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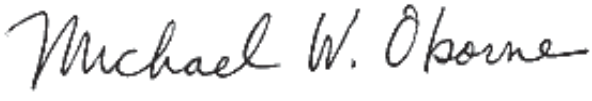
Foreword

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. The potential benefits of a bioeconomy over the short term (up to 2015), the long-term uncertainties up to 2030, and the possible policy responses were evaluated in the OECD's International Futures Programme's project *The Bioeconomy to 2030.*

The project finds that 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. 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.

The bioeconomy project's final report, *The Bioeconomy to 2030: Designing a Policy Agenda*, provides a summary of the main trends in biotechnology up to 2030 in agriculture, health and industry and an extensive discussion of the policy implications. The final report was published by the OECD in April 2009.

The articles contained in this issue of the *OECD Journal* were written for the *Bioeconomy to 2030* project. They provide evidence-based projections on the development of biotechnologies – the building blocks of the bioeconomy – up to 2015 in agriculture and health. Although some of these projections were included in the full project report, these two articles go into much greater detail on the current state and expected developments of biotechnology applications in agriculture and health. In addition, these two papers have been updated, wherever possible, and therefore contain more recent data than available for the final bioeconomy project report. The article on agricultural biotechnology also includes data on plant patents that was not previously available. The future of industrial biotechnology and biofuels are not evaluated here as they are covered extensively in *The Bioeconomy to 2030: Designing a Policy Agenda*.



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Biotechnologies in Agriculture and Related Natural Resources to 2015

Anthony Arundel

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The main current uses of biotechnology for agriculture and related natural resources (ANR) are for plant and animal breeding and diagnostics, with a few applications in veterinary medicine. This encompasses the use of both transgenic and non-transgenic biotechnologies. This study provides an overview of the current state of technological development and, through an analysis of quantitative data related to R&D pipelines and the current literature, presents estimates and projections for the types of biotechnologies expected to reach the market for use in ANR to 2015. The trends indicate that several novel agronomic and product quality traits will reach the market for a growing number of crops. Biotechnologies other than genetic modification (GM) will also be used to improve livestock for dairy and meat. Socioeconomic issues, such as market concentration and public acceptance, are also examined to further refine the analysis of issues that will influence biotechnological developments and adoption for ANR. These results point to a future for ANR where biotechnologies play a substantially larger role than today. This will be visible in an increased use of biotechnologies for a wider range of plants and animals, and the active involvement of a growing number of countries in the development of biotechnologies.

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Abbreviations

ANR	Agriculture and Related Natural Resources
Bt	Bacillus thuringiensis
ETM	Estimated time to market
EPO	European Patent Office
EU	European Union
EUKLEMS	European Union Capital, Labour, Energy, Materials, and Services inputs
FAO	The United Nations Food and Agriculture Organisation
GDP	Gross Domestic Product
GM	Genetic Modification *or* Genetically Modified
GVA	Gross Value Added
HT	Herbicide Tolerant *or* Herbicide Tolerance
ISAAA	International Service for the Acquisition of Agri-Biotech Applications
ISIC	International Standard Industrial Classification
JRC	European Commission's Joint Research Centre
MAS	Marker Assisted Selection
NACE	Classification of Economic Activities in the European Community
NAFTA	North American Free Trade Agreement
NAICS	North American Industry Classification System
nec	Not elsewhere classified
OECD	Organisation for Economic Cooperation and Development
OIE	World Organisation for Animal Health
PCR	Polymerase Chain Reaction
UNU-MERIT	United Nations University – Maastricht Economic and social Research and training centre on Innovation and Technology
USDA	United States' Department of Agriculture
USPTO	United States Patent and Trademark Office

Executive summary

This article covers short-term estimates to 2012-2015 of the use of biotechnology in agriculture and related natural resources (ANR). This includes food and feed crops, animal husbandry, forestry and fishing. The main biotechnologies of relevance to ANR include genetic modification, marker assisted selection, propagation technologies, therapeutics and diagnostics.

Where possible, this article gives qualitative estimates of products that are likely come on the market by 2015, as well as quantitative estimates of the potential or real impacts of biotechnology products. Data are obtained from publicly available sources such as the OECD, Eurostat and the FAO; the UNU-MERIT database of GM field trials, the web-sites of biotechnology firms, European Patent Office (EPO) and United States Patent and Trademark Office (USPTO) patent data, and the published literature. Where available, data are provided for two main types of indicators for each application of biotechnology: current use and trend estimations to 2012-2015.

The contribution of ANR to world gross domestic product (GDP) and employment is difficult to determine, as data on forestry and fishing are not consistently available. In 2006, agriculture alone accounted for approximately 4% of global output of 46.7 trillion and for 40.7% of global employment of 3 billion.

The ANR share of total gross value added and total employment provides an estimate of the maximum possible contribution of biotechnology to economic output and employment in these sectors (for instance if 100% of all agricultural production was dependent, in some way, on biotechnology). Biotechnology applications would then contribute to approximately 2% of gross value-added within the OECD. This assumes no large shifts in the value of ANR products which could occur from improved quality traits for industrial processing or the use of crop species (including plantation trees and grasses) for biofuel production.

Crops

In addition to the literature, three data sources were used to determine the types of crop varieties, based on biotechnology, that could reach the market prior to 2015 and their impact:

- GM field trial data, which are used to identify the focus of research into specific GM traits and predict the types of GM crops that could reach the market by 2015.
- R&D pipeline data on GM varieties derived from the annual reports of the world's largest seed firms.
- Extrapolation from past trend rates in hectares planted to four main GM crop varieties.

Four main trait categories are the focus of current GM plant breeding programmes: herbicide tolerance, pest resistance (including insect, virus, bacteria, fungi and nematode resistance), agronomic traits for improved yield or stress tolerance, and product quality characteristics. These same characteristics are expected to also be the focus of non-GM breeding programmes.

The number of firms active using advanced biotechnology to develop new varieties of plants has been declining over time due to firms leaving the market and to mergers and acquisitions. The degree of increasing concentration is evident from the patent and GM field trial data. Between 1990 and 1994 five firms accounted for 36.7% of biotechnology plant patents granted by the USPTO. The share of the top five firms increased to 80.5% of biotechnology plant patents granted between 2000 and 2004. Between 1995 and 1999, 146 firms applied for at least one GM field trial. Ten years later the number declined by almost half to 76 firms that applied for a field trial between 2005 and 2009.

The public research sector (including universities, research institutes and private non-profit institutions) continues to play an important role in the development of new crop varieties and GM research, both in developed and developing countries. Research institutes in Africa, India and Brazil have used biotechnologies to develop improved crop varieties. The public research sector conducted an estimated 20.7% of all GM field trials in the OECD between 2004 and 2008. The public research sector also accounted for 23.8% of biotechnology plant patent applications at the European Patent Office and for 21.9% of this type of patent at the USPTO between 2001 and 2006.

Due to the absence of regulatory filing requirements (such as those associated with GM crops), there are no consistent data on the share of seed firms that use non-GM biotechnologies such as marker assisted selection (MAS). Data from interviews suggest that almost all seed firms in OECD countries are likely to currently use MAS, GM or other biotechnologies in at least some of their breeding programmes, particularly for large market crops such as maize and soybeans. Almost all varieties of large market crops will probably be developed using MAS or other biotechnologies by 2015 (cotton, maize, potatoes, rapeseed, rice, soybeans, and wheat). The exception is some small market vegetable, berry, and tree fruit crops, where the large cost of identifying markers could limit the use of MAS.

Field trials of GM traits have been conducted for 130 plant species. The 25 species with the highest number of trials account for 94.4% of all field trials of plants. New GM varieties are still most likely to appear in the main GM crops to date of maize, soybeans, cotton and rapeseed. However, GM varieties should appear by 2015 in several plants that do no yet have any commercial GM varieties on the market, including barley, peanuts, peas and sugarcane.

The share of the two main traits that dominate approved products to date, herbicide tolerance and pest resistance, has declined steadily over time. Conversely, investment in GM research programmes for agronomic traits has been increasing, with a ten fold increase in GM trials for agronomic traits since 1990.

A large number of traits appear to have been abandoned, either due to technical failure or lack of commercial markets. In several cases the number of field trials for a specific trait, such as herbicide tolerance in grapes, suggests that the research programme was abandoned even though it was successful or close to success. One possible cause is a concern over public acceptance of products produced from GM crop varieties.

The estimates from the GM field trial data are corroborated with data on GM varieties derived from the annual reports of four of the world's largest seed firms. The four firms

report research programmes for 112 new crop-trait combinations, with maize accounting for 43% of the total, followed by soybeans (33%), rapeseed (13%), and cotton (9%). Pest resistance accounts for 25 research programmes (22%) and herbicide tolerance for 24 research programmes (21%). However, the main GM firms are moving into both second generation product quality traits (34 research programmes or 30% of the total) and agronomic traits (24 research programmes or 21% of the total). There are also six research programmes under pest resistance into the more technically difficult traits for resistance to nematodes and fungi.

