a lack of support for biotechnology could result in the failure to develop improved crop varieties that would benefit the world's poor. The same principle applies to health applications, where biotechnology could help develop affordable antibiotics and other pharmaceuticals with significant therapeutic advantages over existing treatments.

The required mix of policy interventions is linked to the potential impacts of each biotechnological innovation on the wider economy. As with all innovations, new biotechnological products and processes can have incremental, disruptive, or radical effects on other economic activities (see Box 8.1). Each type of effect creates a different set of challenges for policy and for business models.

Box 8.1. **Types of innovations**

Innovation involves the introduction of a novel product or process onto the market. Innovation theory has long recognised that the characteristics of an innovation can influence its effects on the market and broader economy. Depending on these characteristics, an innovation can potentially have incremental, disruptive, or radical economic effects.

Incremental innovations are based on scientific discoveries within a well understood technological paradigm. Their socio-economic effects are largely predictable. An example is the gradual increase in crop yields over the past few decades or the steady increase in survival rates for cancer due to improved diagnostics and prescribing practices.

Disruptive innovations provide entirely new ways of performing a task, such as replacing petroleum feedstock to produce polymers with biomass. These innovations require a new knowledge base and can entirely displace an existing technology, causing the disappearance of firms that are unable to fully exploit the new knowledge. The specific effects of disruptive innovations can be difficult to predict in advance, but they are likely to create economic winners and losers.

Radical innovations are infrequent and, in addition to requiring new knowledge bases, they require new infrastructures and/or new organisational structures. Once these are in place, radical innovations can boost economic productivity. Historic examples include the shift from steam power to electricity and from post, telephone, and television communication systems to the internet. Radical innovations can have substantial and far reaching impacts on society and the economy that are impossible to predict. Two radical innovations that could emerge out of the bioeconomy are predictive and preventive medicine and new microbial production systems for chemicals and fuels based on metabolic pathway engineering and synthetic biology.

The time required for each of these three types of innovation to affect the economy varies. Incremental innovations generally diffuse rapidly throughout an economy because they fit within existing production systems. Disruptive innovations can diffuse very quickly, as with radio, or much more slowly, as with recombinant DNA technology. Radical innovations usually require decades before reaching their full potential to shape economies.

Source: Based on Smith, 2008.

Incremental innovations can create policy challenges by blocking the development of alternative technologies that offer superior economic or environmental benefits. Disruptive innovations are based on new knowledge that replaces existing technologies, leading to the demise of firms and industrial networks that are unable to adapt to the new technology. One policy challenge is to craft sufficiently flexible regulations and institutions to support new technological developments. Radical innovations are built on new knowledge bases, as with disruptive innovations, but they also require

new infrastructures. A transition from one infrastructure to another can be very difficult and costly, posing further policy challenges.

Each type of innovation is also dynamic. Biotechnology was originally based on recombinant DNA techniques that modify the genetic structure of micro-organisms to produce pharmaceutical compounds or plants with novel traits. These recombinant techniques were initially disruptive because of the difficulty in acquiring the necessary knowledge and expertise to use them effectively. This threatened the business models of existing agricultural and pharmaceutical firms. These disruptive effects are now largely over. Large pharmaceutical firms developed the necessary capabilities to use this technology, while agricultural seed firms that were unable to use it to their advantage were taken over by the limited number of major seed firms that could.

Biotechnological research continues to generate new technologies with the potential for disruptive or radical effects on the economy. Table 8.1 provides examples of incremental, disruptive and radical biotechnologies that could shape the emerging bioeconomy of 2030. Radical innovations that disrupt existing businesses and call for major investments in new infrastructure or organisational forms are both infrequent and often difficult to identify in advance. Consequently, the examples in Table 8.1 of radical biotechnological innovations are only suggestive. Nevertheless, the potential of radical innovations to render both existing industrial networks obsolete and to boost future productivity warrants careful evaluation. One appropriate tool might be the further development of foresight research.

This chapter identifies eight general approaches to policy that governments can use to help maximise the benefits of the emerging bioeconomy (see Box 8.2). Many of these approaches can be applied to each type of innovation identified in Box 8.1. As noted in Chapter 5, for instance, public sector support for R&D (research subsidies) lies behind the development of all types of biotechnological innovations.

Table 8.1. **Examples of incremental, disruptive and radical innovations for the bioeconomy to 2030**

	Incremental	Disruptive	Radical
Primary production	Improved yield, product quality, stress tolerance, and pest resistance for food, feed, and fibre crops. Improved varieties of livestock, farmed fish, and beneficial insects such as bees. Inexpensive diagnostics for immediate identification in the field of a range of plant and animal diseases or invasive species in cargo or transport vehicles. Functional foods, particularly enhanced staple crops for developing countries.	Foods (nutraceuticals) tailored to genetic subgroups to reduce the risk of developing chronic diseases. GM plants or micro-organisms to provide fish protein for aquaculture. Cellulosic biofuels based on specially tailored non-food crops. Enhanced tree species for tropical and sub-tropical climates.	The integration of primary production and industrial processing based on biorefineries that produce a wide range of end products (*e.g.* food, fuel, materials, chemicals) from a range of biomass feedstocks could require new infrastructure or organisational changes.
Health	A steady stream of new small molecule drugs, biopharmaceuticals, and recombinant vaccines. Identification of harmful genetic mutations *in utero*. Diagnostics for most chronic and infectious diseases.	Pharmacogenetic information used in a large percentage of drugs and treatments. Regenerative therapies based on stem cells and tissue engineering that provide new treatments and some cures.	Preventive medicine in which risk factors for diseases can be identified years in advance and effectively treated before onset of symptoms, using predictive and preventive treatment based on validated biomarkers to track progress and identify required lifestyle changes.
Industry	Improved enzymes for industrial processing.	Environmentally sustainable methods of biofuel and chemical production using cellulosic feedstock, production of high energy-density biofuels from sugars.	Production of a wide range of chemicals and high energy-density biofuels using micro-organisms or simple plants developed through metabolic pathway engineering or synthetic biology.

Box 8.2. Some policy approaches and tools for the emerging bioeconomy

1. **Research subsidies**: Uses public resources to generate knowledge inputs such as private and public sector research and development and human resources through the education of researchers, scientists, technicians, etc. This could include both mission oriented research to support a specific technology and multidisciplinary research.

2. **Market creation**: Puts in place an incentive structure that could include, among other things, procurement guidelines, production subsidies, pricing incentives, trade barriers (either their establishment or removal), and competition policies.

3. **Regulations/standards**: Mandates actions concerning safety, product registration, advertising, environmental mandates (*e.g.* tradable carbon markets, life cycle assessment), etc. This can also be a tool for *market creation*.

4. **Infrastructure investment**: Creates the underlying framework for systems such as for public healthcare, collaborative science, databases, transportation, energy production and distribution, etc.

5. **Institutional changes**: Modifies the rules for collaboration, trade, knowledge market transactions, etc.

6. **Foresight research***:* Maps the links between evolving research programmes (including targeted and multidisciplinary research), regulatory frameworks, policy initiatives, and the development of new technologies.

7. **Public forums***:* Engenders public discussion, debate, and education in areas such as ethics, benefits and risks, and the utility of biotechnology.

8. **Development commitments***:* Applies financial and other support (technology transfer, collaboration between universities, etc.) to developing countries. This includes initiatives like the United Nations' Millennium Development Goals.

In some cases, however, a specific policy approach could be most effective for one specific type of innovation. Due to the infrastructure changes associated with disruptive and radical innovations, a successful transition to their use will often require more public support for *market creation*, *foresight research*, and *infrastructure investment* than for incremental innovations.

This chapter evaluates some of the underlying policy issues that are raised by biotechnological innovations in health, primary production, and industrial applications and examines cross-cutting policies that could support all applications of biotechnology. For each application, the text identifies policies, drawn from the framework in Box 8.2, to address current and future challenges. The aim is to provide a toolkit of possible options for managing the emerging bioeconomy. Many of these policy approaches cover the same ground. An overarching policy framework is therefore likely to contain elements from several of the approaches in Box 8.2.

Primary production

Biotechnology for primary production includes GM and non-GM technologies (*e.g.* marker assisted selection, intragenics, gene shuffling, and directed evolution) for developing new varieties of plants and animals, diagnostics for plant and animal diseases, and a range of smaller market applications such as animal therapeutics and functional foods and nutraceuticals.

Many of the applications of biotechnology to primary production are incremental innovations, such as crop plants with improved characteristics that replace previous varieties of the same crop. Several biotechnological products could have disruptive effects on existing supply chains. These include pest resistant crops that could disrupt the business of pesticide manufacturers or GM plant-based fish feed that replaces fishery sources. Since almost all primary production biotechnologies involve improvements to existing goods, it is difficult to envisage a radical change in primary production up to 2030. However, greater integration between industrial processing and primary production could be a radical innovation as it would probably require substantial new investment in an agro-industrial infrastructure. This possibility is covered below, using the example of biomass-based biofuel production.

Incremental advances in primary production biotechnology

Plant breeding applications of biotechnology (both GM and non-GM) are a major success. The analysis in Chapter 4 of short-term trends indicates that this success will continue as new food, feed and fibre crops with improved stress tolerance, pest resistance, and quality traits reach the market over the coming decade. Policy issues for incremental innovations concern the regulation of risk, promoting research for small market crops, encouraging market incentives for crop traits that deliver greater productivity and quality, verifying the health benefits of functional foods

and nutraceuticals, and maintaining trade in primary production commodities.

Regulation

Technological development in modern societies requires regulatory frameworks that ensure safety and public acceptance of technological advances. Regulatory systems provide a framework for risk assessment and management associated with biotechnology. Approaches to regulating technological risk are founded on evidence based evaluations as well as citizen perception. Coupled with dialogue between all stakeholder groups, a continual evolution of these approaches is an essential feature to ensure the uptake of safe and effective technology breakthroughs.

The main disadvantage of the current regulatory structure for biotechnology in primary production is its cost. Current regulations require environmental and health safety studies for GM varieties, at a cost between USD 0.5 million and USD 15 million per variety. These costs reduce the economic viability of using GM technology to develop improved small market crops and are a major market barrier for small firms. Most regulatory systems, such as in Europe and Australia, focus on transgenic varieties and do not require environmental and health studies for varieties developed through non-biotechnological methods such as mutagenesis, or biotechnological methods such as intragenics that do not transfer genes across species (Russell and Sparrow, 2008). Canada is an exception, applying the same regulations to all new plant varieties with novel traits, regardless of the method used to develop the variety.

A more consistent approach would require all registrations of commercial plant and animal varieties with novel traits to meet environmental and safety regulations, with the possible exception of varieties developed using conventional breeding methods alone. However, the cost of meeting safety regulations needs to be significantly reduced so that it is financially feasible to use advanced biotechnologies to develop improved varieties of small market crops. Costs could be reduced through international agreement on safety research standards, so that research conducted in one country is readily acceptable in another country. A similar approach has been successful for chemicals, where common tools and policies for environmental and safety regulations (including an approach for mutual acceptance of safety data) amongst OECD countries result in annual savings to government and industry of over USD 65 million (OECD, 1998).[3]

Within the OECD, 14 consensus documents, which are agreed texts that set out scientific information on the components of specific crops (*e.g.* key nutrients, toxicants, anti-nutrients and allergens), have been produced. Their

value lies in their portability – they can be applied across national borders as "mutually agreed" evidence for use during the regulatory review of human food and animal feed safety, thus saving time and substantially lowering costs. Although a positive step, further harmonisation is required to reduce the regulatory costs associated with developing GM plant varieties. A reduction in regulatory costs is not, however, likely to be sufficient to encourage research into small market crops.

Small market crops

The use of GM technology to introduce a set of genes for a valuable trait into multiple varieties of plants and animals gives a competitive advantage to large firms that own elite germplasm[4] for a range of commercially valuable varieties and species (economies of scope) and lowers the cost of each transgene or intragenic event (economies of scale). This has driven mergers and acquisitions and reduced the economic viability of small firms active in major crop varieties (see Chapter 6). A policy challenge that is especially pertinent to development goals is to encourage the diffusion of genetic biotechnologies to small market crops. This could require reducing regulatory costs (as noted above), encouraging collaboration (including with regards to intellectual property) and maintaining the active involvement of the public research sector to identify markers and possibly develop varieties to the proof of concept stage. The fact that public research in GM has fallen precipitously in Europe since the late 1990s (see Box 5.2 in Chapter 5) is a highly unfavourable development that could reduce both leading-edge research in this technology and the number of graduates trained in the use of advanced agricultural biotechnologies.

Functional foods and nutraceuticals

Functional foods provide health benefits beyond basic nutrition. Nutraceuticals are food supplements, based on products isolated or purified from plants or animals, with known or assumed health benefits. Both have been available for decades, such as vitamin D fortified milk or cod liver oil. Biotechnology can play a role in both functional foods and nutraceuticals, such as developing varieties of staple crops with high levels of essential minerals or nutrients or the production of nutraceuticals such as omega-3 oils.

The main policy interest in functional foods and nutraceuticals is their possible health benefits. Well-designed clinical trials have not verified the health claims for many nutraceuticals, such as the claimed benefits of lycopene or anthocyanins in preventing cancer, glucosamine in reducing the effects of osteoarthritis (Hayden, 2008), or pro-biotics in improving general

health. Conversely, there is some evidence to support the health benefits of omega-3 oils. In many countries, including the United States, manufacturers are able to make qualified claims for these products, such as "some evidence suggests that", even when the evidence is very weak. This reduces the incentive to invest in proving health claims. In addition, the market for many functional foods and nutraceuticals is rarely large enough to support the cost of well-designed clinical trials. Advances in functional foods and nutraceuticals could depend on financial support for public research institutes to conduct trials to verify health claims.

In developing countries, using biotechnology to develop nutritionally enhanced varieties of staple crops such as cassava, maize and rice could be a cost effective method of supplying key minerals and vitamins to poor populations that cannot afford a nutritionally diverse diet.

Trade

Although not directly linked to biotechnology, unimpeded trade in agricultural commodities will be essential to the bioeconomy of 2030. India and China will run large deficits in agricultural products and will need to import food and feed, with South America and parts of Africa developing into major sources of these commodities.

