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.

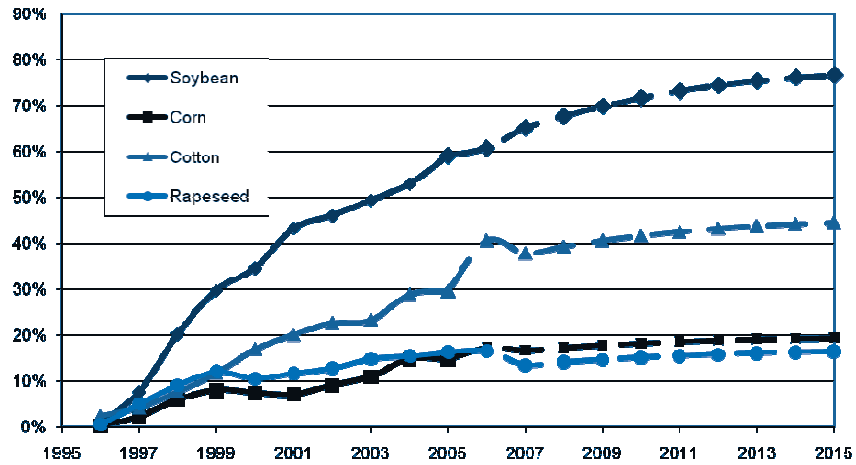
Biotech applications to 2015 for plants

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.

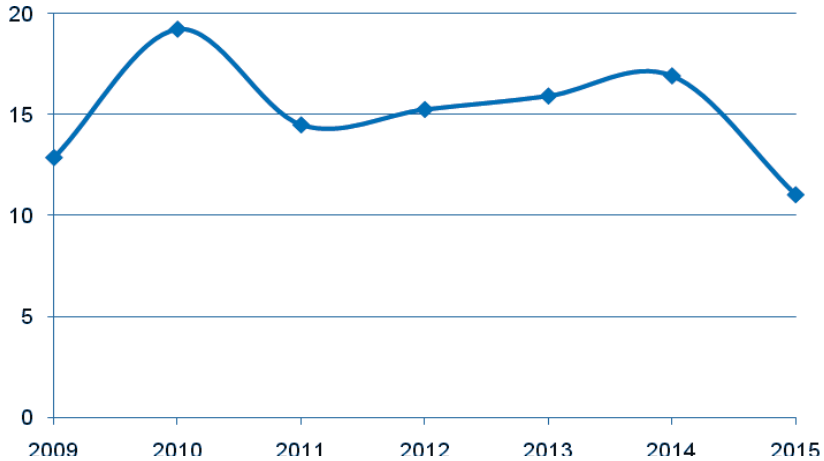
A transition from current healthcare models to a predictive and preventive health system has already begun, but could be slowed due to high costs, the need for long-term follow-up, and a poor fit with existing business models.

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.

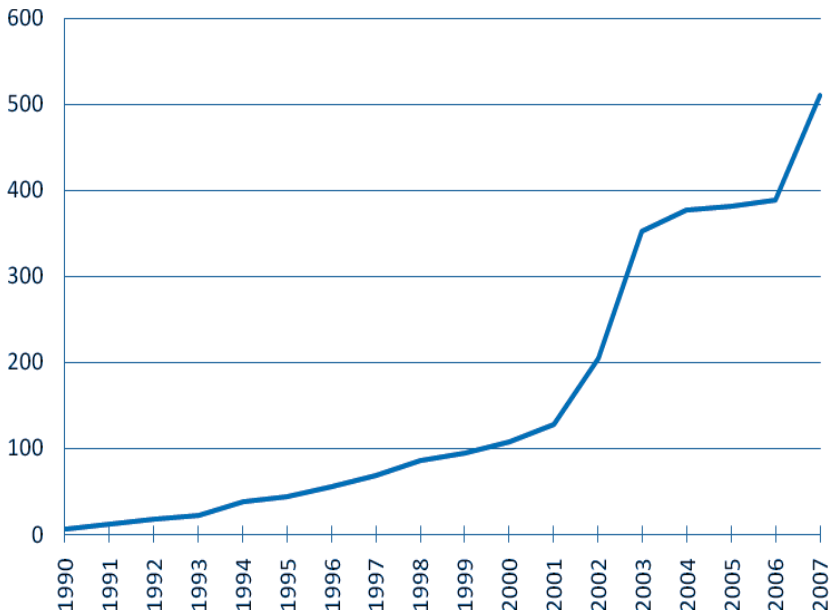
As noted in Chapter 3, the availability and use of *in vitro* diagnostics, and in particular genetic tests, has increased substantially since the mid-1990s. There are no data available that can be used to predict the number of genetic tests that will reach the market in the future. There are about 6 000 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.

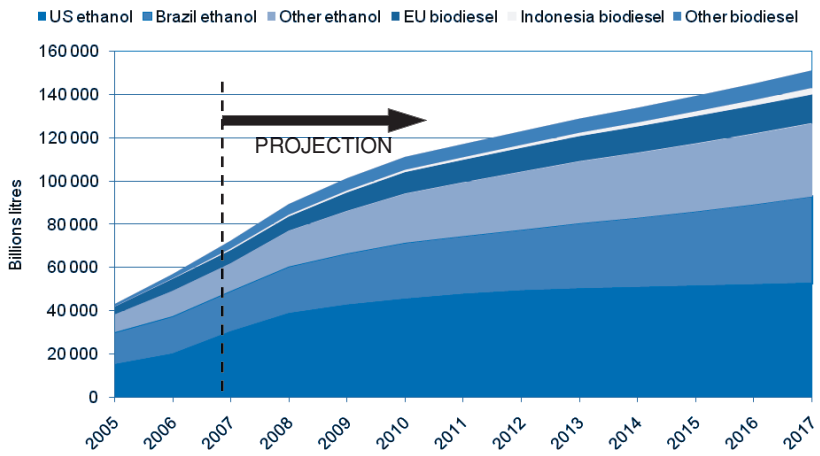
Biorefineries

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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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

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