The number of hectares planted to GM and the GM share of hectares planted is forecast to increase for all four main GM crops to 2015. The fastest uptake of GM technology has been for soybeans, with GM varieties accounting for 65.8% of global cultivation in 2008. Based on past trends, the GM share is estimated to increase to 88.2% of all hectares planted to soybeans in 2015. GM cotton also sees a substantial increase in its global share from nearly 47.1% in 2008 to 72.7% in 2015. Maize could increase from approximately 23% to just over 30% by 2015 and GM rapeseed is forecast to increase from 18.5% to 21.3% of hectares planted. These projections, based on past trends, could be substantially increased by the adoption of GM crops in countries growing a large share of world hectares (*e.g.* China and India adopting GM maize) and by the introduction of significant improvements in GM varieties that result in faster uptake by farmers.

Potential trends – 100% biotech crops

The maximum contribution of biotechnology to the food, feed and industrial feedstock sector would be reached when 100% of crops are based on varieties developed through biotechnology. This is unlikely to occur for any crop because there will continue to be markets for organic or traditional varieties, but GM or MAS varieties of soybeans and maize could be responsible for the vast majority of total plantings by 2012.

There are very few GM varieties on the market for many high value-added crops including vegetables, nuts, fruits, olives and wine grapes. The rate at which varieties based on biotechnology are adopted in this group will depend on consumer acceptance issues and the cost of GM, MAS and other biotechnologies used in plant breeding.

Animal husbandry

Livestock accounts for approximately 40% to 50% of the value of agricultural production in OECD countries, with the main outputs being dairy products, eggs, meat, and fibre (wool, hair, etc). Biotechnology has three main applications for livestock: breeding, propagation, and health applications.

The largest current commercial application of the use of biotechnology in animal breeding is the application of MAS to conventional breeding programmes for pigs, cattle, dairy cows, and sheep. This will continue up to 2015. The most probable application of advanced propagation techniques to reach the market is the cloning of GM animals to produce pharmaceuticals, followed by cloned breeding stock. The first commercial use of the latter technology for meat production could occur in non-OECD countries, where public opposition to meat derived from cloned animals could be less important than in OECD countries.

Generally, the costs of bio-pharmaceuticals combined with limited applications (they are too expensive for chronic disease in animals) are likely to restrict their use in livestock

to either products such as growth or meat quality enhancers (bST and porcine somatotropin) or for economically expensive infective diseases for which other treatments are not available. Over the short term, the most important application of biotechnology to animal health is likely to be for diagnostics for genetic conditions and for recombinant vaccines. Genetic diagnostics for diseases hold great promise, but the technology is not as advanced as other biotechnology applications.

Other applications: fishing, forestry and insects

Up to 2015, the largest potential for biotechnology in fishery applications are for wild stock management, for diagnostics and therapeutics for aquaculture, and the use of MAS and related non-GM biotechnologies for breeding fish, mollusc and crustacean varieties for aquaculture.

Biotechnology applications in forestry include the use of MAS and GM in breeding programmes and somatic embryogenesis for micropropagation of conifer species. Improved growth rate varieties of GM trees could be ready for commercialisation by 2012, and reduced lignin varieties for paper making (or bioethanol) by 2015. MAS could be widely used in breeding programmes, particularly in countries such as Canada and New Zealand with major forestry industries.

Honey bees are the most economically valuable insect species with potential applications of biotechnology. The most probable developments include *(1)* insecticide and pest resistant varieties of honey bees, developed using MAS or possibly GM technology (more likely to appear towards the end of the time period 2012 to 2015), and *(2)* more extensive diagnostic tests for pathogens that attack honey bee hives. The latter should appear continuously over time.

Developing countries

The potential applications of biotechnology to living natural resources in developing countries is enormous, both because developing countries contain more than 70% of the world's agricultural and forest land and because agriculture is relatively more important to their economies, in terms of share of GDP and employment, than in the developed world. Developing countries have been early adopters of agricultural biotechnologies, accounting for slightly less than half of all GM plantings in 2008. Although this initial wave of agricultural biotechnology uptake in the developing world was mainly driven by technologies developed in OECD countries, developing countries are moving towards developing technologies on their own. Agricultural biotechnology R&D budgets in some large developing countries are beginning to approach those of OECD countries and activities such as field trials of GM crops are widespread. To 2015, developing countries will become much more heavily involved in biotech commercialisation, especially for new varieties of indigenous crop species and to adapt other crops to local conditions.

Public attitudes

The application of GM technology to plant and animal breeding has been affected by public opposition. This is by no means limited to Europe. Concern over a lack of markets in many OECD countries, including the United States, could be reducing private sector investment in developing GM varieties of fish, honey bees, and food animals. In crops,

the main application of GM technology has been for animal feed crops and for crops that are used in food processing, with few GM crops on the market that are directly eaten by consumers. If public opposition continues, firms could continue to limit investment in GM to feed and industrial feedstock crops such as trees or bioenergy feedstock plants such as grasses. Non transgenic biotechnologies such as MAS and cisgenesis have not raised public concerns to date, which could encourage wider use of these technologies.

Conclusions

The trends explored in this article indicate that R&D is likely to continue to result in commercially valuable products that will be adopted in an increasingly large number of regions. New crop varieties with improved agronomic traits are expected to reach the market by 2015. These new varieties will not only deliver yield gains, but could reduce the environmental impacts of intensive agriculture. Furthermore they will help agriculture deal with changing environmental conditions due to climate change by improving tolerance to drought, heat or cold, and salinity.

Demand for food, feed and fibre is expected to increase substantially in the future due to population and income increases across the globe. To meet increased demand, a diverse range of solutions are going to need to work in concert. Biotechnological solutions will play a major role, but will not provide a silver bullet. They will need to be combined with other strategies to modernise agricultural methods and increase agricultural productivity (*e.g.* through farmer education, improved water management and conservation, and precision farming).

Introduction

As a technology for propagating and changing the characteristics of living organisms, biotechnology has many current and potential applications in agriculture and related natural resources (ANR), covering the use of plants, animals and insects to produce food, feed and fibre for human use or consumption. ANR can be divided into three main applications fields for biotechnology: *(1)* food, animal feed, and industrial feedstock crops, *(2)* animal husbandry and related activities such as fishing, aquaculture and bee-keeping, and *(3)* forestry. The first group mostly consists of annual and biannual plant species, but it also includes perennials such as grapes, berries, and orchard trees. Biofuels form a fourth application field that can use crop plants, animals (fats for biodiesel) and forestry products as energy sources. The future of biofuels is not evaluated here as they are covered extensively in *The Bioeconomy to 2030: Designing a Policy Agenda* (OECD, 2009).

The main purpose of this article is to identify the types of biotechnology products in ANR that are already on the market, both within the OECD and in developing countries, and to estimate the types of new products that could reach the market by 2015. This introduction looks at the economic and environmental factors influencing the future of ANR (these factors have a strong influence on the use of biotechnology), describes the data sources used in this article, and provides an overview of the potential economic contribution of biotechnology in ANR. The remaining chapters look at specific application fields, with a final chapter on the use of biotechnology in developing countries.

The future of agriculture and related natural resources

Increased demand, higher incomes, and environmental developments are predicted to increase the average price of food, feed and other resource-based commodities up to 2017 compared to the decade before 2008. This will reduce, but not entirely eliminate, the long-term decline in the real price of agricultural and related commodities. This is even the case after the sharp fall in prices in early 2008 (OECD-FAO, 2008).

Demand for food and feed will increase as a result of the world population growing to approximately 8.3 billion in 2030 (UN, 2006),[1] with 97% of the population growth expected to occur in developing countries. An increase in average incomes will have a major effect on increasing demand, with global gross domestic product (GDP) expected to rise 57% from an average of USD 5 488 per capita in 2005 to USD 8 608 per capita in 2030. The GDP share of countries outside the OECD will increase from 21% of global GDP in 2005 to 30% in 2030 (OECD, 2008a). Increased incomes in developing countries will spur demand for meat, fish and dairy products, which require large inputs of animal feed. A third factor which could spur demand for natural resources is a growing market for biofuels.

There are two main methods for increasing the supply of agricultural products to meet future demand. One is to increase the amount of land under cultivation, which increased by 10.4% between 1961 and 2005.[2] 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 second solution is to increase yields through the adoption of improved crop varieties worldwide and intensive agricultural techniques in developing countries. The latter will require investment in education, infrastructure, and technology.

The ability to increase supply could run up against environmental constraints from water scarcity and climate change. The same factors that are contributing to increased demand for agricultural products, such as the rapid increase in global demand for meat and dairy 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, 2008b). Meat production is especially water intensive.[3] Another growing concern is how to manage an expected long-term decline in inexpensive sources of phosphorous, a key plant nutrient (Vaccari, 2009).