Trade regulations for GM crops can close markets for exporters and increase costs for farmers and food processors in importing countries. These regulations have been a subject of serious discussion within regions that have not adopted GM crops on a large scale. There have been concerns about cost increases associated with the rejection of shipments of feed grain that contain even trace amounts of non-approved GM varieties. The problem becomes particularly acute as new varieties of GM crops are developed and cultivated without corresponding regulatory approvals in importing regions. This could increase the cost of sourcing approved livestock feed in countries or regions (such as the European Union) that limit GM technology.

Box 8.3. **Managing incremental biotechnologies for primary production**

1. **Research subsidies** and **Institutional changes**: The application of biotechnology to the development of crop varieties with small markets will probably require public support for applied research. This could include publicly funded translational research up to the proof of concept stage, research consortiums with public and private players, or policies to reduce intellectual property and regulatory costs.

2. **Research subsidies** and **Development commitments**: An effective health promotion strategy relying on functional foods and nutraceuticals will necessitate verified health benefits. In cases where clinical trials are needed to prove the veracity of health claims, public support may be required. To deliver on nutritional goals in developing countries, applied research to develop varieties of staple crops with improved nutrient levels, and the distribution of these varieties to farmers, should be supported.

3. **Market creation**: Trade in primary production commodities is and will continue to be an important tool to reduce frictions over access to resources. Policy should ensure open trade for food, feed and fibre and maintain adequate stockpiles of essential food products.

4. **Regulations/standards**: Regulations governing new plant and animal varieties may need to be modified to ensure the effective management of environmental and safety risks at minimal cost and delay. A potentially powerful tool, to this end, would be the adoption of internationally accepted protocols for establishing safety so that tests do not need to be repeated in each country. Regulatory costs for small firms (so they can compete) and for small market crops (so that new varieties are developed) could also be reduced. Another option is to implement a sliding scale for testing, with fewer tests required to establish safety for well-understood traits.

Disruptive primary production biotechnologies

Several biotechnology innovations in primary production could have disruptive economic effects by displacing other production methods: production of fish protein in GM plants or micro-organisms to replace wild fish for aquaculture, foods that reduce the risks of developing chronic diseases, enhanced varieties of trees for tropical and sub-tropical regions for producing pulp and paper or biofuels, and enhanced varieties of many feedstock crops to replace fossil fuels in chemical and plastics production.

A major environmental disadvantage of aquaculture for carnivorous species such as salmon, shrimp, tuna and cod is that they are fed fishmeal and fish oil obtained from wild fisheries. Even herbivorous fish such as tilapia and carp are fed these products to accelerate growth. Fish oils and other products for aquaculture can be produced in GM plants and micro-organisms. This disruptive innovation could replace wild fish feed with plant based products and reduce the pressure on wild fish stocks.

Predictive and preventive medicine could benefit from foods or nutraceuticals to delay or prevent chronic disease.[5] This will require good evidence for their health effects, as discussed above. If effective, it could reduce the necessity for some pharmaceutical products and reduce healthcare costs.

With adequate water, biomass production per hectare in sub-tropical[6] and tropical regions is between four and ten times the production in temperate regions, due to warmer temperatures (Larson, 2008).[7] This difference should provide a large competitive advantage to sub-tropical and tropical regions for growing low-value crops for pulp and paper, other fibres, and biofuels. Low latitude desert regions close to the ocean can be extremely productive areas for producing crops from marine species of algae. Consequently, research into these and other crops is likely to shift to varieties than can be grown in productive climatic regions. This could have serious disruptive effects on the competitiveness of forestry firms based in Northern boreal forests. These regions may need to increasingly switch to higher value wood products.

Box 8.4. **Managing disruptive and radical biotechnologies for primary production**

1. **Research subsidies** and **Market creation**: Policies may need to be diversified to support research into disruptive biotechnologies for primary production with established benefits for environmental sustainability. Support options include research and procurement subsidies and support for free trade in environmentally sustainable products.

2. **Foresight research**: Sectors facing disruptive change (fish feed for aquaculture or pulp and paper in boreal forests) should be encouraged to develop new business models and shift investment to new markets, supported by foresight research.

Key uncertainties for primary production

Public acceptance of biotechnological methods for developing new varieties of plants and animals is a key uncertainty for primary production. As with computers in the 1970s,[8] public acceptance of a new technology often depends on perceived personal benefits. A common view is that public acceptance of transgenic breeding methods will increase when new products with quality benefits for the consumer reach the market, such as nutraceuticals or healthier functional foods. However, the main market for quality traits is likely to be for crop varieties with improved food processing characteristics, with low visibility for consumers.

This does not mean opposition to transgenic crops in regions such as Europe will be unending. Public opinion could change if biotechnology produces environmental benefits and is shown to help maintain or increase yields in the face of greater stresses from climate change. Such a change in public opinion has already occurred in Australia (Eureka Strategic Research, 2007), driven by public awareness of the effect of long term drought on agriculture. Acceptance of GM in many countries could improve if the public is aware of successes in developing nutrient enhanced food crops for developing countries, crop varieties that reduce the need for environmentally harmful fertilisers and pesticides, or varieties that tolerate drought or salinity, thereby increasing food security in some regions. Public opposition to transgenic and cloned animals in developed countries is likely to continue, possibly beyond 2030, due to a combination of ethical concerns and uneasiness about the idea of transgenic or cloned meat.

Other uncertainties for primary production include the factors that influence production choices. Farmers decide what to plant and where in response to fluctuations in prices and markets. Political concerns, such as recent debates focusing on food versus fuel, can also play a role. These production decisions, which are difficult to forecast more than a year in advance, will affect supply and demand conditions and influence the types of crops that are grown. This could affect the market for biotechnology over the short term (up to 2015), but over the longer term an increasing share of all new crop varieties will be developed using biotechnology. Therefore, the impact of crop prices on the market for varieties developed through biotechnology will decline.

Box 8.5. **Managing key uncertainties for primary production biotechnologies**

1. **Public forums**: Better education on the benefits of biotechnology, perhaps through the involvement of scientists, could help address public concerns over the application of biotechnology to primary production. This method has often been rejected because of concerns that a lack of understanding is not the cause of opposition to new technology. Nevertheless, opinion research (see Chapter 5) shows that public attitudes do respond to information. Public opposition to agricultural biotechnology is also based on concerns over the concentration of ownership of plant varieties in a few firms and intensive farming practices. Forums and other methods of fostering public discussion on expectations for agricultural production systems may help, in part by clarifying the roles of biotechnology and intensive farming in food production.

Health applications

This report considers several possible futures for health biotechnology in developed countries. The first is incremental change based on the annual market approval of a moderate number of new pharmaceuticals and therapies, the gradual implementation of pharmacogenetics: (first to increase safety), improved diagnostics for diseases and for genetic susceptibility to chronic disease, and several improved therapies to treat genetic diseases. This future is a continuation of the estimated supply of new therapies up to 2015 discussed in Chapter 4.

A second possible future includes the success of disruptive technologies based on regenerative medicine such as tissue engineering, stem cell treatments, and gene therapies that offer temporary or long-term cures for chronic disease. Many of these are experimental technologies that are in the research phase, with very few successful therapies having received market approval by early 2008. They are often disruptive technologies. By curing rather than treating diseases, they could replace markets for pharmaceuticals, such as insulin, that treat long-term chronic disease. In addition, their mode of delivery to patients will differ from the delivery system for pharmaceuticals, possibly disrupting how health services are provided.

A third possible future includes both a continued supply of new therapies and the introduction of regenerative medicine, along with the

implementation of radical innovations to support a predictive and preventive healthcare system. This future offers potentially significant improvements to the quality of life by reducing the number of years living with a disability. It could also add several years to the expected baseline increase in life spans of 1-1.5 years per decade.

The first future, based on incremental innovation, will develop under the current healthcare system in developed countries, although there is room for improvement. However, the second and third futures, which potentially offer greater health benefits, could require new policies to support changes in research, business models, institutions, and the infrastructure for healthcare.

Incremental advances in health biotechnology

Long before 2030, almost all pharmaceuticals, as well as therapies based on regenerative medicine, will be developed using biotechnology. Therefore, the regulatory system for all pharmaceuticals is an integral part of the policy agenda for the bioeconomy. Other regulated therapies such as medical devices are also likely to be influenced by biotechnology, though to a lesser degree. One of the main policy challenges is to improve the cost-effectiveness of new therapies. This requires a better alignment between private sector incentives and public health goals (Kaplan and Laing, 2004; Morgan *et al.*, 2006, 2008) and policies to ensure that this alignment supports disruptive and radical innovation.

Despite a number of major therapeutic advances, investment in health biotechnology has been criticised as inefficient (Ernst and Young, 2008), both in terms of the cost of developing new therapies and the aggregate therapeutic benefit obtained from private and public R&D expenditures. Policy papers on drug development costs frequently cite average private sector costs per new pharmaceutical of between USD 800 million and 1.3 billion. Although these could overestimate the actual cost,[9] drug development is clearly expensive and is partly responsible for the high prices of many new drugs. Yet expensive drugs do not always provide major therapeutic advances, as discussed in Chapter 3. Approximately two-thirds of all new drugs applications to the American FDA from 1993 to 2004 are classified as "me too" drugs that offer only small improvements over existing treatments. Furthermore, the cost-effectiveness of drug development, measured by R&D expenditure per new molecular entity (NME) submitted the FDA for approval, has been decreasing over time (GAO, 2006).

A policy agenda for health incentives

Conflicts over the cost-effectiveness of new therapies are largely responsible for the frequent disagreements between funders and pharmaceutical firms over the cost of new treatments. The goal for public health is to obtain highly effective and safe therapies at the lowest possible cost. The goal for health firms is to recover the costs of developing new therapies and earn a profit. This depends on the ratio of development and production costs to future revenues.

Several biotechnological innovations can potentially increase or decrease drug development costs:

- increase costs from the need to validate biomarkers and identify genetic and other factors that influence response to treatment;
- reduce costs from the application of pharmacogenetics and other knowledge to lower the percentage of candidate therapies that fail (OECD, forthcoming);[10]
- reduce costs from smaller and fewer clinical trials from the use of pharmacogenetics and biomarkers;
- reduce manufacturing costs through more efficient production methods.

On the other side of the ledger, several factors, not all of which are linked to biotechnology, influence the potential revenue from each new therapy:

- the potential market size for the therapy, based on the prevalence of the targeted disease;
- market losses from prescribing restrictions due to pharmacogenetics and possible losses or market gains from post market assessments of the efficacy and safety of a therapy;
- the patent life remaining before the introduction of generics, which will influence the price that can be charged;
- the price that can be charged for treatment during the time the therapy is covered by a patent and the price after patent protection ends.

Many of the current policy debates focus on one or more of these factors. The current business model of many pharmaceutical firms and the market incentive structure ensure that it is in the firm's interest to reduce development costs, increase the size of the potential market (*e.g.* through

direct to consumer advertising,[11] off-label prescribing, or seeking regulatory approval for multiple indications) and extend patent protection for as long as possible.

Several policy approaches could help to reduce the development costs for new therapies.

Increasing public support for biomedical research is one option, although each of several waves of biotechnological innovation has promised a leap of magnitude in the efficiency of pharmaceutical research and each wave has passed by and increased costs (Pisano, 2006; Hopkins *et al.*, 2007). Although scientific progress could create enormous gains in therapeutic efficiency, the fact that it has not happened so far suggests a need to search for other solutions. Other possible options include support for "translational medicine"[12] and greater collaboration to increase the speed and effectiveness of transferring knowledge from the public research sector to firms.

Another option is to reduce costs through changing the structure of clinical trials, which are estimated to account for between 30% and 58% of total drug development costs (Rawlins, 2004). Cost savings from this strategy depend on several factors. Both the size of clinical trials and their number depends on the efficacy of the drug, with more effective drugs requiring smaller trials than drugs with minor benefits over placebo. Pharmacogenetics, by identifying subgroups of patients that respond to treatment, could reduce the size of clinical trials for establishing efficacy, but larger trials would still be required to establish safety. Consequently, the impact of pharmacogenetics on reducing the size of clinical trials is likely to be highest for cancer and other fatal diseases where the benefits of treatment can be much greater than the risk of adverse effects.[13] Conversely, non-fatal diseases are likely to continue to require trials that are large enough to establish safety.

Savings in manufacturing costs are particularly relevant for many biopharmaceuticals, where the cost of production using GM micro-organisms in bioreactors is very high. Producing biopharmaceuticals in GM plants or in the milk of GM animals could potentially result in large cost savings (Frost and Sullivan, 2004). This would require regulatory systems to manage the use of GM crops and animals to produce high value non-food products and mechanisms to ensure that these products do not enter the food chain.

Other polices could increase the potential revenue from new therapies, but these need to be linked to evidence of significant improvements in therapeutic value.

An alternative method for improving the ratio of drug development costs to future earnings is to increase the effective patent life by shortening the time required to obtain marketing approval. This could be achieved by shifting some of the late stage clinical trials for safety or efficacy to the post approval stage,[14] but at a potential cost in terms of greater safety risks.[15] Regulatory systems already contain the flexibility to rapidly move promising treatments for cancer and other serious diseases from clinical trials to market approval (Dukes, 2008). Therefore, the potential impact of this method on the average effective patent life will depend on the share of all new pharmaceuticals that target potentially fatal diseases such as cancer and the degree to which higher risks of adverse effects will be accepted for drugs that target non-fatal disease.

To improve the cost-effectiveness of new therapies, policies to increase revenues must be combined with strong incentives to support the development of highly effective new drugs. Experiments with several incentive mechanisms are underway, whereas others remain theoretical and require further study. Several countries already link the level of reimbursement to health outcome measures such as Quality Adjusted Life years (QALYs). There is also greater interest in setting clear reimbursement targets for priority drugs to provide an incentive for investment. A theoretical option is to introduce a prize system, an example of which is described in the scenario "Muddling Through" (see Chapter 7), where the financial reward is based on the therapeutic advance offered by the therapy. Identifying the best treatments can also benefit from publicly funded comparative trials of different treatment options (Kaplan and Laing, 2004).

Incentives to encourage more effective therapies are likely to increase costs to health providers, although some of these higher costs could be recouped by reducing payments for marginally effective treatments. This dynamic may be temporary, however, as better financial incentives lead to more effective and consequently more expensive new therapies. The trade-off would be significant benefits for public health. In the end, the challenge for governments is how to implement and finance new incentive systems.