Current trends towards greater water scarcity, combined with a possible increase in the frequency of droughts from climate change, could result in a massive increase in the number of people living in areas under water stress (see Table 1). 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 share of the global population living in areas with low or no water stress is expected to increase by only 4%. Water pollution could also increase, with an estimated 5 billion people (1.1 billion more than today) in 2030 without connection to a sewage system (OECD, 2008b). An increase in the use of fertilisers to improve yields could also have a negative impact on water quality.

Table 1. **Population living in areas under water stress[1,2] (in millions)**

Water stress level	2005	% of world population	2030	% of world population	Total population change (2005-30)
Severe	2 837	44%	3 901	47%	38%
Medium	794	12%	1 368	17%	72%
Low	835	13%	866	11%	4%
None	2 028	31%	2 101	26%	4%
Total	6 494	100%	8 236	100%	27%

Source: OECD, 2008b.

Notes: 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.

Global warming will also play a role. 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 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 (Stern, 2006; IPCC, 2007).

Agricultural systems in developing countries are likely to acutely experience all of these supply and demand effects. By 2017, they 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). These countries have also been at the forefront of the adoption of genetically modified (GM) crops. If adoption rates continue at past trends, GM crop plantings (as measured in hectares planted) in developing countries will surpass that of the developed world in 2012 (Sawaya and Arundel, 2009).

Sustained high demand and prices for food and water will provide a strong incentive for investment in technologies that can increase agricultural productivity while reducing the environmental impacts of intensive agriculture. Agricultural biotechnologies, especially those that increase yield and tolerance to salinity and drought in commercially valuable plant varieties, are a possible solution in many parts of the world. Of note, biotechnology is not the only solution to future supply constraints. Other methods include education, water harvesting and improved irrigation practices, precision farming, integrated pest management, and improved storage to reduce after harvest losses from pests.

Estimating the use of biotechnology in ANR

The term "biotechnology" covers a wide range of technologies. In this article we limit biotechnology to modern, technologically advanced biotechnologies for use in breeding programmes to develop new varieties of living organisms, propagation, and for managing the health of commercially valuable plant and animal stocks (see Box 1).

Box 1. **Main advanced biotechnologies used in agriculture and related natural resources**

Breeding: New varieties of food and feed crops, fibre crops (trees and grasses), animals for meat, dairy and fibre, and fishes and molluscs for aquaculture are continually developed by firms and public sector research institutions. Breeding programmes can increase yields, pest and herbicide resistance, resistance to environmental stresses such as cold, heat, and drought; and improve product characteristics. The application of biotechnology to breeding can reduce the time required to develop a new variety and make it easier to introduce valuable novel traits. The goals of breeding programmes are determined by economic and environmental factors. Biotechnologies for breeding can be divided into two groups, based on the current regulatory structure for new varieties:

Non-transgenic breeding methods: This includes the use of marker assisted selection and related genomic technologies such as genotyping, polymerase chain reactions (PCR), and high throughput sequencing to speed up conventional breeding. It does not use interspecies gene transfer, as with GM. Marker assisted selection (MAS) uses molecular or physical markers to identify desired genetic traits for subsequent breeding. Other non-transgenic biotechnologies are used to increase genetic variety or access desired traits, such as molecular mutagenesis, gene shuffling, cisgenesis (Jacobsen and Schouten, 2007), and intragenetic vectors (Conner *et al.*, 2007).

Genetic modification (GM): The insertion of a gene or genes from one species into another species that cannot interbreed under normal conditions (transgenes). This technology also uses many of the biotechnologies identified above under "non-transgenic breeding methods".

Propagation: Advanced reproduction methods include plant tissue culture,[4] cloning, apomixis and somatic embryogenesis

Health (diagnostics and therapeutics): Biotechnology based diagnostics are used in the surveillance and identification of plant and animal diseases. Therapeutic drugs are primarily used in animal husbandry. The application of diagnostics and therapeutics to ANR is closely related to similar technologies developed for human health applications. A therapeutic class limited to ANR is biopesticides, which use insects or microorganisms to attack plant pests.

Several data sources are used to identify current uses of biotechnology and to estimate trends in the three main application areas, as summarized in Table 2. The reliability of the forecasts varies by application field, due to data availability. The most robust forecasts are for new varieties of species developed through GM technology, followed by new varieties using MAS and related biotechnologies. Due to regulatory requirements, quantitative data on field trials of new GM plant varieties are available for 27 of the 30 OECD countries, plus non-OECD countries that are members of the European Union.[5] The field trial data were obtained from public sources in Australia, Japan, Mexico, New Zealand, the United States and the European Union. The data include information on the date of the field trial, the country where it was conducted, the organisation applying for the trial, the type of trait, and the plant species. The longest data series is for the European Union and the United States, beginning in 1987. For all countries, data are available up to December 31, 2008.

Table 2. **Data availability for biotechnology by application**

Application field	Data sources by type of biotechnology		
	New varieties	Propagation	Diagnostics & therapeutics
1. Food, feed, and industrial feed stock crops (incl. pharmaceuticals)	UNU-MERIT GM field trial database Annual reports of seed firms for GM pipeline Annual reports of seed firms for MAS activity FAO, ISAAA and other sources for crop hectares and prices FAO BioDec database	Literature	Literature
2. Animal farming - dairy, meat and wool - aquaculture and marine - beneficial insects (honey bees)	Literature, interviews FAO BioDec database	Literature	Literature
3. Forestry	UNU-MERIT GM field trial database FAO BioDec database	Literature	Literature

The second best data coverage is for the use of MAS, with almost all breeding firms developing the ability to use this and related technologies. However, regulatory requirements for new varieties based on MAS and other non-GM biotechnologies such as gene shuffling are much less strict than for GM, and therefore data are much less comprehensive.

The number of plant patent applications at the European Patent Office (EPO) and the United States Patent and Trademark Office (USPTO) are used to evaluate the level of concentration in plant biotechnology and the contribution of the public research sector to new inventions in plant biotechnology. The patent data for the EPO cover patent applications between 1980 and 2006 inclusive. The USPTO data cover applications from 2001 to 2007 and patent grants from 1980 to 2006.

The analyses of the patent data are limited to patents assigned to at least one of IPC classes A01H1 to A01H4, C12N15/82, C12N15/83, or C12N15/84. The results exclude patent applications or grants for new plant varieties only (IPC classes A01H5 – A01H17). It is important to exclude patents that are only assigned to the latter IPC classes because many firms choose to protect plant varieties in the United States through a patent rather than through plant breeder's rights. Many of these varieties could have been developed without the use of modern biotechnology.[6] Annex B provides full details on the IPC classes used in this article.

This paper assumes that the types of plant breeding research programmes underway using GM technology are indicative of the types of research programmes that are underway using non-transgenic breeding technologies. This is a reasonable assumption because similar economic goals are likely to drive all plant breeding programmes. In both cases, firms focus their development on economically valuable traits for crops with large markets. The main difference between GM and non-transgenic biotechnologies from the perspective of the firm is that the latter is not influenced by regulatory barriers and, to date, political opposition to their use.

While this article's goal is to provide quantitative estimates for all technology areas, only qualitative information is available for the use of biotechnology to develop new varieties of animals. Where available, data are provided for two main types of indicators for new varieties of plants and animals: current use and trend estimations to 2012-2015. Examples for GM crops are as follows:

1. **Current use:** Data on current use are obtained from publicly available sources, such as the International Service for the Acquisition of Agri-Biotech Applications (ISAAA) for GM crops and estimates of the total hectares planted to specific types of target GM crops worldwide and by major region (OECD, EU, North America, and South America) from FAO data.

2. **Forecasts to 2015**: Forecasts are based on projections from past adoption rates for biotechnology and from data on ongoing research projects. For example, ISAAA data on the number of hectares planted to GM crops per year over the past decade are used to estimate GM crop hectares up to 2015. GM field trials (a measure of investment in specific research projects) and data from the annual reports of seed firms are used to estimate the types of new GM varieties that should reach the market between 2008 and 2015.

Maximum potential impact of biotechnology in ANR

An important issue for both Government policy and firms is the maximum potential of biotechnology applications to output in the ANR sectors. This potential can guide both public policy and public and private investment in biotechnologies of relevance to this sector. The upper limit would be reached if biotechnology contributed to 100% of economic output. As an example, the upper limit for maize production would occur if maize varieties, developed using biotechnology, accounted for all hectares planted to maize. Of note, the maximum potential impact is not expected to be reached in the foreseeable future, due to many factors that are likely to maintain markets for other technologies.

The maximum potential for the ANR sectors can be estimated from national account data for the sector "Agriculture, hunting, forestry and fishing".[7] Agriculture includes growing all crops, all forms of animal husbandry, and related services such as seed production and propagation. Hunting (largely trapping) is a very minor part of ANR in all OECD countries and can largely be ignored. Forestry includes logging and related services such as tree planting, plantation management, and propagation of tree varieties. The most important activity that is not included under "Agriculture, hunting, forestry and fishing" is animal veterinary products (pharmaceuticals and diagnostics), which is assigned to the manufacturing sector under pharmaceuticals.

The full contribution of ANR to world GDP and employment is difficult to determine, as data on forestry and fishing are not consistently available. In 2006, agriculture alone

accounted for approximately 4% of global output of USD 46.7 trillion and for 40.7% of global employment of 3 billion.

Table 3 gives basic statistics on the economic importance of the ANR sectors for the EU-25, most non EU members of the OECD, plus a few comparable results for Brazil, Russia, India and China. The contribution of ANR to total national gross value added (GVA)[8] equals 1.77% of total GVA in the EU-25 in 2004 and 1.73% of total gross value added in the United States, with agriculture accounting for most of the value-added from ANR: 86% in the EU-25 and 95% in the United States. Unfortunately, separate value-added data for agriculture (Column *(3)*) are not available for the other OECD countries.

These results suggest that the maximum potential contribution of the use of biotechnology in the ANR sectors ranges from 1.25% of GDP in Japan to 9% of GDP in New Zealand, with an OECD average of approximately 2%. Elsewhere, we provide a "probable" estimate of the contribution of biotechnology in the ANR sectors within the OECD in 2030, based on potential applications in forestry, agriculture and fishing. The average contribution across all OECD countries in 2030 is estimated at 1% of OECD GDP in 2030.

Of note, the maximum and probable contribution of biotechnology in the future is not directly equivalent to economic impacts, which depend on the additional value-added from using biotechnology compared to alternative technologies. The concept of a "contribution" assumes that alternative technologies are no longer economically competitive, even though the difference in productivity could be relatively minor.

In absolute terms, the GVA of ANR sectors has declined in the European Union but increased in the United States between 1996 and 2004. However, the ANR share of total value added has declined on average by 2.47% per year in the EU-25 and by 1.05% per year in the United States. The only OECD countries with an increase in the ANR share of total value added are Australia and New Zealand. The share of total employment in ANR has declined in all countries. This trend is likely to continue into the future: even if biotechnology contributes to 100% of ANR sectors, the share of these sectors in the total value added and employment of OECD countries could continue to decline, unless there is rapid growth in new applications such as biofuels or the production of valuable chemicals in plants.

In 2007, the European Commission's Joint Research Centre (JRC) estimated the current contribution of modern biotechnology to the European life resources sectors (essentially equivalent to ANR) as between 0.01% to 0.02% of GVA (Reiss *et al.,* 2007). The higher estimate is equivalent to approximately USD 2.5 billion, or 1% of European Union ANR output. Only 19% of the contribution of biotechnology to European ANR sectors was from breeding and propagation biotechnologies, due to the low use of GM in Europe and uncertainty over the use of MAS. The estimated biotechnology contribution is largely due to activities that are not included in national accounts in ANR sectors, such as veterinary products, diagnostics, and feed additives (81% of the total contribution). Given the evidence of the use of MAS in seed development (see the section on "Food, feed, and industrial feedstock crops"), this is likely to be a substantial underestimate of biotechnology's current contribution to European ANR output.

Table 3. **Basic economic statistics for the Agriculture and related Natural Resource (ANR) sectors: 2004 or latest available year**

	USD	ANR share of total gross value added (%)	Agriculture share of total gross value added (%)	Average annual change in ANR share of total gross value added (%)	Total employment (000)	ANR share (%) of total employment	Average annual change in ANR share of total employment (%)
EU-25	12 000	1.77	1.55	-1.82	202 760	5.86	-2.47
US	10 980	1.83	1.73	0.52	149 512	2.42	-1.05
Australia	645	3.82	-	1.39	9 207	4.76	-1.14
Canada	1 089	2.21	-	-5.75	15 314	2.65	-5.04
Iceland	14	9.34	-	-2.65	0.159	6.88	-4.04
Japan	4 911	1.25	-	-4.81	66 222	5.96	-2.01
Korea	897	3.78	-	-6.23	21 557	8.82	-3.12
Mexico	742	3.79	-	-6.10	-	-	-
New Zealand	99	9.19	-	5.29	1 443	0.65	-0.69
Norway	262	1.46	-	-7.62	2 310	3.60	-4.02
Switzerland	387	1.36	-	-4.55	-	-	-
Brazil	943		8.0		96 340	20.0	
China	2 500		11.9		798 000	45.0	
India	796		19.9		509 300	60.0	
Russia	733		5.3		73 880	10.8	

Sources: EUKLEMS for EU-25 and the United States, OECD STAN database for other OECD countries. Data on agriculture alone are only available from EUKLEMS. CIA World Factbook (2007) for GDP for other OECD member states and for all data for Brazil, China, India and Russia.

Notes: 1. Value-added data are for 2004 for the EU-25 and the US, 2003 for Japan, Korea, Mexico and Norway, 2002 for Iceland and Switzerland, and 2001 for Australia, Canada, and New Zealand.

2. Total gross value-added data for Australia, Canada, Japan, Korea, Mexico, New Zealand, Norway, and Switzerland are GDP estimates for 2006. All data for Brazil, Russia, India and China are estimates for 2006. ANR employment is limited to agriculture.

3. Employment data are for 2004 for the EU-25 and the US, 2003 for Canada, Iceland, Japan, Korea, New Zealand and Norway, 2001 for Australia.

Food, feed and industrial feedstock crops

Biotechnology has two main applications for food, feed and industrial feedstock crops. The first is transgene GM, where a gene from one species is inserted into another species. The second application is the use of breeding technologies derived from biotechnology research and applied to conventional breeding, without the transfer of genes between incompatible species. These include biotechnologies such as MAS, cisgenesis, and gene shuffling combined with directed evolution. Other uses of biotechnology, such as biopesticides or diagnostics for the detection of plant diseases and pests, are so far of secondary importance to food, feed and industrial feedstock crops.

The International Seed Federation (2008) estimated that the 2008 global seed market was approximately USD 36.5 billion, of which 64% (USD 20.5 billion) is in OECD countries.[9] A large number of firms are involved in developing new seed varieties, including firms ranging in size from less than 50 employees to over ten thousand employees, but there is a lack of data on the number using biotechnologies in plant breeding.[10] Between 2004 and 2008 inclusive, 300 firms applied to patent a process for plant breeding or a biotechnology plant patent at either the EPO or the USPTO. This provides a minimum estimate of the number of firms over these five years that could have used biotechnology in plant breeding within the OECD.[11]

The adoption of biotechnology in the agricultural sector varies by crop variety. For example, only four crops, soybean, maize, cotton and rapeseed (canola), account for the vast majority of all hectares planted with GM varieties. Therefore, estimates of the current adoption of biotechnology and of future trends are best calculated on a crop by crop basis.

The economic and environmental effects of new crop varieties are due to the characteristics of the trait that is included in the plant variety. 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 insect 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.

In addition, GM research often involves *Technical traits,* such as molecular markers. Research into technical traits improves the efficiency of breeding programmes, but has little or no commercial value for growers.

Increasing concentration

A healthy, competitive sector is often characterised by a large number of firms that are capable of using scientific and technological knowledge to develop new and improved products and processes. However, many sectors, such as the automobile industry, have gone through a "shake-out" period in which capabilities are increasingly concentrated in fewer and fewer firms (Klepper, 1996). This can improve the rate of innovation by allowing the remaining firms to benefit from economies of scale and thereby increase their investment in innovation. Conversely, increasing concentration can reduce the number of firms that can experiment with a technology, leading to a decline in the rate of innovation. In the ANR sectors, increasing concentration would be of concern if it reduced the use of advanced biotechnology to develop improved varieties of a large number of crops, particularly small market crops. Concentration can be measured by both the number of firms active in a technology and the concentration of activities in a few firms. For plant biotechnology, concentration can be measured using plant patents and GM field trials.

Firms with head offices in the United States dominate plant patents for genetic modification or for plant breeding processes (patents for plant varieties only are excluded from these analyses). Out of 3 049 plant patent applications by firms at the EPO between 1980 and 2007 (for which full data are available for the application year and the name of the applicant), American firms accounted for 41.0%, European firms for 40.9%, and other countries for 18.1%. However, American dominance in 3 786 USPTO patent grants to firms between 1980 and 2006 is much higher, with American firms accounting for 75.1% of the grants, European firms for 15.2%, and other countries for 9.7%.

The number of firms applying or receiving a plant patent has been increasing over time, with the number of applicant firms at the EPO increasing from 36 firms between 1980 and 1984 to 252 firms between 2000 and 2004 (the results for 2005 to 2006 are not comparable because they cover a much shorter time period). Similarly, the number of firms granted a plant patent in the United States increased from 57 between 1980 and 1984 to 235 between 1995 and 1995, as shown in Table 4. The sudden decline in patent grants at the USPTO after 1999 is due to changes in the criteria for plant patents, including stricter disclosure rules, which delayed approvals (Blank, 2009; Lawrence, 2004). The decline in patent grants in the last time period of 2000 to 2004 is not reflected in the number of patent applications between 2003 and 2007, with 274 firms making 2 962 patent applications.