Two technical advances will probably help improve the cost-effectiveness of new therapies: pharmacogenetics and the use of bioinformatics to construct databases of the prescribing histories and long-term health outcomes for millions of individuals.[16] Furthermore, these technologies are fundamental to the development of predictive and preventive medicine. Both of these technical advances, as well as emerging business models to take advantage of opportunities created by pharmacogenetics and predictive and preventive medicine (see Chapter 6), could help support a better alignment between incentives and public health goals.[17]

Finally, facilitating the use of pharmacogenetics and biomarkers will support preventive medicine, through an increase in the number of diagnostic tests for disease risk factors. This in turn could encourage people to make lifestyle changes or receive treatment that could prevent or delay the onset of disease. These tests will need to be reliable. A false positive diagnosis could create anxiety while a false negative diagnosis could result in failure to provide treatment. Furthermore, the widespread use of tests to identify very rare diseases or very low risk factors for chronic diseases could drive up healthcare costs without significantly improving health benefits. These and other concerns over the clinical validity, regulation, and advertising of diagnostic tests are currently being addressed by many governments (OECD, 2001a, 2007).

Box 8.6. **Managing incremental biotechnologies for health**

1. **Regulations/standards**: Policies to improve the ability of pharmaceutical and other health technology firms to recover high R&D costs should better align private sector incentives with public health goals. Care is required to ensure that incentives and regulatory systems also support the future development of beneficial disruptive and radical innovations, such as predictive and preventive medicine or the production of biopharmaceuticals in plants.

2. **Foresight research**: Policy research should urgently explore methods to improve the incentive structure for effective breakthrough therapies and to reduce drug development costs. Options for the former include setting clear reimbursement targets for diseases that lack adequate treatments or setting prices based on health outcomes. Options for the latter include translational medicine and changes to regulatory systems that do not conflict with the public health interest in safety and efficacy.

3. **Foresight research**: Further research is required into the effect on total healthcare costs of financial incentives to improve the therapeutic value of new healthcare treatments and on the willingness of taxpayers or insurers to pay for these costs. Higher therapeutic costs, for example, could be compensated for by a decline in other healthcare costs. Alternatively, higher costs for therapeutics could be acceptable to the taxpaying public if there is a noticeable improvement in health benefits.

4. **Foresight research**: Testing for future disease risks raises a number of potential challenges for healthcare, including the management of tests for genetic risk factors *in utero*, the detection of risk factors for chronic diseases that may or may not develop, and the accuracy of such tests. Further research is required into the ethical, cost, and psychological effects of genetic testing and the types of policy actions that might help to reduce potential risks.

Disruptive and radical health biotechnology

Regenerative medicine could have several disruptive effects. Its use to replace damaged tissue, teeth or bone could significantly reduce pharmaceutical markets for several chronic diseases, including Type 1 diabetes, rheumatoid arthritis, and neurological and cardiovascular diseases. Furthermore, some types of regenerative medicine could also disrupt current business models in the health sector.

The patentability of regenerative medicine poses several policy issues. The development and diffusion of regenerative medicine might be delayed if laboratory techniques or methods of differentiating cells that are important to all regenerative medicine applications are given broad patent rights and only licensed at high cost (or not at all). The opposite problem might develop for regenerative medicine based on autologous cells. Even if these cells are patentable, intellectual property rights might fail to provide an incentive for investment in this technology. With personalised treatment, it would be difficult for patent owners to determine if their patent was infringed, for instance by patients seeking lower cost treatment in countries where infringement is difficult to detect.

Predictive and preventive medicine is a potentially radical innovation that could seriously affect the business models of healthcare firms and healthcare delivery services. Several organisations such as Kaiser Permanente have already established some of the basic requirements for predictive and preventive medicine, such as an electronic data infrastructure for linking medical records on treatments, outcomes, and genetic and environmental risk factors over an entire lifetime. Despite potential benefits, this can create concerns over privacy and the release of confidential information to insurers and employers (OECD, 2001a, 2008a; Hempel *et al.*, 2008). Other aspects of predictive and preventive medicine will require changes to how healthcare is provided. Doctors will need to scrupulously follow best-practice recommendations for diagnostics, prescribing, and treatment. This will involve a major shift away from the current "medicine as art" approach of many medical practitioners, in which, recent evidence shows, there is widespread failure to follow best-practice rules[18] and extensive off-label prescribing. Future best-practice methods will be identified through long-term analysis of integrated data records, comparative clinical trials, and experimentation with doses. This is a proven strategy that has been verified for childhood cancers.[19] In order to discourage inappropriate prescribing and ensure that both doctors and patients comply with best practice, this approach to medicine is likely to require stricter rules on advertising and on advertising claims.

Due to high costs and a poor fit with current business models, predictive and preventive medicine is unlikely to reach its potential without public funding for research, including long-term trials to identify best practice. This should build on the model of the very successful research programmes into treatments for childhood cancer and for heart attacks.

Box 8.7. **Managing disruptive and radical biotechnologies for health**

1. **Research subsidies** and **infrastructure investment**: Predictive and preventive medicine could require further targeted investment to support infrastructure for integrated databases and extensive long-term public support for research due to high costs and long lead times required to obtain results.

2. **Foresight research**: Research is required into the effect of regenerative and predictive and preventive medicine on the provision of healthcare services and their implications for data confidentiality, physician training, and human resource needs.

3. **Foresight research**: Current business models are based on earning revenues from selling products such as tissue scaffolds or drugs, or from licensing patented knowledge. This model could fail to provide sufficient revenues to fund private investment in regenerative and predictive and preventive medicine. Private sector success in both of these new approaches may require shifting business models towards earning revenue from providing personalised services. A thorough evaluation of the implications of both biotechnologies on the ability of private sector firms to profit from R&D investments, and possible changes to policy to support such investment is required.

4. **Foresight research***:* Public healthcare systems separate the private supply of drugs and other therapies from the public provision of healthcare services. This could affect the introduction of regenerative and predictive and preventive medicine. Research is required into how public healthcare systems might need to adapt to take advantage of these emerging approaches to medicine.

Key uncertainties for health biotechnology

In addition to the scientific and technical hurdles facing health biotechnology, there are two important uncertainties that need to be examined.

Longevity

A key uncertainty is the effect of advances in health biotechnology (and other factors) on longevity and the quality of extra years of life. The baseline forecast by the US Census Bureau estimates that average life expectancy in the United States will increase by 1.3 years per decade, giving an average life expectancy of 80.5 years in 2030 (Sonnega, 2006). Average life expectancies in many European countries, Japan and Australia could reach 84 to 86 years by 2030. Advances in healthcare due to biotechnology could increase longevity above these baseline estimates.

A common concern is that longer life spans could substantially increase total healthcare costs, especially if the extra years of life are spent in poor health or suffering from dementia (see for example BBC News, 2008). New healthcare technologies employed to meet these challenges are also likely to increase costs further exacerbating the problem (OECD, 2006). These combined effects could place enormous financial stress on both the healthcare and the pension systems. Some disagree with this assessment however. At least one positive "win-win" scenario, developed by SRI Business Intelligence (2008), sees health biotechnology leading to both longer and healthier lives. This would engender a fall in the share of GDP spent on healthcare, although this is an exception to most research, which finds that new healthcare technology increases costs.

Elements of the positive scenario are supported by research showing that the elderly are healthier than in the past, thus reducing the expected increase in healthcare costs (Romanov, 2002). Furthermore, it is not clear if the number of years with dementia has been increasing with longer life spans. One study reported both a decline in the prevalence of dementia over time and in the number of years with dementia (Langa, 2008). Other research finds an increase over time in the number of years with dementia for men but a decline for women (Sauvaget *et al.*, 1999).

Longer life spans could require a shift in the distribution of income from working age populations to retired populations, triggering changes to a wide range of social policies and practices. Advances in biotechnology that increase life spans may however be balanced by advances that increase the number of years of life without serious disability. Pension systems could adjust to greater longevity if people remain healthy into old age and if there is a commensurate increase in the percentage of older people that remain in the work force. If health in old age does not improve, an increase in the average lifespan will increase healthcare and pension costs without a proportionate increase in the quality of life. This imbalance in the costs and benefits of medical advances could create intergenerational conflict over the

costs as well as widespread fear over ageing, with a reduction in the quality of life for many people.

Developing countries

A second unknown is the future role of major developing countries such as China, India and Brazil as regulators, producers, and markets for health biotechnology products.

China and India, as with other major developing countries, currently have weak regulatory systems for pharmaceuticals. Yet both countries are moving towards a stronger regulatory system that is similar to that in Europe. This is because regulatory improvements in China and India are not only driven by domestic demand to improve the quality of domestically manufactured healthcare products,[20] but also by an interest in accessing the world's largest markets for health therapies. The EMEA and Canadian regulatory systems are currently favoured by the BRIC countries. One of the perceived disadvantages of emulating these two systems is that both, compared to the American system managed by the FDA, limit public access to data that could be used to improve health research (Vitry *et al.*, 2008). Fundamental improvements have already been made in China, with the regulatory system moving towards international standards on marketing approval, licensing of manufacturing plants, and detection of counterfeit drugs (Dukes 2008).

Developing countries offer growing markets that could provide new revenues for pharmaceutical firms, possibly offsetting a decline in revenues in OECD countries from smaller markets for new drugs. Between 2002 and 2006, the pharmaceutical markets in India grew at an annual rate of 7.3% and in China by 17%. Neither growth rate is likely to be sustainable to 2030, but China is already expected to be the world's seventh largest pharmaceutical market by 2010 (Pharma Futures, 2007).

However, several factors could limit the market potential of developing countries. Average income in both countries in 2030 will be substantially less than in developed countries, limiting the ability of individuals to pay for costly therapies. China could also strengthen its public healthcare system and place limits on the level of reimbursement for drugs. Domestic demand could also be increasingly met by domestic firms with low production costs. By 2030, research intensive Chinese and Indian pharmaceutical and medical device firms, which are already involved in R&D outsourcing, are likely to be competing globally and could drive down pharmaceutical prices in OECD countries.

Box 8.8. Managing key uncertainties for health biotechnology

1. **Foresight research**: Research is required into the social, ethical, and economic consequences of possible increases in longevity. There is a strong public interest in supporting health research that improves the quality of life and minimises the years spent with major disabilities.

2. **Public forums**: In all OECD countries, including the United States, publicly funded institutions are the major source of finance for healthcare and often for health research as well. Consequently the public should participate in a discussion on what they want from healthcare. What are their views on longevity versus long-term disability? What level of health benefits would they be willing to pay for?

3. **Development commitments**: Countries with robust regulatory systems should continue to assist developing countries to craft appropriate systems, but the wider goal should be to improve all regulatory systems. One approach involves greater transparency. This could require increasing access to some clinical trials results. While this might reduce development costs and provide support to further research into improving health outcomes, there are significant hurdles to be overcome in order to reach a consensus on how to move forward on opening up clinical trial data. Some options are discussed below.

Industrial applications

Industrial biotechnology faces multiple futures: from providing a limited number of incremental improvements to major changes in how products are produced and delivered. Industrial biotechnology has the potential to significantly reduce the environmental impacts of chemical and fuel production, but in some cases other technologies for achieving the same ends could be superior. The extent to which industrial biotechnology will be used by 2030 will depend on policy choices, private investment decisions, infrastructure development, technological breakthroughs and the competitiveness of biotechnological solutions compared to other alternatives.

Incremental advances in industrial biotechnology

Industrial biotechnology can provide substantial benefits such as lower operating costs and a reduced environmental footprint (OECD, 2001b), but

it must compete with alternative production technologies. The main challenges for industrial biotechnology are scaling up biobased production to an industrial scale and ensuring a secure supply of biomass feedstock of a known and consistent quality. Successes have been realised however, particularly in areas where industrial biotechnologies provide a significant yield or efficiency advantage or where government support has driven investment.

An example of the former is industrial enzymes, which are widely used in the production of food, animal feed, textiles, and detergents. The production of fine chemicals, including vitamins and pharmaceutical precursors, is another example where efficient biobased production using micro-organisms in bioreactors is often the preferred method. The use of biotechnology to produce enzymes and fine chemicals should continue to grow to 2030.

Biotechnology has been used less frequently to produce bulk low-value chemicals. None the less, steady technological progress has expanded the range of specialty and bulk chemicals that can be produced with the assistance of biotechnology. Further use will depend on high prices for fossil based feed stocks, experience in scaling up production, and policy interventions to create and sustain markets for biochemicals.

The production volume of biopolymers continues to increase, but they currently only have a very small share of the global polymer market. Rapid growth is expected in niche areas such as biodegradable plastics for consumer and food packaging. Other types of biopolymers will increase more slowly and require the development of new processes. Remaining challenges for biopolymer uptake include meeting performance criteria, security of feedstock supply and measurement of sustainability.

Governments currently support biofuels via subsidies, mandates, and trade restrictions (OECD, 2008b). In the absence of past support or a continuation of these policies, very little ethanol or biodiesel would currently be produced from food or feed crops (with the exception of sugarcane ethanol), and only very small volumes of biodiesel from animal fats and waste cooking oils. Not only is the cost of producing biofuel higher than petroleum-derived fuel, but crop-based biofuel is subject to the vagaries of the weather and other forces affecting crop yields and competes with crops for food and feed.

Due to their disadvantages, the future of bioethanol or biodiesel from food or feed plants will be limited to countries with ample supplies of low cost vegetable oil or sugars. Incremental developments in industrial biotechnology will focus on improving fermentation processes and will be coupled with the development of new biofuel crop varieties with improved

yields. In other regions bioethanol and biodiesel from food or feed plants are likely to only be a short-term solution and will be replaced by higher energy-density biofuels, or from biofuels made from non-food sources. These have the potential to substantially reduce dependence on fossil fuels for transport and are consequently discussed in the next section.

Due to strong price competition from other technologies, the financial viability of biorefineries will depend on improved economies of scale and flexible production, where a variety of end products can be manufactured in a single facility. Ethanol biorefineries already produce animal feed as a by-product, but novel by-products could increase the value added of the final product mix. For instance, recent research has found ways of converting glycerol, a by-product of biodiesel production, into plastics.

There is a high potential for the use of modern biotechnology in environmental services. Both biosensors and bioremediation could play a major role in ensuring human and environmental safety. For example, real-time biosensors are a powerful tool for identifying invasive species in cargo. While carefully selected micro-organisms could be used in bioremediation, genetically modified organisms are likely to be more efficient and can be more quickly adapted to site specific conditions. The drawback to their use is high regulatory costs that are in the millions of dollars combined with relatively small markets. The future use of biotechnology for environmental services is likely to be highly dependent on policies to create and sustain markets and on the design of regulations.

Box 8.9. **Managing incremental biotechnologies for industry**

1. **Research subsidies**: Public R&D funding for industrial biotechnology is very low compared to agricultural and health biotechnologies and could be increased to take advantage of the potential of many industrial biotechnology applications to reduce pollution and energy consumption. Research is particularly needed to develop reliable feedstock from non-food crops.

2. **Research subsidies**, **Market creation**, and **Regulations/standards**: The development and application of promising industrial biotechnologies for environmental remediation and biosensors are hindered by the combination of high R&D costs and small markets. Subsidies and procurement policies to create demand and reductions in regulatory costs could be based on their potential for environmental benefits.

Disruptive and radical industrial biotechnologies

Several industrial processes based on biotechnology could have disruptive effects on economies by replacing production systems based on petroleum feedstock. Other processes might have radical effects, such as the use of micro-organisms or simple plants developed through metabolic pathway engineering. This could disrupt current methods of producing chemicals and require new infrastructure for large scale chemical production. The latter might also produce unimaginable new chemicals with possible disruptive effects on other economic sectors.

Biofuel production is a good example of the potential of industrial biotechnology to result in either disruptive or radical innovation. The main difference between biofuel as a disruptive or radical innovation is possibly the scale of production. Large scale production, either through the use of biomass or through direct production in micro-organisms, would need substantial investment in new knowledge and infrastructure. For example, the former would require investment in new crop varieties to provide an adequate supply of biomass, technical solutions to reduce the cost of transporting biomass to biorefineries, new biomass transportation infrastructure, and possibly (if based on ethanol) specialised pipelines or tankers to distribute the biofuel to markets. Greater integration between agriculture and industrial processing would also be necessary, creating an "agro-industrial" economic sector.

The evolution of developments in industrial biotechnology is often hard to ascertain due to a lack of data. However, due to recent interest, a great deal of new information has been collected for biofuels. This provides an opportunity to examine what changes may be radical and disruptive. Some of the issues discussed below, such as the potential for tensions between new production methods, will also be applicable to the production of other chemicals and biomaterials. In other areas of industrial biotechnology, such as environmental services and resource extraction, radical changes are not foreseen.

There are two competing technological approaches to industrial biotechnology, both of which will disrupt supply chains and production methods for chemicals and fuels based on petroleum feedstocks. The main difference between the two approaches is the source of energy and carbon to produce compounds such as biofuels, bioplastics and bulk organic chemicals. The first approach uses biorefineries in which micro-organisms such as yeast convert biomass into useful products, drawing energy, carbon and nutrients from the biomass itself. The second approach uses enhanced micro-organisms or plants to produce a similar range of products, but draws energy from sunlight and carbon from the atmosphere. Nutrients can be

added artificially or obtained from the soil or from animal or human wastes. In each approach, transgenic, intragenic, directed evolution, gene shuffling or synthetic biology techniques could be used to produce enhanced varieties of plants or micro-organisms.

These two technological approaches are potential competitors. Given technological breakthroughs, biofuels and many other bulk chemicals could be produced more cheaply using the second approach than through the two-step processes that are currently in use or under development for biorefineries. There is a possibility of a future clash of business models and a loss of capital investments in the infrastructure for biorefineries. Alternatively, the two solutions could complement each other. Biorefineries could be competitive in humid sub-tropical and tropical regions with ample biomass resources and with high biomass production rates per hectare. The direct production of biofuels from marine algae or synthetic micro-organisms could be the dominant production method in regions with a lack of low-cost biomass resources, such as Japan, or in low latitude desert areas with ample sunlight and access to brackish or salt water, such as the South Western United States, Northern Mexico, Australia, Eastern India, Spain, North Africa, and the Middle East.

For environmental, food security, and technical reasons, a shift in biofuel production from the current focus on bioethanol to cellulosic fermentation of biofuels with higher energy-densities and ultimately, in suitable regions, to direct production of high energy-density biofuels by algae or micro-organisms, is preferable. In addition to concerns over the effect of bioethanol on the environment and on food security, bioethanol is only a short-term solution because it is an inferior fuel. It provides only 65% of the energy per volume as petrol and is also miscible in water, which makes it difficult to transport in pipelines. It is primarily used in low-percentage blends with petrol (around 10%). Higher ethanol concentrations, of more than 30%, require modifications to vehicle engines (OECD, 2008b). For these reasons, it is unlikely to be able to compete with improved biofuels, such as high energy-density fuels made from sugar cane or cellulosic crops.[21]

The future competitiveness of cellulosic biorefineries for both biofuels and biochemicals depends on solving difficult technical and organisational challenges. A biorefinery needs to flexibly use different biomass feedstocks and produce different products, depending on input and output prices. Due to high transport costs, feedstock is likely to be obtained from high yielding GM tree, grass, or shrub varieties that are sourced from an area relatively close to the plant. This will limit the volume of feedstock and require efficient small or medium sized biorefineries. Similarly, the efficient production of biofuels or other products from micro-organisms or algae

requires solutions to the issues of scaling up production and preventing contamination by undesirable organisms.

Large firms are likely to dominate biorefineries because of high capital costs and the need for familiarity with complex production plants. SMEs active in industrial biotechnology face several barriers, including access to finance and to proprietary and tacit knowledge on scaling up production plants. For both reasons SME involvement in biorefineries is likely to be based on collaboration with large firms. Greater opportunities for SMEs exist in synthetic biology, particularly for obtaining venture capital, which could be attracted by faster rates of return than in pharmaceuticals (a 5-8 year development time *versus* 12-14 years) (Podtschaske and Mannhardt, 2008).

Over the long term (and possibly well before 2030), it will not be possible to reduce significantly GHG production with biofuels unless they are produced directly by micro-organisms or algae. In the absence of this technology, a shift towards electric vehicles powered by solar, wind, geothermal, tidal, or nuclear energy could be a preferable option. The potential production volume of biofuels from biomass crops is constrained by global limits on the supply of low cost biomass and low output levels per hectare.

The highest observed yields for bioethanol are from sugar cane, which can produce 5 200 litres of petrol equivalent fuel per year per hectare.[22] To meet 100% of the predicted global demand for liquid fuels in 2030 would require almost 10% of the global land area (excluding Antarctica) to be used for sugar cane or other high yield bioethanol crops. This is approximately equal to all land currently under cultivation worldwide. In contrast, microalgal production of high energy-density biofuels, using marine species adapted to salt or brackish water, could theoretically provide enough liquid fuel to meet global demand in 2030 on 0.9% of the global land area (excluding Antarctica) and it would preferentially use semi-desert or desert lands instead of high quality farmland.[23] A radical shift to algal production would require pre-treatment of salt water to remove competitors or the development of algal varieties that can thrive in water that contains other species.

A transition to biofuels has both advantages and disadvantages as compared to other non-fossil fuel based transport systems. Widespread use of ethanol and other comparable low energy-density biofuels, is likely to have relatively high infrastructure cost requirements. This is due to the potential need for dedicated shipping pipelines and, if ethanol rises to above 20% or so in the fuel blend, the need for special "flex fuel" motors and refurbishment of filling stations (Yacobucci and Schnepf, 2007). Higher

density biofuels will avoid many of these costs, but they will need new production facilities that could be located in areas that will require some new infrastructures to gather the fuel and distribute it to consumers. Other alternatives to current fossil fuel-based transportation systems, such as electric cars or electric-fuel hybrids, would also require new infrastructure for recharging vehicles. If reducing GHG is part of the goal, new high-voltage transmission lines would be needed to link geographically dispersed solar, wind, geothermal, and tidal plants. Nuclear energy production would fit more easily into existing electrical grids.

Biofuels face a classic transition problem for a new technology. Today's fossil-fuel based transportation systems have been put in place over the last century and the shift to biofuels and other energy sources that have the potential to reduce GHG emissions could require expensive new infrastructure. Some of the past research into minimising the costs of producing and distributing fossil fuels will favour biofuels (NIC, 2008). However, any serious transition will still be very costly and is likely to necessitate public involvement. Private investment in biofuels will not proceed without a niche market willing to pay high prices, or a reduction in the risks of competition, either through Government subsidies for biofuels, as has been the preferred method to date, or an increase in fossil fuel costs. In the long term, biofuels will not be competitive without subsidies unless the cost of producing biofuels falls. This requires long-term investment in both research *and* in solving problems of scaling up production.

Within the IEA countries, publicly funded research spending on biofuels accounted for 3% of all public expenditures on energy research in 2006,[24] with more public spending on fossil fuel research than for all renewable sources of energy combined. Venture capital investment in clean energy has been increasing rapidly, from USD 279 million in 1999 to USD 5.99 billion in 2007,[25] although the data do not differentiate between biofuel and other sources of low carbon energy. The promise of high energy-density biofuels is unlikely to be met without an increase in both public and private investment in research into high yielding plant or algal varieties and into solving problems of scaling up production.

Box 8.10. **Managing disruptive and radical biotechnologies for industry**

1. **Research subsidies** and **Foresight research**: Research support programmes need to address both current bottlenecks and long term possibilities. Well-designed support for research into biomass fuels based on cellulosic, sugar, and starch crops should continue as these products will play a role in reducing GHGs and promoting energy security over the next decade. Research to reduce the high transport costs for biomass are required, possibly by improving the characteristics of feedstock plants for biofuels or chemical production. For the longer term future, research incentives should be directed towards biofuels that meet three criteria: high energy-density, minimal environmental impacts and a high compatibility with existing infrastructure designed for fossil fuels.

2. **Research subsidies** and **Market creation**: A major technical problem for all types of bioproducts is scaling up from prototype plants to full-scale commercial production. There is a role for greater public sector research into the core technologies for bioproducts, with the results made available to all firms. Firms could then compete on their abilities to scale up production at low cost. Public funding for prototype plants may also be needed, but it should be available for all firms. Otherwise, subsidies for prototype plants could be anti-competitive.

3. **Market creation** and **Regulations/standards**: "Green" production of biofuels and other bioproducts produced in biorefineries will not be effective or sustainable unless there are: *(1)* standards and enforcement methods to prevent displacing rainforest, peat bogs and other carbon sinks with tree plantations, food or feed crops and *(2)* market mechanisms to support the competitiveness of bioproducts. The former will require performance standards, based on a robust life cycle analysis (LCA) methodology, to assess the level of GHGs and other pollutants from biotechnological and other methods of producing chemicals, plastics and fuels. Mandates or incentives are required to create a market for bioproducts with favourable LCA scores. Carbon will need to be priced high enough to maintain the competitiveness of low GHG energy in the face of inevitable declines in fossil fuel prices from a fall in demand.

4. **Market creation** and **Infrastructure investment:** Government subsidies or mandated targets for biofuels or other bioproducts should be designed to prevent lock-in into sub-optimum fuels or expensive infrastructure that only support one product. This could be a major roadblock to the future adoption of superior technologies.

Key uncertainties for industrial biotechnology

The main uncertainty is the economic competitiveness of industrial biotechnology to produce bioproducts compared to alternative technologies. Biofuels fit easily into existing transport infrastructures and therefore have an initial advantage over other low GHG transport fuels. This advantage could be eroded if problems of energy storage and costs for electrical vehicles are solved. These types of advances could limit the biofuel market to air transport and heavy vehicles.

It is also possible that biorefineries are neither the most economically nor environmentally beneficial solution for the production of many bulk chemicals. The global chemical industry, with sales of USD 1 300 billion in 2004, only used approximately 4% of global petroleum consumption. Using petroleum feedstock combined with efficient recycling could be a more economical and environmentally responsible method of producing many bulk chemicals. Only full life cycle analysis can identify the most environmentally sustainable options.

Box 8.11. **Managing key uncertainties for industrial biotechnology**

1. **Research subsidies** and **Market creation**: Targeted policy support for biotechnological solutions for renewable energy or chemical production at some time will need to become technology neutral, with research and other support granted on a competitive basis to the most promising solutions. Until then, life cycle analysis can help identify the most sustainable technologies.

Cross-cutting issues

Several policy issues are relevant to all applications of biotechnology and to incremental, disruptive and radical innovations. These issues include intellectual property, collaboration, and integration across applications. Intellectual property issues are closely linked to collaboration and consequently these two topics are evaluated together.

Intellectual property and collaboration

Firms will not invest in innovation unless there is a reasonable probability that they will be able to recover, or appropriate, their

investments in the cost of developing new products and processes. Intellectual property rights such as patents, trademarks, trade secrecy, and copyright provide mechanisms for firms to protect their investments in innovation from competitors. These methods are often combined with other appropriation strategies such as building lead time advantages over competitors (Arundel, 2001; Cohen, 1995).

In jurisdictions with functioning intellectual property rights, patents are possibly the most useful form of intellectual property for biotechnology firms because they can be used to buy, sell and trade knowledge. These characteristics can facilitate mechanisms such as licensing (OECD, 2002; Herder and Gold, 2008), collaboration and knowledge markets for sharing knowledge between firms. The main challenge is to facilitate the efficient dissemination of intellectual property to potential users and reduce R&D costs.

In health, creating knowledge markets for proprietary information on failed or abandoned pharmaceutical projects, toxicology data (usually kept secret), or intellectual property that is not part of a firm's core activities can reduce research replication and therefore costs. In addition, many types of collaborative models exist in all applications where intellectual property rights can be used to encourage knowledge sharing and reduce research costs. They include research consortiums that minimise transaction and licensing costs for their members, collaborative networks of researchers to develop technologies for targeted problems, patent pools where several firms agree to share their patents, and open source models that follow rules on intellectual property established by the open software community.