In contrast to the growing number of firms making at least one patent application at the EPO or USPTO, or receiving a patent grant at the USPTO, plant patent ownership has become increasingly concentrated, particularly for USPTO patents. The top five patent applicant firms in Europe applied for 22.6% of all plant patents between 1985 and 1989, but for 31.4% of plant patents between 2000 and 2004. In the United States, concentration has grown to a much higher level. Between 1980 and 1984 the top five firms received 31.6% of all plant patent grants, increasing to 49.6% in 1995 to 1999. The level of concentration is even higher for the more recent data for USPTO patent applications. Between 2003 and 2007, the top firm accounted for 63.2% of all plant patent applications and the top ten firms for 71.7%.[12] Of note these results underestimate the concentration of patenting because patenting by subsidiaries are not reassigned to the parent firm.

Table 4. **Percent of plant patents by leading firms: 1980-2007**

			Share of all patents		
	Number of firms	Number of patents	Top firm	Top 5 firms	Top 10 firms
EPO Patent applications					
1980-1984	36	63	9.5%	31.7%	54.0%
1985-1989	100	248	5.6%	22.6%	40.7%
1990-1994	134	442	6.7%	28.3%	44.4%
1995-1999	219	939	10.5%	32.3%	45.9%
2000-2004	252	1 008	9.4%	31.4%	44.1%
2005-2006	105	349	12.1%	42.4%	55.3%
USPTO patent grants					
1980-1984	57	135	8.8%	31.6%	47.8%
1985-1989	107	474	9.7%	35.7%	50.4%
1990-1994	137	875	13.0%	36.7%	54.4%
1995-1999	235	1 705	24.2%	49.6%	61.1%
2000-2004	56	597	55.6%	80.5%	87.1%
USPTO Patent applications					
2003-2007	274	2 962	28.4%	63.2%	71.7%

Source: Authors, based on EPO patent applications, USPTO patent grants (1980-2004) and USPTO patent applications (2003-2007). Excludes the public research and private non-profit sectors and individual patentees.

Notes: 1. Limited to patents assigned to either plant process IPC codes or plant genetic modification IPC codes and to patents for which full information is available on the application year and the applicant name.
2. The top firm in USPTO patent applications between 2003 and 2007 is DuPont Pioneer Hi-Bred, followed by Monsanto, Syngenta, BASF and Ceres. The latter is involved in energy crops.
3. EPO data for 2005-2006 include 31 patents applications after 2006.
4. See Annex B for a description of eligible IPC codes.

Increasing concentration is also apparent in the GM field trial record. Peak activity in the number of firms active in GM field trials occurred between 1995 and 1999, with slightly over 6 000 field trials of plant varieties conducted by 146 firms. In an equivalent five year period between 2004 and 2008, the number of GM field trials had decreased 17% to slightly over 5 000, but the number of firms active in field trials had declined by 50% to 76 firms. Monsanto, the leading firm in both time periods, increased its share of all field trials from 31.7% between 1995 and 1999 to 47.2% between 2004 and 2008.[13] Table 5 shows that the share of all GM field trials by the top five firms increased from 60.8% between 1995 and 1999 to 79.4% between 2004 and 2008. In the second time period, 97.4% of all field trial applications were conducted by the leading 25 firms.

Over the same two time periods, the ability to use GM technology has been increasingly concentrated in American firms, whose share of all GM field trials increased from 64.2% of the total between 1995 and 1999 to 81.5% of the total between 2004 and 2008. The share of field trials performed by European firms declined from 32.8% to 16.2% over the two time periods. Firms based in other countries accounted for 3.0% of all trials in the first time period and 2.3% in the second period.[14]

Table 5. **Percent of GM plant field trial applications by leading firms**

	1995-1999 6 091 field trials	2004-2008 5 029 field trials
Top firm[2]	31.7%	47.2%
Top 5 firms[3]	60.8%	79.4%
Top 10 firms	72.1%	90.3%
Top 20 firms	82.3%	95.7%
Top 25 firms	84.9%	97.4%

Source: Authors, based on UNU-MERIT (2009).

Notes: 1. As measured by number of field trials conducted.
2. The top firm in both periods was Monsanto.
3. The top five firms between 1995 and 1999 were Monsanto, Hoechst, Pioneer, Dekalb and DuPont. Between 2004-2008 the top five firms were Monsanto, Targeted Growth, DuPont Pioneer Hi-Bred, Syngenta, and Bayer CropScience.
4. See Annex A for a description of the UNU-Merit field trial database.

The above results show that the number of firms applying for a plant patent has increased over time, although patent ownership is increasingly concentrated in fewer firms, particularly for USPTO patents. Research in plant biotechnology continues to be diversified, either because firms believe that they can license new technology to one of the major plant breeding firms or because the plant patent is a by product of other research (many of the firms that apply for or receive a plant patent are not active in plant breeding, although this share has been decreasing over time).

In contrast to the patent record, the number of firms active in GM field trials has declined sharply, possibly because of increasing costs for seed development from the application of biotechnologies such as GM, MAS, and gene shuffling, and high regulatory costs for GM varieties (OECD, 2009). Both factors could have reduced the financial viability of many small and medium sized firms. In addition, there has been a substantial increase in the share of GM field trials conducted by the leading firms.

The results for both plant patents and GM field trials point to a large decline in the number of firms that can use biotechnology to develop new plant varieties. The question then is if this increase in concentration is having, or likely to have, a negative effect on innovation in the plant breeding sector? The decline in the number of firms active in GM field trials, which are close to the commercialisation phase, is potentially more worrisome than the increase in concentration of plant patents. The results given in this article suggest that the growing level of concentration could be a problem because most GM research has been focused on a limited number of large market crops – though GM research has expanded into other crops. Currently, small and medium sized firms continue to be active in non-GM plant breeding, although their numbers have been depleted through acquisitions by the major seed firms. The apparent inability of many of the remaining small and medium sized seed firms to use biotechnology could reduce the rate of innovation by these firms. This is of concern because these firms are often active in small market and regional crop varieties where the major seed firms are less active.

Role of the public sector

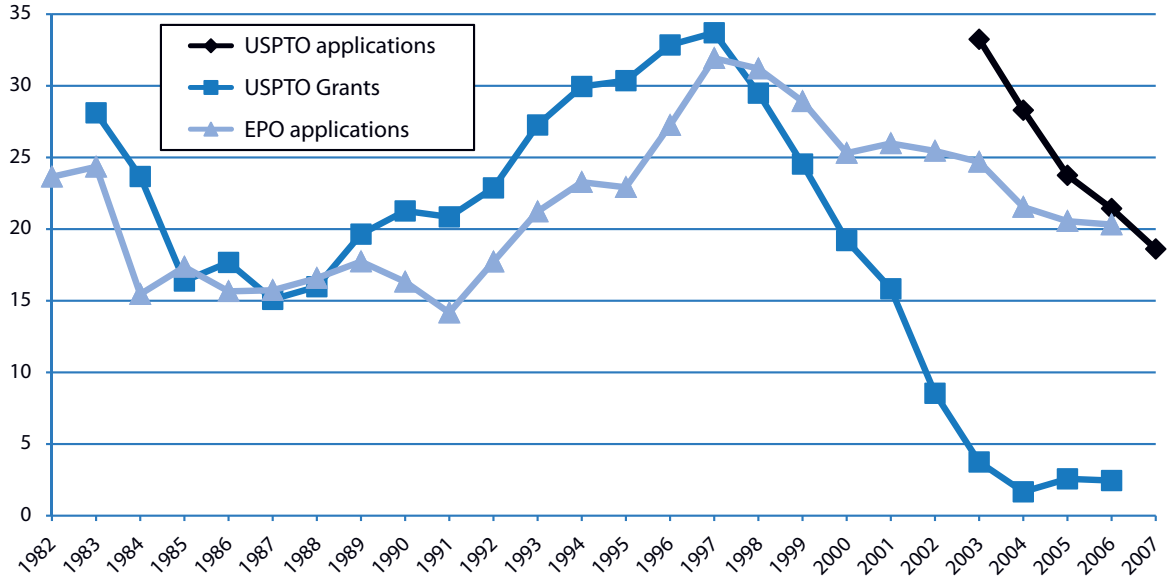
The public research sector (defined here to include universities, government research institutes and private non-profit research institutes) continues to play an important role in the development of new crop varieties, both in developed and developing countries,

where research institutes in Africa, India and Brazil have used biotechnologies to develop improved crop varieties. A major success is NERICA rice, developed by the Africa Rice Center (WARDA) using molecular biology and plant cell culture.

Between 1980 and 2006, the public sector applied for 23.8% of plant patents at the EPO, received 21.9% of plant patent grants from the USPTO, and made 24.9% of plant patent applications at the USPTO between 2001 and 2007.[15] This is considerably higher than the public sector contribution to all types of patents, estimated by Graff *et al.* (2003) at only 2.7% of USPTO patent grants between 1981 and 2000.

However, the role of the public sector peaked in the late 1990s and early 2000s, as shown in Figure 1, particularly for USPTO patent grants and applications. It is not known if this is due to a fall in public sector investment in plant breeding or to a conscious decision not to patent inventions made in the public sector. In either case, the private sector share of plant patents has increased substantially, particularly for USPTO patents.