The public research sector is a major contributor to the pool of biotechnology patents, accounting for 21.5% of all biotechnology PCT patents originating in OECD countries between 1996 and 2005 inclusive.[26] The justification for patenting inventions from universities or government research institutes, instead of putting the information in the public domain at no cost to firms, is that firms will be unwilling to invest in developing an invention to the commercial stage without exclusive patent rights that prevent competitors from developing the same invention. However, over half of university licenses are non-exclusive,[27] with some patents licensed to hundreds of firms. These non-exclusive licenses earn revenue for the university, but they do not provide an incentive for innovation, since the same invention can be licensed to many competing firms. In other cases poor granting of exclusive rights could result in a failure for the invention to be adequately developed. In recognition of these problems, the University of California has introduced patent guidelines to support the social goals of faster and less expensive innovation.[28] Changes in patenting practices that

reduce the cost of access to biotechnology inventions could increase the uptake and diffusion of knowledge.

Intellectual property, as it relates to biotechnology, is a particularly contentious issue.[29] Governments will need to find a common agreement on how to manage intellectual property in a way that protects and compensates innovation, while encouraging the diffusion of biotechnologies with potentially large socioeconomic benefits.

Box 8.12. **Managing intellectual property for the bioeconomy**

1. **Institutional changes**: There is a strong policy interest in promoting knowledge markets and collaborative mechanisms such as networks, research consortiums, patent pools and open source models that could reduce research costs, prevent replication and bring knowledge quickly to a large number of potential users. These mechanisms will evolve with changes in competition and regulatory policies.

2. **Institutional changes**: Publicly-funded universities should be encouraged to adopt patenting guidelines that incorporate the public interest in rapid innovation, as when enabling and platform technologies are made broadly available. One option is to encourage public universities to limit exclusivity unless it is necessary to attract follow-on investment and to require the licensee to commit to "diligent development" of the invention.

Knowledge spillovers and integration

Biotechnology is based on a generic knowledge base. Knowledge of how to sequence genomes and determine the function of genes can be applied in primary production, industry and health. The benefits of biotechnological research will therefore be magnified if knowledge produced for one application "spills over" and is adopted by researchers working in a different application.

The integration of two biotechnology applications could create entirely new economic benefits that would not otherwise be obtainable. An example is the integration of primary production with industrial processing to produce chemicals, plastics and biofuels. The economic competitiveness of these products will depend on both the application of biotechnology to improve the characteristics of biomass feedstocks *and* the application of biotechnology to develop more efficient industrial processes that use

biomass. In this case researchers working on modifying plant varieties need to collaborate closely with researchers working on industrial processes.

Both knowledge spillovers and integration across applications would magnify the private and social returns from investment in biotechnology by increasing the size of future markets. As noted in Chapter 7, biotechnology has potential applications in sectors that account for between 6% and 8% of the GDP of OECD countries. Knowledge spillovers and integration to create new applications, along with emerging trade opportunities that expand markets, could further increase the economic potential of biotechnology to more than 8% of OECD GDP.

Box 8.13. **Managing knowledge spillovers and integration**

1. **Institutional changes**: Knowledge spillovers and integration will affect government ministries responsible for research, education, agriculture, industry, health and the environment. Policy coordination across these ministries can help promote greater integration and consequently maximise the potential economic and environmental benefits of biotechnology.

2. **Foresight research**: Integrative applications of biotechnology could disrupt existing processes and value-added chains, creating economic losers. Foresight research can help to identify potential opportunities for entrant firms into new value-added chains and determine if there is a role for policy in reducing barriers to integration.

The global challenge

Biotechnology can offer solutions to numerous global challenges, such as climate change, healthcare, energy supply, food security and clean water. In some cases these challenges can be met by national policies, but in other cases either regional agreements or wider international collaboration among governments might be necessary.[30]

National actions by both governments and firms have taken large strides towards finding solutions to some of these problems. Denmark and Brazil have, respectively, become the global leaders in industrial enzymes (used in environmentally sustainable chemical production) and bioethanol, partly due to policies that helped domestic firms build on national strengths. American

and European firms are world leaders in agricultural biotechnology, selling improved crop varieties on several continents.

Solving other challenges would benefit from regional agreements that create sufficient economic and political clout to establish powerful *de facto* environmental standards, based on life cycle analysis, for specific goods such as bioplastics or agricultural products. Another example is the ongoing harmonisation of pharmaceutical regulations by the American, European and Japanese drug regulatory agencies. This could provide a model for global regulatory standards for the safety and efficacy of pharmaceuticals.[31]

The rate at which the bioeconomy moves forward would benefit from greater global collaboration on research. The public sector in many countries is a major participant in biotechnology research. Developing improved crop varieties for developing countries or new drugs for antibiotic resistance or neglected diseases would benefit from greater research funding, strategies to build international networks of scientists, and improved access to research outcomes. There are many innovative options here, such as creating an international pool of research funds, with contributions based on per capita GDP,[32] or private-public research partnerships. Another option is to assist universities and research centres in developing countries to take part in collaborative international research networks. These options should improve the research capabilities of both developed and developing countries and increase the global pool of highly skilled scientists using biotechnology. Examples include the Drugs for Neglected Diseases initiative (DNDi)[33] which created a virtual network of researchers, the international AIDS Vaccine Initiative (IAVI), and the Noordwijk Medicines Agenda (NMA) to develop and deliver medicines, vaccines and diagnostics for neglected and emerging diseases.[34]

International collaboration (at a minimum between the major economies) could be essential in four areas of relevance to the bioeconomy: to reduce GHG production, prevent disease pandemics in animals and humans, reduce trade frictions that would stifle the emerging bioeconomy, and to manage endangered biological resources.

National and regional policies can encourage investment in low GHG energy such as biofuels. Yet these policies would be more effective if combined with international agreements on GHG production, performance standards for environmentally sustainable biofuels, and source-of-origin rules to prevent unwanted side effects such as deforestation. In the longer term, agreement by the major GHG producing countries on a mechanism to price carbon is essential. Otherwise, a shift towards low GHG energy sources will reduce demand for fossil fuels, driving the price of oil down, and undercutting the competitiveness of low GHG energy.

In health, global collaboration is essential to maintaining the surveillance system for infectious diseases in animals and humans as a first line of defence against pandemics. This system will benefit from research into DNA microarrays that can detect pathogens.

The emerging bioeconomy for primary production and industry would benefit from unhindered trade to prevent frictions over access to resources and to support the development of competitive markets. The global community of nations will also need to insure against the threat of hoarding, which will exacerbate disputes over food or fuel shortages, by building up reserves. In 2008, cereal stocks declined to the lowest level in 25 years (FAO, 2008).

Genetic fingerprinting, a biotechnology which can identify specific species through genetic markers, can be used to identify the source of origin of rainforest timber, wild fish stocks of tuna or cod, or other endangered living resources. Fingerprinting could prevent the sale of illegally harvested goods, but it requires international agreement on its use and the active enforcement of restrictions. As an example, without effective global enforcement, most commercial stocks of ocean fish species could collapse by 2050.

Box 8.14. **Managing challenges at the global level**

1. **Institutional changes** and **Development commitments**: Governments should support mechanisms to develop the capabilities of scientists in developing countries to conduct basic and applied research in biotechnology. This could be supplemented by institutional arrangements to promote the sharing of research results.

2. **Institutional changes***:* Continue pursuing consensus within relevant international fora (*e.g.* World Trade Organization, Biological Weapons Convention, etc.) to ensure that the socioeconomic benefits of biotechnology are realised.

3. **Public forums** and **Development commitments**: Forums could promote regional and international agreements that act as an incentive for investment in biotechnology. These include agreements on greenhouse gases (GHGs), Life Cycle Analysis (LCA) methodologies and performance standards, protection of endangered species and habitats, and trade in biotechnology products.

Timing

Some of the challenges facing the bioeconomy are sequential, with solutions required to one set of problems in order to clear the way for future applications. Policies can therefore be divided into two groups: those that need to be implemented reasonably quickly (within five years) in order to pave the way for future applications of biotechnology, and those that can be implemented later. The second group includes some policies that will need to be in place over the long term, possibly up to 2030.

Over the short haul (over five years)

In primary production, the application of biotechnologies to developing improved plant and animal varieties is constrained by public opposition in some regions, a lack of low cost access to enabling technologies, and the concentration of expertise in a few major firms. These barriers to the full application of biotechnology need to be overcome, particularly in developing countries which are the largest market for primary production biotechnologies.

In health, the technologies to create and analyse integrated "cradle to grave" health records are already available and promise significant improvements in healthcare treatments. However, it may be difficult to fully implement these technologies without a solution to confidentiality issues, modifications to regulatory structures, and funding for post-marketing trials and long-term comparative trials of different therapies to identify the most effective treatments. Once a supporting regulatory, research funding, and health record system are in place, the cost of developing personalised and preventive medicine may fall to a level conducive to rapid improvements in healthcare.

The development of many biotechnology applications in industry is likely to require government support for the creation of markets, for instance through economic instruments such as mandates, environmental taxes, or subsidies. The cost to consumers or taxpayers of these instruments will be difficult to justify without good evidence for environmental benefits. The latter is constrained by a lack of environmental performance standards for bioproducts. Agreement on life cycle methodologies and a mechanism to link economic instruments to the results of life cycle analyses could be essential for maximising the uptake and environmental benefits of many bioproducts.

Over the long haul (up to 2030)

In primary production, long-term international agreements will be required to protect living resources such as forests, ocean fisheries and arable land. Biotechnology can be applied to each of these areas, such as the use of genetic fingerprinting to protect fish stocks. Free trade in primary production products, particularly food and feed, must be maintained to prevent friction over resources.

In health, governments need to analyse the long-term structural effects of regenerative and personalised medicine on healthcare, including data confidentiality, new models for healthcare delivery such as home healthcare, new relationships between patients and doctors, the robotic administration of drugs, etc. There will be a need for long-term planning to provide the necessary human resources and infrastructures for regenerative and personalised medicine. In countries with public healthcare systems, governments should examine the possible effects of regenerative and personalised medicine on the provision of public healthcare services. Research into the social, ethical and physical consequences of longer life spans is also required.

Many bioproducts and biofuels will not be competitive with petroleum feedstocks without long term support. This could require mandates or carbon to be priced at a high enough level to cover its environmental costs. At some time in the future, direct subsidies or mandates should be withdrawn, for instance when the production of high-energy density biofuels produced from cellulose or by algae approaches competitiveness with petroleum products. Maintaining subsidies and mandates as a result of competition from other low carbon energy sources would however probably decrease the probability of achieving goals for reduced GHG emissions.

For all applications, drawing developing countries into a global research network for biotechnology will increase the benefits of the emerging bioeconomy. The ability of developing countries to benefit from biotechnology will partly depend on the choices made by their firms and governments to invest in biotechnology research and to collaborate in international research networks, for example to develop new antibiotics, other necessary drugs, or crop varieties. Developed countries can play an active role by meeting their commitments to capacity development, Millennium Development Goals, and free trade, especially in sub-Saharan Africa, southeast Asia, and less developed regions of South America.

The complex policy context

The emerging bioeconomy will be based on a mix of incremental, disruptive, and radical innovations in three major applications fields. This will require both short term policies and long-term policy approaches that can prepare for future needs. Not surprisingly, this creates a complex set of policies to support the emerging bioeconomy. Many incremental innovations can be managed with adjustments to current policies. Conversely, other goals, such as using biotechnology to improve health or address climate change, will require policies to manage disruptive or radical innovations.

Policy support for radical innovations (and some disruptive innovations) in biotechnology will require a broad mix of the eight types of policy actions discussed above. These include using foresight research to identify opportunities and risks, substantial resource mobilisation through research subsidies, commitment to biotechnology during its uncompetitive phase by creating markets through procurement and pricing incentives, the management of risk and uncertainty through regulations and standards, sustained problem solving through collaborative invention, creation and support of new infrastructures and institutions, public forums to help integrate public and business sector commitments, and international collaboration to support the emerging global bioeconomy.[35]

The interdisciplinary nature of many challenges associated with the use of disruptive and radical technologies will require the active participation of various government ministries and agencies. This adds complexity to the already difficult task of determining which government ministries should take the lead in implementing government policy. Governments should recognise this from the outset and dedicate resources early on to setting up effective management structures to design policies for the bioeconomy that include all relevant actors.

The policy options described in this chapter should help governments to maximise the public benefits from a wide range of different types of biotechnology. The implementation of multiple policy actions will need to be carefully crafted. While some actions can be undertaken in parallel, others will need to be developed in sequence. For instance, a government decision to commit resources to building infrastructure for the deployment of one technology could hinder the development of another. Indeed, many of the policies to support incremental innovations are required to lay the ground work for future disruptive and radical innovations. Facilitating a transition to predictive and preventive medicine – a radical innovation - could require a shift in the incentive structure for developing incremental

pharmaceutical innovations. These time sensitive interactions need to be considered in detail when developing policy.

The next chapter summarises the main messages of this report.

Notes

1. See, for example, the policy recommendations by European Commission (2002) and Canadian Biotechnology Advisory Committee (2006).
2. See paragraphs 8.48 to 8.49 of Nuffield Council on Bioethics (1999).
3. The yearly savings estimate is based on information for 1995 to 1996. It was converted from French Francs to USD using the official exchange rate of 1 Euro = 6.55957 French Francs and 1 EUR = USD 1.34, which is the average of monthly exchange rates from June 2005 to September 2008. An updated savings estimate due to the OECD's work on chemical safety is currently being prepared, but was not available at the time of writing.
4. Elite germplasm refers to crop varieties that are optimised for local or regional conditions.
5. This is by no means a new idea. Examples include low cholesterol diets or special foods for diabetics.
6. Much of the south-eastern United States is within the sub-tropical climatic region.
7. See Figure 10 of Larson (2008).
8. It is frequently forgotten today, but in the 1970s there was widespread opposition to the use of computers at work, due to concerns over exposure to radiation from video display terminals (VDTs) and the risk of repetitive strain injuries. This opposition rapidly withered away after the introduction and market take-off of home computers in the early 1980s, which brought the benefits of computers to individual users.
9. Many of these estimates are based on updating drug cost estimates by DiMasi *et al.* (2003). The study estimated total average development costs of USD 802 million in 2000 dollars for 68 drugs that received marketing approval between 1994 and 2001. Two factors could lead to an

overestimate of costs. First, the drugs evaluated by DiMasi *et al.* may not have been representative of all drugs, with a high average number of clinical trial patients per drug in the DiMasi *et al.* study. Second, almost half (49.8%) of the DiMasi *et al.* estimate is due to opportunity costs that assume an annual discount rate of 11%. This equals the average return on capital invested in the stock market during the 1990s. As average stock market prices, using the S&P 500 have changed little during the past decade, opportunity costs during the 2000s would be markedly lower than in the 1990s and approximately equal average dividends of between 3% and 4% per annum.

10. Herceptin, developed by Genentech, originally failed in clinical trials. It was rescued after post-failure analysis determined that it was effective in a group of patients with the HER-2 receptor (PwC, 2005).

11. The effectiveness of direct to consumer advertising in increasing revenues is emphasised in a study to assist investors in the pharmaceutical sector (Pharma Futures, 2007).

12. Translational medicine refers to methods of rapidly "translating" discoveries in the public research sector to commercial applications.

13. The regulatory system for drug approval evaluates safety on a risk-benefit basis. Higher safety risks are accepted for drugs that treat fatal diseases than for drugs to treat non-fatal diseases such as mild depression or arthritic pain (Dukes, 2008).

14. This is sometimes described as a "living license". Policy documents from the private sector, governments and academics have supported this concept (PwC, 2007; DG Enterprise, 2007; Tait *et al.*, 2008).

15. Safety risks take time to identify. A study by Giezen *et al.* (2008) found that the probability of a biological drug receiving a safety warning by up to three and ten years after marketing approval was 14% and 29% respectively, for biologicals that received marketing approval in either the United States or Europe between 1995 and June 2007. Biologicals that were first in their class had a higher probability of a safety warning and all biologicals appear to have a higher probability than small molecule drugs.

16. As noted in Chapter 4, these large databases permit researchers to identify adverse drug reactions, drug interactions, and the most effective treatments.

17. A few of the regulatory options under discussion to improve public health are the adoption of a life-long approach to the risks and benefits of treatment, strong regulatory authority before and after market approval, support for comparative clinical trials, and restrictions on consumer

advertising of new drugs until sufficient safety data are available. These options are supported by the Institute of Medicine (2006). The private pressure group FasterCures supports both faster approval processes and stronger requirements for post marketing follow-up (Simon, 2006).

18. Stolk (2008) reports large differences between the prescribing habits of doctors in seven EU countries and national best-practice prescribing guidelines.

19. The large fall in childhood mortality rates from 100% in 1950 to 25% in 2000 from acute lymphoblastic leukaemia (ALL) was due to careful experimentation with drug dosages and treatment regimes, with no new pharmaceuticals available over the past three decades. Further improvement will require new drugs and better diagnostics (Kruger, 2007). Research by Yang *et al.* (2009) indicates that genetic differences account for some of the variation in response to treatment, opening up the possibility of personalising treatment through genetic testing.

20. Counterfeiting and poor product quality is a problem in India, partly due to inadequate enforcement. An examination of the situation in one Indian State for the World Bank by Dukes (2008) found that the State Inspectorate routinely inspected four drug manufacturing plants of fair but not distinguished standing. However, eight other manufacturing firms in the same city existed, none of which was registered with the inspectorate.

21. Of note, the environmental advantages of cellulosic biofuel crops compared to food biofuel crops would be substantially reduced if cellulosic demand led to deforestation (OECD, 2008b).

22. Bioethanol production from sugar cane ranging from 6 800 to 8 000 litres per hectare exceeds estimates for cellulosic production from switchgrass (3 100 to 7 600 litres per hectare) or poplar (3 700–6 000 litres per hectare) (Marris, 2006; Sanderson, 2006).

23. This assumes production rates of 50 000 litres of biodiesel per hectare per year and a global demand for oil (in diesel equivalents) in 2030 of 6 trillion litres (5 575 Mtoe), based on IEA (2007). The maximum production rate for algal biodiesel is one-third of the maximum estimated by Sheehan *et al.*, (1998). Estimates of land requirements are from Briggs (2004).

24. Total expenditures were USD 8.93 billion, of which USD 3.45 billion was spent on nuclear research (both fission and fusion), USD 1.01 billion on fossil fuels, USD 889 million on all renewables, and USD 255 million on biofuels (IEA, 2007).

25. By the second quarter of 2008, there was USD 3.34 billion VC investments in clean energy technologies (Cleantech, 2008).

26. PCT (Patent Cooperation Treaty) patents are filed in multiple countries and therefore are taken out on inventions that have a high expected economic value. The public research sector includes patenting by universities and government, with the latter largely due to government research institutes. The share of public research sector patents is higher in the United States, at 26.4%. Hélène Dernis of the Economic Analysis and Statistics division of the OECD kindly provided the data on university biotechnology patents.

27. According to the AUTM, in the United States in 2006, 61% of licenses from universities and 72% of licenses from hospitals and research institutions were provided on a non-exclusive basis. However, there are no data on the percentage of inventions that are licensed on an exclusive basis. (AUTM, 2006).

28. See also relevant recommendations by Gold *et al.* (2008).

29. Detailed information on some of these debates can be found in the background documents to *The Bioeconomy to 2030* project at www.oecd.org/futures/bioeconomy.

30. Many of these challenges would benefit from both national and international strategies to promote innovation. The OECD has pioneered innovation studies since the 1980s. These studies relate growth to innovation in the economy and focus on areas such as biotechnology and ICT. For instance, see *www.oecd.org/innovation/strategy* and (OECD, 2005a, 2005b, 2005c, 2008a).

31. The International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) has been working since 1990 to improve harmonisation. The ICH includes representatives from the pharmaceutical industry and the regulators from Europe, the United States and Japan. The ICH also collaborates with the World Health Organization (WHO) to set standards in a larger group of countries, such as for clinical trials. See *www.ich.org/cache/compo/276-254-1.html*.

32. The literature on prizes as an incentive for health research provides many examples of possible solutions to global governance issues (Love and Hubbard, 2007).

33. See *www.dndi.org*.

34. See *www.oecd.org/document/45/0.3343.en_2649_34537_39163757_1_1_1_1.00.html*.

35. For an example of the role of policy to support a radical transition to low carbon energy, see Smith (2008).

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Chapter 9

Conclusions: On the Road to the Bioeconomy

Obtaining the full benefits of the bioeconomy will require purposive goal-oriented policy. This will require leadership, primarily by governments but also by leading firms, to establish goals for the application of biotechnology to primary production, industry and health; to put in place the structural conditions required to achieve success such as obtaining regional and international agreements; and to develop mechanisms to ensure that policy can flexibly adapt to new opportunities. There are nine main challenges, summarised in this chapter.

A bioeconomy uses advanced biotechnological knowledge and renewable biomass to produce a diverse range of products and processes. The modern bioeconomy has its origins in the first commercial uses of recombinant micro-organisms in the early 1980s. Since then, an increasing number of products and processes in primary production, health, and industry have been produced through an expanding range of biotechnologies.

By 2030, all applications of biotechnology could account for 2.7% of the GDP of the OECD countries and possibly a higher share of the GDP of developing countries. The impact of biotechnology could even be higher within the OECD, since this estimate does not include biofuels. Well before 2030, biotechnology will be used in the development of all new pharmaceuticals and most new varieties of large market crops such as wheat, rice, maize, soybeans, potatoes and cotton.

The bioeconomy will create winners and losers, often within the same sector. The production of feed for farmed fish by GM micro-organisms or algae could replace the use of wild fish as feed, resulting in a fall in fishery production. Other biotechnology applications could negatively affect petroleum-based industries, regenerative medicine and pharmacogenetics could reduce the market for pharmaceuticals, and pulp and paper production in boreal forests could be replaced by fast-growing, disease and drought resistant tree plantations in sub-tropical and tropical regions. The winners will include firms that can take advantage of new business opportunities, consumers from an improvement in food security and health outcomes, and the environment from more sustainable production methods.

The full benefits of the emerging bioeconomy will not, however, develop without purposeful goal-oriented policy. This will require leadership, primarily by governments but also by leading firms, to establish clear goals for the application of biotechnology to primary production, industry and health; to put in place the structural conditions required to achieve success such as obtaining regional and international agreements, and to develop mechanisms to ensure that policy can flexibly adapt to new opportunities.

The following section summarises nine main findings of this report and describes the types of policy actions (in italics) that are needed to support the emerging bioeconomy.

Main findings

1. Reverse the neglect of primary production and industrial applications

In the early 2000s, over 80% of research investments in biotechnology by the private sector, and a similarly high share of public investment, were for health applications. Conversely, approximately 75% of the future economic contribution of biotechnology is likely to be in primary production and industrial applications, where there are also large environmental and social benefits. This suggests that there is a strong mismatch between current investment patterns and future opportunities for maximising the social and economic benefits of biotechnology.

A promising strategy for the bioeconomy is to boost research investment in primary production and industrial biotechnologies with environmental and social benefits. Governments should consider giving priority to funding research to support long-term sustainability goals.

Depending on the application, boosting research can be met by increasing public research investment, encouraging private-public partnerships, or creating and sustaining markets for environmentally sustainable biotechnology products (*e.g.* some biofuels and biopolymers).

The application of biotechnology to primary production is a major success, but the cost of regulation is serious barrier, particularly for small market crops and small firms. Regulations on the use of biotechnology in primary production, especially for GM crops, could have serious impacts on long-term competitiveness and innovation. An open debate on the issue and review of regulations in these terms could be important to maximising the benefits of technology.

Investment in many industrial biotechnologies requires market incentives for bioproducts. Over the short term, these incentives could increase costs for consumers. Higher prices would be difficult to justify without good evidence that such bioproducts meet environmental sustainability goals. Developing performance standards for environmental sustainability, based on robust methodologies for life cycle analysis that include global land use effects, could be essential. Performance standards should ensure that undesirable environmental impacts are not simply shifted from one region to another.

2. Prepare for a costly but beneficial revolution in healthcare

Developments in health biotechnology could substantially improve health, but obtaining the full benefits could require either disruptive or radical changes to existing healthcare systems, including how health products are regulated and health services delivered. Many health technologies that are emerging from the application of biotechnology are likely to increase healthcare and pension costs. These higher costs will be difficult to justify without significant improvements in the effectiveness of health therapies. A key requirement is to better align private incentives for developing health therapies with the public interest in accessible, effective and safe treatments.

Governments should evaluate the implications for innovation and public health of a progressive regulatory system for healthcare products that incorporates pharmacogenetics and medical databases for long term research on adverse effects and other health outcomes.

Regenerative medicine and personalised and preventive medicine could change how healthcare is delivered, alter the relationship between doctors and patients, increase life spans and the quality of life, and open up new business models for biotechnology based on closer links between the provision of healthcare services and the development of treatments. One concern is that new business models to take advantage of these developments might be simpler to implement in countries with private healthcare systems, but the majority of OECD member countries have publicly funded healthcare systems that are strongly supported by their citizens.

Governments need to analyse the long-term structural effects of regenerative and personalised medicine on healthcare, including data confidentiality, new models for healthcare delivery such as home healthcare, new relationships between patients and doctors, robotic administration of drugs, etc. New developments in medicine could also increase life spans, with implications for pensions, employment, and the quality of life for elderly citizens. Governments need to fund research into the social, ethical and physical consequences of longer life spans.

3. Manage the globalisation of the bioeconomy

The bioeconomy of 2030 will be a global endeavour. Growing populations and wealth will shift the main markets for primary production and for many industrial biotechnologies from developed to developing

countries. Countries will need to collaborate to effectively use biotechnology to manage global resources such as ocean fisheries and forests, control the risks of infectious diseases in animals, plants and humans and achieve economically competitive and sustainable biotechnologies for low carbon energy and for environmentally sustainable primary production.

International agreements to promote collaborative research, regulatory systems, and market incentives for the use of biotechnology will likely be essential to addressing many global problems.

Drawing developing countries into global collaborative research networks for biotechnology will increase the benefits of the emerging bioeconomy by increasing the number of researchers working on scientific challenges and by applying biotechnology to the specific problems of the developing world. International collaboration is likely to focus on products with large social benefits, such as new antibiotics, other necessary drugs,[1] and improved crop varieties.

Regulatory requirements to establish the efficacy and/or safety of primary production, health and industrial biotechnology products vary by country. These variations increase costs to firms, particularly when research in one country is not accepted in another. Regulatory agencies in both developed and developing countries are collaborating in some areas, such as on the safety and efficacy requirements for health products. Conversely, there is a need for better international agreement on data sharing and the types of data that are acceptable for establishing the safety of primary production and industrial products produced through biotechnology. Regulations should not be unduly burdensome, but they must also protect the public interest in safety and/or efficacy. In addition, effective international regulation and enforcement is required to protect global resources, such as fishing stocks and forests, and to control infectious diseases.

International agreements to create and sustain markets for biotechnology products would increase investment in biotechnological research. In addition to support for free trade in biotechnological products, agreements could include performance standards to support environmental sustainability, possibly supported through carbon trading systems or environmental taxes.

Of note, international collaboration does not require the agreement of all countries.[2] In many cases, consensus among a few regions or several important actors could be sufficient to launch the bioeconomy's potential, such as for sustainable industrial production.

4. Turn the economically disruptive power of biotechnology to advantage

Biotechnological research is generating innovations that will disrupt current business models and economic structures. Nevertheless, there is a policy interest in supporting these technologies when they offer substantial social and economic benefits. For example, disruptive and radical innovations such as regenerative medicine and personalised, preventive medicine could help reverse the declining rate of health innovation, providing effective prevention and treatment for chronic illnesses such as cancer, diabetes, arthritis and coronary heart disease. Metabolic pathway engineering and synthetic biology could revolutionise industrial processing and provide environmentally sustainable and low-cost methods of producing a wide variety of chemicals and biofuels.

Although a difficult challenge, policy makers will need to implement flexible policies that can adapt to and support socially and economically beneficial disruptive and radical biotechnologies.

This will require foresight research to identify disruptive biotechnologies, incentives (market and other) for investment in necessary infrastructure, education and training needs to create a pool of skilled workers that can use disruptive technologies, long-term support requirements for research, and regulations and standards that support emerging business models.

5. Prepare for multiple futures

Some of the commercial possibilities of biotechnology are impossible to predict – there are multiple futures that will vary depending on regional resource endowments or investment in existing technological systems. For example, industrial biotechnology could draw energy and carbon from biomass or from sunlight and the atmosphere, two methods that may or may not be mutually exclusive. Past investment in healthcare services could make it difficult to introduce new business models or methods of providing healthcare.