Figure 1. **Share of plant patent grants or applications made by the public sector**



Source: Authors, based on EPO and USPTO data.

Notes: 1. The results are three year moving averages.

2. Plant patents are limited to IPC classes for genetic modification in plants and for processes for plant breeding. Plant patents for varieties only are excluded. Trials conducted jointly by the private and public sectors (12.0% of public sector plant patent grants from the USPTO) are assigned to the public sector.

The public research sector within the OECD also plays an important role in GM field trials, with 19.2% of all plant field trials within the OECD between 1987 and 2008 conducted by public research institutions. Unlike the patent record, the public sector share has increased slightly to 20.7% of all plant field trials between 2004 and 2008.

Table 6 gives the number of field trials performed by public sector institutions and private sector firms and the percentage distribution of all trials by trait category. Compared to private firms, the public sector conducts a higher share of trials for second generation agronomic and product quality traits and for technical traits that form the foundation for

advances in GM technology. As an example, technical traits account for 25.2% of all trials by the public sector compared to 11.2% of all trials by private firms. The most frequent purpose of technical trials in the public sector is to identify markers. An analysis of agricultural patents between 1982 and 2000 also found that the public sector focused on agronomic traits such as stress resistance (Graff *et al*., 2003).

The public sector is also more active in small market crops, with most of private sector investment in the commercially more attractive large market crops (maize, rapeseed, soybean, cotton, rice, wheat and potatoes). Between 1987 and 2008, the public sector conducted 39.9% of its GM field trials on small market crops, over twice the 17.6% share of private sector trials for small market crops. These shares are roughly stable over time.

Table 6. **Distribution of GM trials for specific plant traits by the public and private sectors (1987-2008)**[1]

	Public sector		Private sector	
	Number	Percent	Number	Percent
Herbicide tolerance	575	11.0	8 152	35.7
Pest resistance	1 407	26.9	6 338	27.8
Product quality	900	17.2	3 362	14.7
Technical	1 320	25.2	2 553	11.2
Agronomic	845	16.2	2 348	10.3
Other	181	3.5	62	0.3
TOTAL	5 228	100.0	22 815	100.0

Source: Authors, based on UNU-MERIT (2009).

Notes: 1. The public sector includes 122 plant GM field trials by private non-profit institutes. The total number of trials by trait (28 043) is greater than the number of GM plant field trials (21 464) due to trials that test more than one type of trait.

2. See Annex A for a description of the UNU-Merit field trial database.

Current status of biotechnology

An estimate of the current use of biotechnologies by seed firms can be constructed from publicly available data on the use of GM and an estimate of the prevalence of MAS capabilities among seed firms. This information provides an estimate of the share of seed firms that have the technical capabilities to use biotechnology in their breeding programmes. This section also examines the types of GM varieties that have reached the market and the extent of their use.

Non GM biotechnologies

While the number of firms active in GM technology can be readily identified from publicly available GM field trial data, there are no consistent data on the share of seed firms that use other biotechnologies such as MAS, molecular mutagenesis, or cisgenesis. The available data are largely limited to the use of MAS, which can speed up breeding programmes. The technological capabilities that are required to use MAS are also necessary for all other types of biotechnology for plant breeding. A series of interviews with five French and German firms active in breeding maize varieties found that all five firms used MAS. The larger firms appeared to use MAS in every maize breeding programme, with

100% of all turnover due to MAS maize varieties, but the one smaller firm estimated that only 33% of its turnover was from MAS maize (Menrad *et al.,* 2006).[16]

Data from the European Seed Association for 2006 were analysed to explore the use of biotechnology by 41 member firms active in plant breeding. The combined turnover of these firms in 2006 was approximately 50% of the USD 7.9 billion European seed market. Of the 41 member firms, 25 (61%) had conducted GM field trials, including many medium-sized firms with less than 500 employees.[17] The websites for the remaining 16 firms were checked to see if they used other biotechnologies and to evaluate the relationship between firm size, market specialities, and the use of biotechnology. Five of the 16 firms reported using MAS in their breeding programmes or had close research links with other firms or institutes that used MAS. Seven of the remaining nine firms were small firms with less than 100 employees that were primarily involved in breeding vegetable varieties. One large firm with 600 employees and active in forage crops did not contain any references to MAS on its website. Another firm has its head office in Japan and provides very little information on its English language website on breeding programmes. The smallest firm that was identified as a MAS user had 160 employees.

The results on the use of MAS and increasing concentration in the sector suggest that, with the exception of small seed firms active in breeding vegetable varieties, almost all seed firms are likely to currently use MAS, GM or other biotechnologies in at least some of their breeding programmes for new crop varieties.

A possible barrier to the adoption of MAS that was identified in the interview study cited above is the cost of identifying markers. It could be difficult to recoup these costs in small market crops such as vegetables, which could also explain the number of small breeding firms that are still active in this market segment. The cost of MAS could also limit its use in other crops over the short term. However, the benefits of using MAS, due to faster development times for improved traits, suggest that almost all varieties of some large market crops in developed countries, such as maize and soybeans, are probably already developed using MAS or GM. Almost all varieties of other large market crops will probably be developed using MAS or other biotechnologies by 2015 (alfalfa, cotton, potatoes, rapeseed, sugar beet, tomatoes, and grains such as rice, wheat, barley, rye and oats).

GM crops

GM technology has a major advantage over all other types of plant breeding technologies. Once a gene or set of genes for a desirable trait has been identified, the gene can be inserted into different plant species. For example, *Bt* genes that provide resistance to lepidopteran insects have been inserted into both cotton and maize.

GM approvals and adoption

Table 7 and Figure 2 provides details on the types of GM crops and traits that have been approved for commercial use in the United States or for which commercial use is pending approval. 74% of all approved or pending traits are for first generation traits such as herbicide tolerance, insect/virus resistance, or a combination of the two.

Second generation traits include agronomic and product quality traits. These account for 19% of the total, of which over half are for different tomato varieties with altered ripening characteristics. Agronomic traits include yield enhancement and tolerance to adverse growing conditions such as cold, drought or heat. These types of traits could be

particularly valuable in the future to manage the effects of climate change and to meet growing demand. Of note, no traits for yield improvement or tolerance have been approved to date, although the pest resistance traits can increase yields by reducing crop predation. Two agronomic traits are pending: one is for freeze tolerant Eucalyptus and the other is for drought tolerant maize.

The remaining 7% of approved or pending GM traits are for male sterility. Sterility is a valuable trait that prevents crossing between GM varieties and non GM crop varieties or wild relatives, but it has no direct economic benefit to farmers.

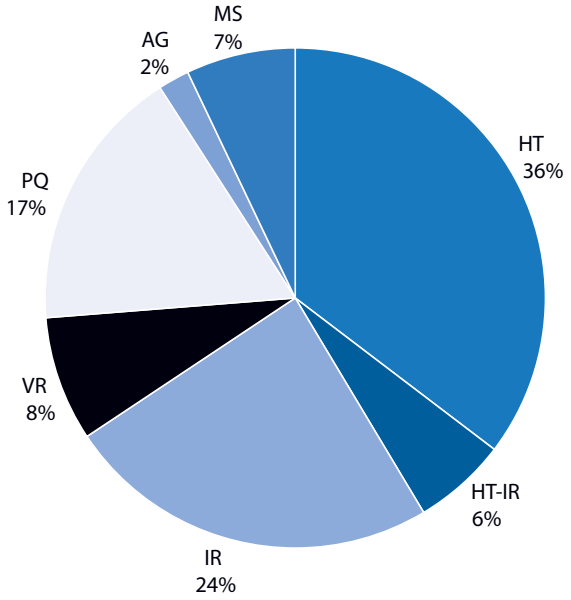
Table 7. **USDA approved and pending GM crop varieties as of August 8, 2009**

Plant	Number of varieties	Status[2]	Year of first approval[1]	Traits[1]							
				HT	HT-IR	IR	VR	PQ	AG	MS	PQ trait
Alfalfa	1	P		1							
Beet	2	A	1998	2							
Beet, sugar	1	A	2008	1							
Chicory	1	A	1997							1	
Cotton	12	A	1994	6	1	5					
Cotton	2	P	-		1	1					
C.bentgrass	1	P	-	1							
Eucalyptus	1	P	-						1		
Flax	1	A	1998	1							
Maize	22	A	1994	6		10		1		2	High lysine
Maize	6	P	-	2	4	1		1	1	1	Starch processing[3]
Papaya	1	A	1996				1				
Papaya	1	P	-				1				
Plum	1	A	2004				1				
Potato	5	A	1994			5	3				
Rapeseed	7	A	1994	6				1		2	Improved oil profile
Rose	1	P	-					1			
Rice	2	A	1999	2							
Soybean	7	A	1993	6				1		1	Improved oil profile
Soybean[4]	5	P	-	1		1		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[5]	*94*			*35*	*6*	*24*	*8*	*17*	*2*	*7*	

Source: Authors, based on USDA (2009a).

Notes: 1. HT = herbicide tolerance, HT-IR = combined herbicide tolerance and insect resistance, VR = virus resistance, PQ = product quality trait, AG = agronomic trait, MS = male sterility. Status: A = approved, P = pending.
2. Gives the data of the 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.
3. Variety includes thermostable alpha-amylase which accelerates the conversion of starch to sugar and should decrease the cost of ethanol production. See "Klevorn, TB, Syngenta's Product Pipeline", *www.bio.org/foodag/action/20040623/klevorn.pdf* (last accessed 7 January, 2008).
4. The traits of two pending soybean varieties were not disclosed.
5. Columns do not sum do to stacked traits.

Figure 2. **USDA approved and pending GM traits, by type, as of August 8, 2009**

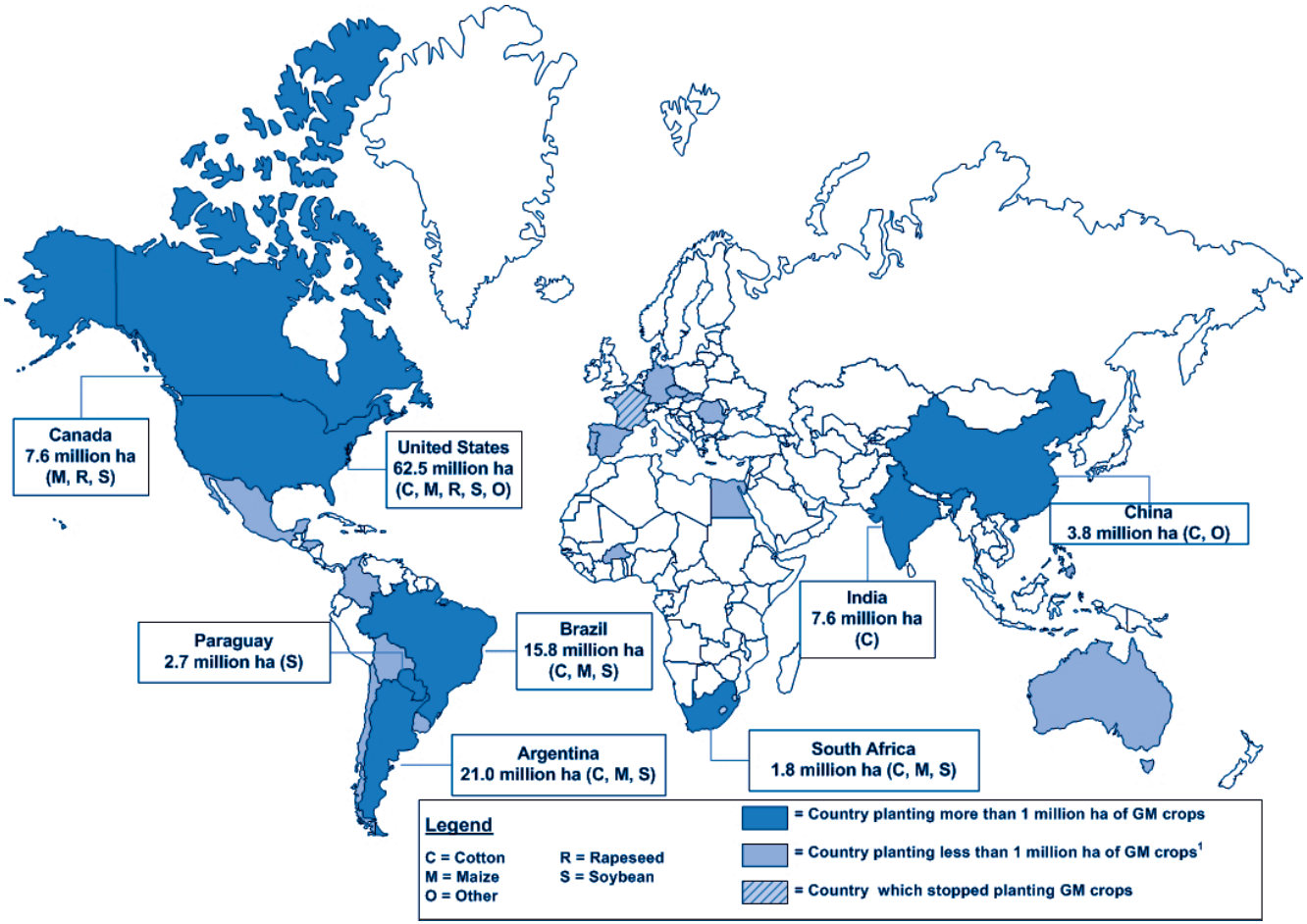


Source: Authors, based on USDA (2009a).

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

Although GM varieties of over a dozen different plant species 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 15 non-OECD countries in 2008. France, which planted GM maize in 2007, discontinued all GM plantings. Figure 3 displays all the countries that had approved biotech crop plantings in 2008 and highlights the eight countries (two OECD and six non-OECD) that planted a minimum of 1 00 000 hectares. Globally, 125 million hectares were planted with GM crops in 2008, accounting for approximately 10.3% of global hectares planted with all crops. GM varieties accounted for 70.3% of all hectares planted with soybean, 23.3% of maize hectares, 47.0% of cotton hectares, and 18.5% of all rapeseed hectares in 2008 (see the section on "Forecasting for GM crops).[18]

Figure 3. **Approved GM crop plantings, 2008**



Source: Salim Sawaya, based on data from James (2008).

Note: Countries planting less than 1 000 000 hectares in 2007 include: Australia (200 000 ha), Bolivia (600 000 ha), Burkina Faso (<50 000 ha), Chile (<50 000 ha), Colombia (<50 000 ha), Czech Republic (<50 000 ha), Egypt (<50 000 ha), Germany (<50 000 ha), Honduras (<50 000 ha), Mexico (100 000 ha), Philippines (400 000 ha), Poland (<50 000 ha), Portugal (<50 000 ha), Slovakia (<50 000 ha), Spain (100 000 ha), Romania (<50 000), and Uruguay (700 000 ha).

GM field trials

Field trials of GM traits have been conducted in over 130 plant species. The 25 species with the highest number of trials is given in Table 8 and account for 94.4% of all field trials. Maize accounts for almost 40% of all trials. In total, one or more varieties from 13 of the plant species in the top 25 for the number of trials (shaded rows) have been approved or pending in the United States for commercial (unregulated) use as of August 8, 2009 (see Table 7). In addition, several plant species have been approved for use after less than 50 field trials: chicory (42 trials), flax (43 trials), papaya (39 trials), plum (11 trials), and rose (8 trials). An example of GM field trials in a specific type of crops, forage crops (grasses and clovers), are given in Box 2.

Table 8. **Total field trials by plant species: leading 25 plants, as of end 2008**

Species	Number of field trials	Percent of total[1]	Cumulative percent
Maize	8 170	38.1	38.1
Rapeseed	2 120	9.9	48.0
Soybean	1 770	8.2	56.2
Potato	1 628	7.6	63.8
Cotton	1 242	5.8	69.6
Wheat	921	4.3	73.9
Tomato	770	3.6	77.5
Alfalfa	685	3.2	80.7
Beet	540	2.5	83.2
Tobacco	462	2.2	85.3
Rice	331	1.5	86.9
Creeping bentgrass	203	0.9	87.8
Poplar	202	0.9	88.8
Mustard	200	0.9	89.7
Melon	164	0.8	90.5
Pine	156	0.7	91.2
Barley	107	0.5	91.7
Grape	101	0.5	92.2
Lettuce	97	0.5	92.6
Sugarcane	77	0.4	93.0
Squash	72	0.3	93.3
Apple	64	0.3	93.6
Safflower	61	0.3	93.9
Eucalyptus	58	0.3	94.2
Sunflower	56	0.3	94.4

Source: Authors, based on UNU-MERIT (2009).

Notes: 1. The UNU Merit database contains a total of 21 464 plant field trials conducted from 1987 to end 2008.
2. Shaded rows indicate a plant species for which a GM variety has been approved or is pending approval for commercial use in the United States.
3. See Annex A for a description of the UNU-Merit field trial database.