Identifying and preparing for multiple futures in order to prevent "lock-in" to inferior technological solutions may provide countries with a competitive advantage.

Some of the policy options are similar to those for disruptive and radical biotechnologies: invest in foresight research to identify future opportunities and bottlenecks, support investment in multi-purpose infrastructure rather than in single use infrastructure, provide training to smooth transitions, and

fund basic and applied research into alternative technologies to keep options open.

6. Maximise the benefits of integration

Greater integration between the different research disciplines and commercial applications of biotechnology will create knowledge spillovers that can maximise the social and economic benefits of the bioeconomy. The greatest potential for integration is between primary production and industrial applications, where close integration could pave the way for environmentally sustainable production of many products. Integration can be supported by policy, but this requires coordinated government actions that draw on the expertise of government ministries responsible for industry, agriculture, natural resources, and research. There is little current evidence of a lasting coordination structure for the bioeconomy in governments.

Co-ordinating policies across government ministries has always been a challenge, but the economic benefits from promoting the integration of biotechnology research and applications might be well worth the effort.

7. Reduce barriers to biotechnology innovation

High costs for acquiring or sharing knowledge or corporate concentration that blocks new entrants can hinder innovation. In the former case, knowledge markets or greater collaboration can reduce transaction costs for accessing knowledge and free up knowledge that is hidden within firms and organisations. Corporate concentration, by creating economies of scale and scope, can support innovation, but it can also block the entry of new firms, in part by limiting access to enabling biotechnologies.

Governments should identify factors that might prevent the development of highly competitive and innovative markets for biotechnology and examine possible policy actions that could free up markets and access to knowledge. The latter could include support for knowledge markets and collaborative mechanisms for sharing knowledge, plus encouraging public research institutions to adopt intellectual property guidelines that support rapid innovation.

8. Create a dynamic dialogue between governments, citizens and firms

Economic sustainability will require bold policy actions. Examples include carbon taxes to mitigate climate change or a reduction in water allowances for farmers in increasingly drought sensitive areas. Biotechnology can help ease the transition to such policies by offering technological solutions, such as biofuels that meet environmental performance standards or GM crop varieties that are drought tolerant. Furthermore, some of the health benefits of personalised and preventive medicine will require citizens to take responsibility for nutrition and other lifestyle changes, while other developments could increase healthcare costs. None of these potential applications of biotechnology will be possible without public support.

Governments need to address the misconceptions that surround biotechnology and describe the different alternatives for managing sustainability and costs. Governments also need to conduct a dialogue with firms on the types of regulations, standards and other policies that provide a commercially and politically viable framework for new business models for biotechnological innovations.

Governments should create an active and sustained dialogue with society and industry on the socio-economic and ethical implications, benefits, and requirements of biotechnologies.

9. Prepare the foundation for the long-term development of the bioeconomy

The long-term development of the bioeconomy will require foresight research and policies that can last for several decades, such as to create and maintain markets for environmentally sustainable products. Other policies need to be implemented over the next five years in order to establish a foundation for future biotechnology applications. Some of these short-term policy challenges are summarised below.

In **primary production**, the application of biotechnologies to developing improved plant and animal varieties is constrained by public opposition in some regions, a lack of low cost access to enabling technologies, and the concentration of expertise in a few major firms. These barriers to the full application of biotechnology need to be overcome, particularly in developing countries which are the largest future market for primary production biotechnologies. Over the long term, the main challenge

will be to maintain international agreements that support sustainability and manage food and feedstocks.

In **health applications**, the technologies to create and analyse integrated "cradle to grave" health records are already available and promise significant improvements in healthcare treatments. However, it may be difficult to fully implement these technologies without modifications to regulatory structures that could include requiring post-marketing trials and public funding for long-term follow-up studies. Once a supporting regulatory, research funding, and health record system are in place, the cost of developing personalised and preventive medicine may fall to a level conducive to rapid improvements in healthcare.

In **industrial applications**, the main short term tasks are to increase support for research into high-energy density biofuels and to ensure that biotechnology supports environmental sustainability. The latter requires international agreement on life cycle analysis methodologies so that the environmental effects of competing technologies can be accurately compared. The results of life cycle analysis must also be linked to instruments such as mandates or environmental taxes to ensure that economic incentives preferentially reward the most environmentally sustainable technologies. In the long term, the main challenge is to implement and maintain international agreements to sustain markets for environmentally sustainable products and processes.

Concluding comments

The full potential of the bioeconomy in 2030 will not develop automatically. Success will require intelligent and flexible government policy and leadership to support research, markets, and create incentives for private firms to invest in biotechnology.

The financial crisis that began to impact the global economy in late 2008 creates an opportunity for governments to invest domestically, and in a targeted fashion, internationally in areas which will provide short and long term stimuli to the economy. If suitable policies are implemented, the bioeconomy could meet many of the requirements for such ambitious investment: it offers improvements to economic productivity which are also linked to environmental sustainability. Possible areas for immediate investment include the funding of comparative clinical trials of pharmaceuticals, research into new antibiotics, biosensors, and real-time diagnostics for animal and plant diseases; support for universities and agricultural colleges to create freely accessible marker libraries for small market crops such as barley, oats, orchard fruits, and vegetables; and

increased support for research and prototype plants to produce high-energy density biofuels from cellulosic crops or algae.

International collaboration will also be essential, both because the major markets for many industrial and primary production biotechnologies will be in developing countries and because collaboration will be necessary to solve global problems such as resource constraints and climate change. With appropriate policy and good leadership, the bioeconomy of 2030 should provide a higher quality of life and a more prosperous and environmentally sustainable future for all of the world's citizens.

Notes

1. For example see the OECD's Noordwijk Medicines Agenda at *www.oecd.org/sti/biotechnology/nma*.
2. The OECD's Innovation Strategy Project is examining how to use innovation policy to address global issues. First results are due in mid-2009 and final results will be published in 2010.

Annex A

Members of the Bioeconomy to 2030 Steering Group

Some members of the Steering Group were replaced during the two years of the Bioeconomy Project and/or were assisted by other experts from their organisations. The representatives of those organisations are listed below (titles and affiliations are those held during the course of the project).

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Annex B

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External experts were called upon to draft papers and provide comments on the various topics addressed by the project. (Titles and affiliations are those held during the course of the project.)

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Glossary of Selected Scientific and Technical Terms

The following glossary defines some of the scientific and technical terms in this book. Where relevant, the source of a term is given in parentheses at the end of each entry.

Agronomic traits – Genetic traits that can improve plant yields and provide resistance to stresses that can reduce yields, such as heat, cold, drought or salinity.

Amino acid – A compound containing both amino (-NH2) and carboxyl (-COOH) groups. In particular, any of 20 basic building blocks of proteins having the formula NH2-CR-COOH, where R differs for each specific amino acid (FAO, n.d.).

Amylase – An enzyme that catalyzes the chemical reaction in which amylose (starch) molecules are hydrolytically cleaved ("broken") to form smaller molecules (*e.g.* the polysaccharides maltose, maltotriose, and a-dextrin) (Nill, 2001).

Antibody – Antibodies are part of the immune system. They identify and help neutralise foreign bodies such as bacteria, viruses, or foreign transplanted tissue. They attach to an antigen (usually a protein or polysaccharide) on the surface of the foreign body.

Antisense therapy – Treatment of a genetic disease by blocking the translation of a protein with a DNA or an RNA sequence that is complementary to a specific mRNA (FAO, n.d.).

Aquaculture – Farming of aquatic organisms, including fish, molluscs, crustaceans and aquatic plants (FAO, n.d.).

Autologous cell – Cells taken from an individual, cultured (or stored), and, possibly, genetically manipulated before being transferred back into the original donor (FAO, n.d.).

***Bacillus thuringiensis* (Bt)** – A bacterium that produces a toxin against certain insects, particularly Coleoptera (beetles) and Lepidoptera (moths and butterflies) (FAO, n.d.). The genes for the toxin are used to create GM crops that resist attack by Coleoptera and Lepidoptera species.

Biobanks – A collection of samples of tissue and DNA for multiple individuals. The samples are used in a systematic way to identify genes for genealogical and clinical research (OECD, 2006).

BioBricks™ – A standard biological part that meets the technical and legal standards set forth by the BioBricks™ Foundation (BBF). Each distinct BioBrick™ standard biological part is a nucleic acid that codes for a specific molecular biological function (*e.g.,* turn on/off gene expression), along with the associated information defining and describing the part (BioBrick, n.d.).

Biodiesel – A liquid biofuel suitable as a diesel fuel substitute or diesel fuel additive or extender. Biodiesel is typically made from vegetable oils (*e.g.,* soybean, rapeseed, or sunflower) or from animal fats. Biodiesel can also be made from hydrocarbons derived from agricultural products such as rice hulls (USITC, 2008).

Biodiversity – The variability among living organisms from all sources, including terrestrial, marine and other ecosystems and the ecological complexes of which they are part. The term includes diversity within species, between species and of ecosystems (FAO, n.d.).

Bioethanol – A biofuel that can be used as a fuel substitute (hydrous ethanol) or a fuel extender (anhydrous ethanol) when blended with petroleum fuels (OECD-FAO, 2008).

Biofuel – In the wider sense defined as all solid, fluid or gaseous fuels produced from biomass or by living organisms. The term is often limited to fuels that replace or are blended with petroleum-based transport fuels, including bioethanol produced from sugar crops or cereals and biodiesel produced from vegetable oils, waste oils, or animal fats (OECD-FAO, 2008).

Bioinformatics – The organisation and analysis of complex biological information such as bio-molecular databases (particularly DNA sequences), protein structures, or metabolic pathways. Computer algorithms are used to analyse the data.

Bioleaching – The recovery of metals from their ores, using the action of micro-organisms, rather than chemical or physical treatment. For example, *Thiobacillus ferroxidans* has been used to extract gold from refractory ores (FAO, n.d.).

Biomarker – A protein, metabolite, other compound, gene, or biological event that indicates a relevant biological condition (*e.g.* disease, predisposition to a disease, disease progression, disease regression, or inflammation, etc.) (Nill, 2001). Biomarkers can be used to measure a biologically effective dose, early biological response, altered structure or function, or susceptibility to a disease or infectious agent (Kaplan and Laing, 2004).

Biomass – Organic matter that can be used either as a source of energy or for its chemical components (FAO, n.d.) Biomass is usually obtained from plants, but animal matter such as fats can also be used.

Biomining – The use of microorganisms to extract metals and minerals from ores in the mining process. Biomining allows environmentally friendly ways of extracting metals from low-grade ores (ores with a low percentage by weight or volume of the target metal) (Government of Canada, 2008).

Bionanotechnology – The combination of biotechnology and nanotechnology.

Bio-oxidation – A process for the recovery of one or more metals from an ore, using bacteria or enzymes to oxidise and extract the metal.

Bioplastic – Plastics derived from biopolymers.

Biopolymer – Any large polymer (protein, nucleic acid, polysaccharide) produced by a living organism. Includes some materials (such as polyhydroxybutyrate) suitable for use as plastics. *Synonym*: biological polymer (FAO, n.d.)

Bioprospecting – Research into naturally occurring organisms to identify a useful application, process or product. This is also known as biodiversity prospecting. In many cases, bioprospecting involves a search for useful organic compounds in microorganisms, plants, and fungi that grow in extreme environments, such as rainforests, deserts, and hot springs (US National Park Service, 2006).

Bioreactor – A tank in which cells, cell extracts or enzymes carry out a biological reaction. Often refers to a fermentation vessel for cells or micro-organisms (FAO, n.d.).

Biorefinery – A facility that converts biomass into fuels, power, or chemicals. The biorefinery concept is analogous to today's petroleum refineries, which produce multiple fuels and products from petroleum (NREL, 2008).

Bioremediation – The use of living organisms such as microorganisms or plants to clean up contaminated soil or water.

Biosensor – A device that uses an immobilised biological agent (such as an enzyme, antibiotic, organelle or whole cell) to detect or measure a chemical compound. Reactions between the immobilised agent and the target molecule are converted into an electric signal (FAO, n.d.).

Biosimilar – Generic versions of biologic drugs (large molecule biopharmaceuticals produced by hybridoma cells or by recombinant microorganisms, animals or plants).

Cellulosic ethanol – A biofuel produced from the enzymatic conversion of cellulose into sugars. The cellulose is obtained from wood, grasses, shrubs, or stalks of crop plants such as maize.

Cisgenesis – The genetic modification of a plant using a gene obtained either from the plant variety itself or from a different variety of a sexually compatible plant, such that the two plant varieties can be cross-bred (Schouten, Krens and Jacobsen, 2006).

Clinical trial – The scientific testing of a drug in humans to assess its safety and effectiveness (JHM, 2007).

Cloning – Techniques for the production of genetically identical organisms, usually plants or animals.

Diagnostic – A test or assay used to determine the presence of a specific substance, organism or nucleic acid sequence. (FAO, n.d.).

Directed evolution – A method used in protein engineering to harness the power of natural selection to evolve proteins or RNA with desirable properties not found in nature (Wikipedia, 2009).

DNA – DNA (abbreviation for deoxyribonucleic acid) constitutes the genetic material of most known organisms and organelles. It is usually in the form of a double helix, although some viral genomes consist of a single strand of DNA (FAO, n.d.).

DNA fingerprinting (or genetic fingerprinting) – The identification of unique patterns of DNA fragments in order to identify an individual organism or a variety of an organism.

DNA sequencing – Procedures for determining the nucleotide sequence of a DNA fragment. The procedure has become increasingly automated in recent years (FAO, n.d.).

DNA synthesis – Artificial synthesis of a known sequence of nucleotides into a chain called an oligonucleotide (of which genes are made) or DNA (deoxyribonucleic acid) (Nill, 2001).

ELISA – Abbreviation for enzyme-linked immunosorbent assay. The technique uses a protein to identify the presence and quantity of specific molecules in a sample. The method generates a colour change in the presence of the target molecule (FAO, n.d.).

Enzyme – A protein that catalyses specific chemical reactions but is not used up in the reaction. Enzymes are classified into six major groups according to the type of reaction they catalyse: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. Generally enzymes are named by the addition of the suffix -ase to the name of their substrate (FAO, n.d.).

Fermentation – More generally, refers to the chemical conversion of carbohydrates into alcohols or acids. A stricter definition is the anaerobic breakdown of complex organic substances, especially carbohydrates, by micro-organisms (FAO, n.d.).

Field trial – An experiment in which plant varieties are grown under natural conditions (outdoors). The test can determine the genetic stability of the variety over a generation plus other factors such as growth rates, yields, or response to environmental conditions such as pest infestations or fertiliser levels.

Functional food – A functional food is similar to a conventional food but is demonstrated (or assumed) to have additional physiological benefits beyond basic nutrition and/or reduce the risk of chronic disease (Health Canada, 1998).

Gene – A functional unit of heredity that is a segment of DNA, found in plants and animals on chromosomes in the cell nucleus. Genes direct the formation of an enzyme or other protein (NIH, 2008).

Gene delivery vector – A particle derived from a living organism for artificially delivering genetic material to a cell nucleus.

Gene gun – A technique to deliver genetic material to a cell nucleus or mitochondria. DNA-coated small metal particles (tungsten or gold) are propelled at a high enough speed to puncture target cells. Provided that the cell is not irretrievably damaged, the DNA is frequently incorporated into the cell's own DNA. The technique has been successfully used to transform animal, plant and fungal cells (FAO, n.d.).

Gene shuffling – The creation of genetic mutations by breaking up DNA and recombining it in a different order.

Gene therapy – The treatment of an inherited disease by introducing a correct copy of a defective gene (the cause of the disorder) into the cell nuclei of the affected individual. In germ-line (or heritable) gene therapy, reproductive cells are altered. In somatic-cell (or non-inheritable) gene therapy for adults, non-reproductive cells are modified (FAO, n.d.).

Genetic disease – A disease caused by a genetic abnormality involving a chromosome or sequence of DNA. The term usually refers to inherited diseases, but somatic mutations can also cause disease without being inherited (FAO, n.d.).

Genetically modified organism (GMO) – An organism that has been transformed by the insertion of one or more genes (FAO, n.d.) obtained from a second organism that cannot interbreed with the transformed organism.

Genetic test – A test to determine if a person (or animal) has a genetic condition or disease or is likely to get the disease. Genetic tests include techniques to identify genes or markers near the genes (LBL, n.d.).

Genome – The entire hereditary material in a cell. In addition to the DNA contained in the cell nucleus (known as nuclear DNA), an organism's cells contain DNA in mitochondria (Nill, 2001).

Genomics – The study of the genome (the sum total of the genetic material present in a particular organism) and its action (Kaplan and Laing, 2004).

Genotype – The total genetic or hereditary material that an individual receives from his or her parents. The genotype differs from the phenotype, which is the sum of observable characteristics (Nill, 2001).

Herbicide tolerance (HT) – A genetic trait that allows a plant to resist the effects of specific herbicides. HT has been developed using both GM technology and other breeding techniques.

High energy-density biofuel – A biofuel that contains the equivalent amount of energy (or more) per volume or mass as petrol. For comparison, bioethanol is a low energy density biofuel, with slightly less than 65% of the energy content of petrol per kilogram.

Immunoconjugates – A combination of a diagnostic or therapeutic substance and specific immune substances such as immunoglobulins, monoclonal antibodies or antigens. Often the diagnostic or therapeutic substance is a radionuclide. These conjugates are useful tools for targeting drugs or radioisotopes to cancer cells (Medical Dictionary Online, n.d.).

Immunological test – Diagnostic techniques to demonstrate or measure an immune response, including antibody production or assay, antigen-antibody reactions, serologic cross-reactivity, delayed hypersensitivity reactions, or heterogenetic responses (Medical Dictionary Online, n.d.).

Immunotoxins – Semisynthetic conjugates of various toxic molecules, including radioactive isotopes and bacterial or plant toxins, with specific immune substances such as immunoglobulins, monoclonal antibodies, and antigens. The antitumor or antiviral immune substance carries the toxin to the tumour or infected cell where the toxin exerts its poisonous effect (Medical Dictionary Online, n.d.).

***in vitro* diagnostic** – A diagnostic test performed outside of the test subject, for instance in a glass or plastic container (see Diagnostic).

***in vivo* diagnostic** – A diagnostic test performed inside of the test subject (see Diagnostic).

Indication – A disease or medical condition for which a drug manufacturer may legally claim its drug has a beneficial effect (JHM, 2007).

Intragenics – The use of recombinant technology to introduce genetic fragments into an organism, where the fragments are obtained from the same species. This allows breeders to transfer genes from within the gene pool to the target variety, without using foreign DNA (Connor *et al*, 2007).

Lignin – An organic polymer that is part of the cell wall of plants and red algae. In plants, lignin provides structural strength and assists with water transport.

Marker-assisted selection (MAS) – Identifiable DNA sequences (or markers) that are located close to a gene for a beneficial trait. They are used by commercial breeders to select plants or animals that possess the gene of interest (Nill, 2001).

Metabolic pathway – A series (or pathway) of chemical reactions within a cell that result in the production of a specific chemical. Each reaction is dependent on one or more previous reactions.

Metabolic pathway engineering – The alteration of a metabolic pathway to induce a cell to either produce a desired substance or consume a substance (as for environmental remediation).

Microarray – A large number of cloned DNA molecules arranged in a compact and orderly pattern of sub-microlitre spots onto a solid matrix (typically a glass slide). Microarrays are used to analyse patterns of gene expression, presence of markers, or nucleotide sequences. The major advantage of micro-arrays is their speed, enabling large numbers of individuals to be simultaneously genotyped at many loci. *Synonym*: DNA chip (FAO, n.d.).

Microbial enhanced oil recovery – The use of microorganisms to retrieve additional oil from existing wells, thereby enhancing the petroleum production of an oil reservoir (Government of Canada, 2008).

Micropropagation – A technique to mass produce identical copies (genetic clones) of a plant variety.

Monoclonal Antibody (mAbs) – An antibody, produced by a hybridoma cell, that attaches to a specific antigen (FAO, n.d.). A mAb can be used as a diagnostic or to attack specific cells, such as cancer cells that express unique proteins. The mAb can induce an immunological reaction or deliver a cell toxin.

Mutagenesis – A process that produces a permanent change in the genetic sequence of an organism. Mutagenesis can be caused by exposure to radiation or some types of chemicals. Breeders can use these methods to create genetic variation in an organism.

Mycorrhiza – A symbiotic (mutually beneficial) fungal infection of the roots of specific plant species. The fungi extract minerals and nutrients such as phosphorous from the soil and supply them to the plant roots. In return, the plant roots provide nutrients such as sugar molecules to the fungi (Nill, 2001).

Nanotechnology – The set of technologies that enables the manipulation, study or exploitation of very small (typically less than 100 nanometres) structures and systems. Nanotechnology contributes to novel materials, devices and products that have qualitatively different properties than materials constructed from larger particles (OECD, 2008).

Nucleotides – A building block of DNA or RNA, consisting of one nitrogenous base, one phosphate molecule, and one sugar molecule (deoxyribose in DNA, ribose in RNA) (HHMI, n.d.).

Nutraceutical – A product, isolated or purified from plants or animals, with demonstrated (or assumed) physiological benefits or which provides protection against chronic disease (Health Canada, 1998). Nutraceuticals are usually sold as dietary supplements.

Oligonucleotides – A short string of nucleotides (a single-stranded segment of DNA) often used as a probe to find a matching sequence of DNA or RNA (HHMI, n.d.).

Orphan disease – A disease that affects a small percentage of the population. In Europe, orphan diseases affect 1 or fewer people per 2 000 (Orphanet, n.d.). The American definition is approximately equal to a disease that affects 1 per 1 500 people. The definition of an orphan disease can vary by region or over time.

Orphan drug – A designation of the FDA for a therapy for treating a rare disease (one affecting less than 200 000 people in the United States). The US government offers additional incentives to drug companies (*i.e.* tax advantages and extended marketing exclusivity) to develop drugs for rare diseases (UVA, 2009).

Pest resistance – A genetic trait that improves the ability of a plant to resist harmful pathogens such as insects, viruses, bacteria, fungi and nematodes. The most common form of GM pest resistance uses a gene from the bacteria (*Bacillus thuringiensis*, or Bt) to emit an organic toxin that kills some pest species.

Pharmacogenomics – The general study of all of the many different genes that determine drug behaviour (NCBI, 2004).

Pharmacogenetics – The study of inherited differences (variation) between individuals in drug metabolism and response (NCBI, 2004).

Phenotype – The visible appearance of an individual (with respect to one or more traits) which reflects the reaction of a given genotype with a given environment (FAO, n.d.).

Polymerase chain reaction (PCR) – A molecular procedure to produce multiple copies (amplification) of a specific DNA sequence, provided that the base pair sequence of each end of the target is known (FAO, n.d.).

Priority disease – A general term for diseases that attract targeted policy actions because they pose a significant risk to public health and /or there is a lack of effective diagnostics or treatment therapies. Priority diseases vary by country, region, and over time.

Priority drug – Either a drug candidate that is expected to provide a significant therapeutic improvement to existing therapies for treating a specific disease or condition, or a drug that effectively treats serious conditions.

Product quality trait – Genetic traits that change the composition of a plant. They include modified flavour, colour, starch or oil composition, or production of valuable medical and industrial compounds.

Protein – A molecule composed of amino acids linked together in a particular order specified by a gene's DNA sequence. Proteins perform a wide variety of functions in the cell; these include serving as enzymes, structural components, or signalling molecules (HHMI, n.d.).

Proteomics – The scientific study of an organism's proteins and their role in an organism's structure, growth, health, or disease status (and/or the organism's resistance to disease, etc.). (Nill, 2001).

Real-time diagnostic – A diagnostic that gives results very quickly, without delays due to laboratory testing. A simple example is a digital thermometer.

Recombinant DNA – DNA that contains DNA fragments from two or more different sources (FAO, n.d.). Genetic engineering is usually used to introduce new DNA sequences into the host DNA.

Recombinant vaccine – A vaccine consisting of a single protein from a virus or other infectious agent. The protein is obtained from recombinant bacteria or fungi that have been genetically engineered to produce the protein. The immune system makes antibodies to the protein, creating immunity to the disease agent.

Regenerative medicine – The study and development of artificial organs, specially-grown tissues and cells (including stem cells), laboratory-made compounds, and combinations of these approaches for the treatment of injuries and disease (UPMC, 2009).

RNA – Abbreviation for ribonucleic acid. An organic acid polymer composed of the bases adenine, guanine, cytosine and uracil. RNA forms the genetic material of some viruses. In other species, RNA is derived from DNA by transcription and either carries information (messenger RNA), provides sub-cellular structure (ribosomal RNA), transports amino acids (transfer RNA), or facilitates the biochemical modification of itself or other RNA molecules (FAO, n.d.).

RNA interference (RNAi) – A gene-silencing process in which double-stranded RNAs trigger the destruction of specific RNAs, interfering with their activity in the cell (NIGMS, n.d.).

Scaffold – A material that provides a structure for young cells as they grow into mature tissue (UPMC, 2009).

Small RNA-induced gene activation (RNAa) – The opposite of RNAi. In this case, double stranded RNAa switches on or activates a gene.

Somatic embryogenesis – In plant culture, the process of creating new plant embryos from vegetative cells (SIVB, 1990).

Somatic nuclear transfer cloning – A technique that combines an enucleated egg (nucleus removed) and the nucleus of a somatic cell to make an embryo. The technique can be used for therapeutic or reproductive purposes (NIH, 2008).

Stem cell – Cells that can differentiate and grow into the various cells or tissues of the adult organism. Stem cells can be derived from embryos, while others are present in adults.

Synthetic biology (synbio) – Synthetic biology refers to both: *(1)* the design and fabrication of biological components and systems that do not already exist in the natural world; and *(2)* the re-design and fabrication of existing biological systems (syntheticbiology.org, n.d.).

Technical trait – Genetic traits, such as for markers, that are essential for plant or animal breeding programmes. They rarely have a commercial value for growers.

Therapeutic vaccine – A vaccine which prevents or eases the severity of problems from an infection that has already occurred (Wiktionary, 2008a).

Tissue engineering – A group of technologies that provide functional substitutes for damaged tissues, such as liver, cartilage, or skin. Tissue engineering can produce both fully artificial tissue replacement or be based on creating natural tissues, such as through the manipulation of stem cells.

Transesterification – The reaction of an ester with an alcohol in order to replace the alkoxy group. It is used in the synthesis of polyesters and in the production of biodiesel (Wiktionary, 2008b). In the latter case, the process results in glycerin (a byproduct) and methyl/ethyl esters used as biodiesel.

Vaccine – A preparation of dead or attenuated (weakened) pathogens, or of derived antigenic determinants, that can induce the formation of antibodies in a host, and thereby produce host immunity against the pathogen (FAO, n.d.).

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The Bioeconomy to 2030

DESIGNING A POLICY AGENDA

The biological sciences are adding value to a host of products and services, producing what some have labelled the "bioeconomy". From a broad economic perspective, the bioeconomy refers to the set of economic activities relating to the invention, development, production and use of biological products and processes. If it continues on course, the bioeconomy could make major socioeconomic contributions in OECD and non-OECD countries. These benefits are expected to improve health outcomes, boost the productivity of agriculture and industrial processes, and enhance environmental sustainability. The bioeconomy's success is not, however, guaranteed: harnessing its potential will require coordinated policy action by governments to reap the benefits of the biotechnology revolution.

The Bioeconomy to 2030: Designing a Policy Agenda begins with an evidence-based technology approach, focusing on biotechnology applications in primary production, health, and industry. It describes the current status of biotechnologies and, using quantitative analyses of data on development pipelines and R&D expenditures from private and public databases, it estimates biotechnological developments to 2015. Moving to a broader institutional view, it also looks at the roles of R&D funding, human resources, intellectual property, and regulation in the bioeconomy, as well as at possible developments that could influence emerging business models. Fictional scenarios to 2030 are included to encourage readers to reflect on the interplay between policy choices and technological advances in shaping the bioeconomy. Finally, the book explores policy options to support the social, environmental and economic benefits of a bioeconomy.

The International Futures Programme (IFP) of the OECD undertook *The Bioeconomy to 2030* project with the support of other interested OECD directorates, OECD Government Ministries, and outside partners.

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