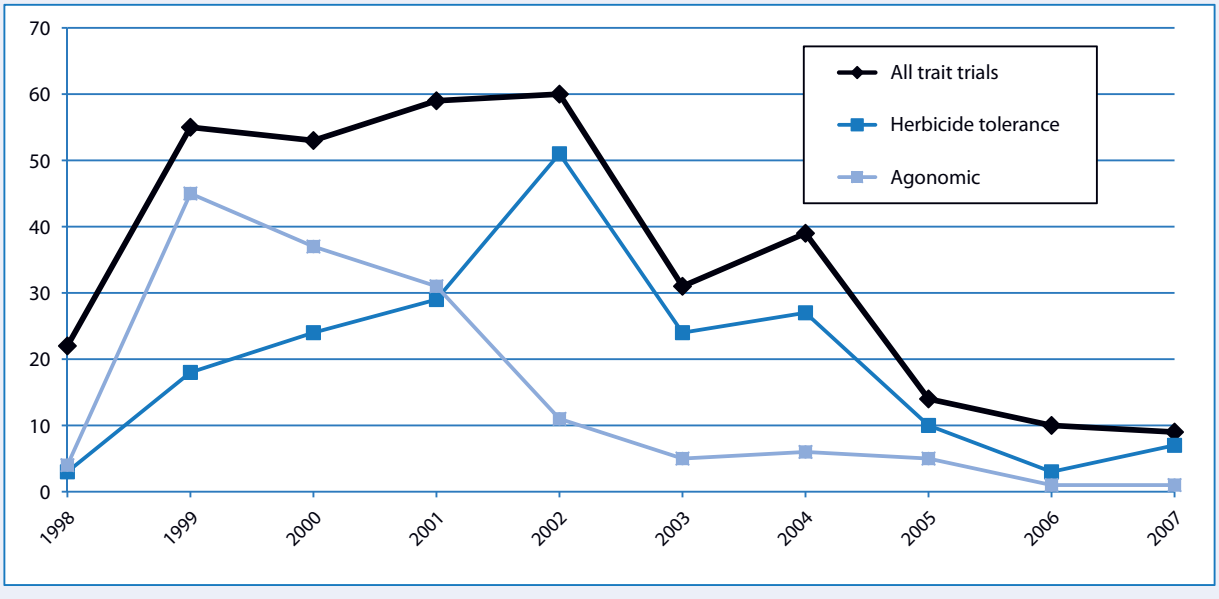
The total number of plant field trials over time is highly variable, as shown in Figure 4. The total reached a peak of 2 244 trials in 1998, declined to 1 139 in 2003, before increasing again to 1 507 trials in 2007. The variation in trials is partly due to the rapid decline in field trials in the EU after 1999, but most of the decline is caused by the completion of specific breeding projects. The decline after 1998, for example, is due to the successful completion of projects on herbicide tolerance and pest resistance using the *Bt* gene. Similarly, new research projects can cause a sudden increase in trials that can extend over several years.

Box 2. **GM field in forage crops**

Grasses and clovers have also been the subject of significant GM R&D. As shown in the figure, there were over 50 trait trials per year for grasses and clovers between 1999 and 2002. Interest has declined after 2004. The focus also shifted after 2001 from agronomic traits to herbicide tolerance.

While it is difficult to determine if interest in developing new GM varieties of grasses and clovers will continue to decline, interest in fibrous crops as a feedstock for lignocellulosic biofuels may spur interest. It may also be that interest is declining because few grass and clovers varieties have sufficiently large markets to justify the research cost. Research into GM grasses has been concentrated in a small number of species. Creeping bentgrass has been the target of nearly 60% of all grass and clover field trials and it is the only grass which has been approved for use in the United States.

GM field trials for forage grasses

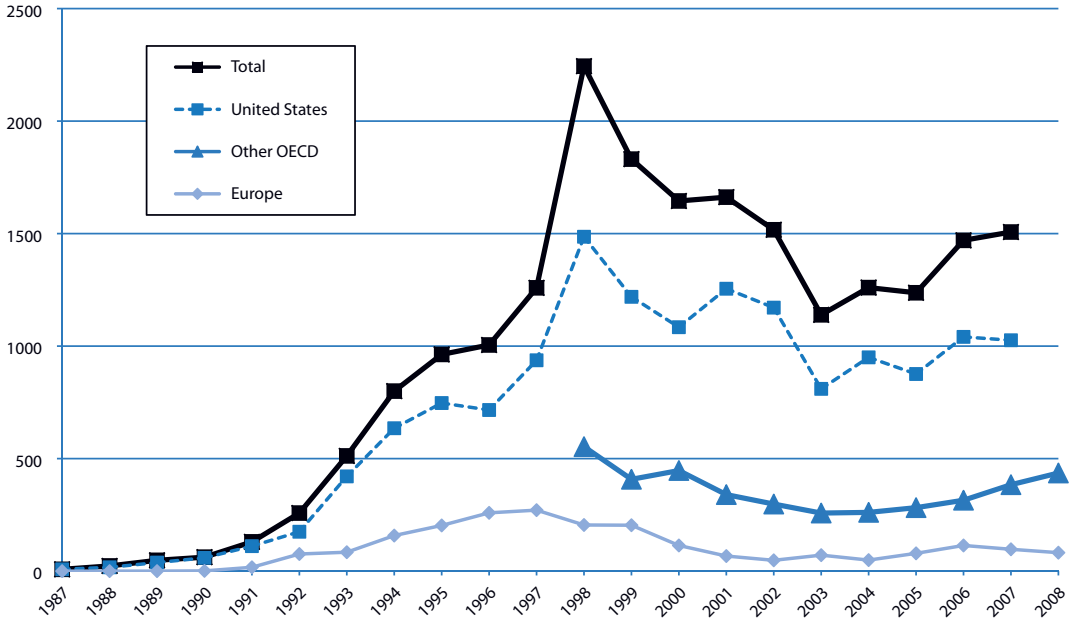


Source: Authors, based on UNU-MERIT (2009).

Notes: 1. Includes bahiagrass, clovers, bermuda grass, canary seed, ryegrasses, St. Augustine grass, switchgrass, tall fescue, and velvet bentgrass.

2. See Annex A for a description of the UNU-Merit field trial database.

Figure 4. **Number of GM field trials of plant varieties by region: 1987 to 2008**



Source: Authors, based on UNU-MERIT (2009).

Notes: 1. See Annex A for a description of the UNU-Merit field trial database.
2. Data for 2008 is not shown due to possible incomplete records for the United States.

Forecasting for GM crops

The development of a new plant variety takes between eight to twelve years. The initial steps begin in the laboratory with a search for valuable genetic traits, followed by small trials in greenhouses. The final stage, which can require several years, consists of open field trials under natural climatic conditions. Due to the time lag between field trials and commercialisation, field trial data can be used as leading indicators of the types of GM plant varieties and traits that are likely to reach the market by 2015, as well as indicators of research trends. However, field trial data can only provide a rough estimate of future trends because firms can abandon a research project after the failure of a series of field trials or decide not to apply for market approval. The estimates from the GM field trials are therefore corroborated with data on GM R&D derived from the annual reports of the world's largest seed firms. The two sets of data provide comparable forecasts up to 2015.

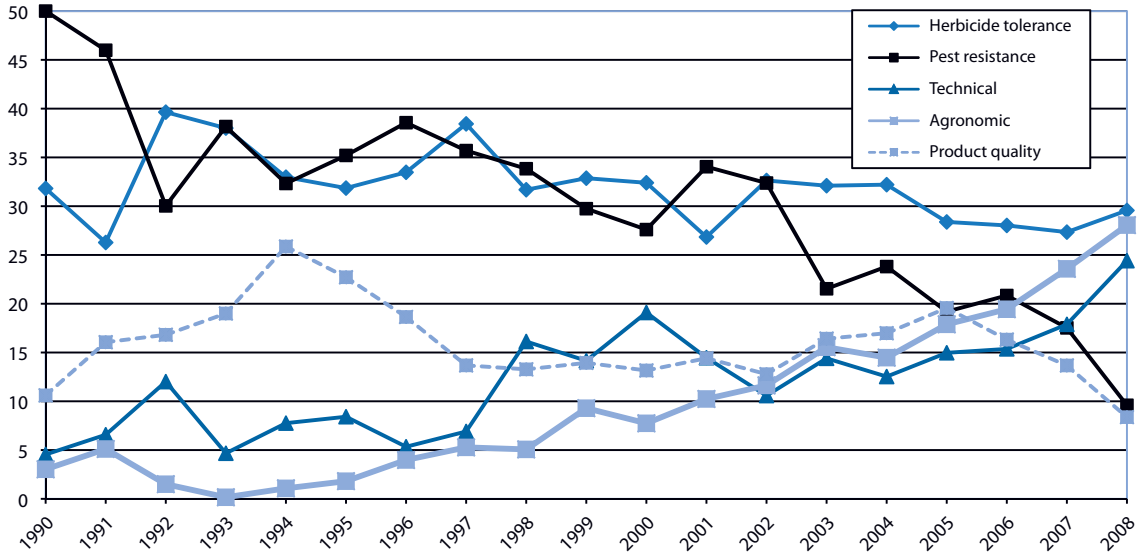
A second forecast uses past trend rates in GM plantings of four main GM crop varieties to estimate the future share, in hectares, of GM varieties for each of these crops. Unfortunately, there are no available data for estimating the future marketing of new crop varieties developed through the use of non-GM biotechnology.

Forecasting using GM requires examining traits in specific crops. A field trial can test more than one trait, due to stacking more than one GM trait in a plant variety. Traits can be stacked within a trait category, for example when a GM variety includes traits that confer

resistance to two types of herbicides or several types of pests, or they can be stacked across categories, as when a GM plant includes a gene that confers herbicide resistance and insect resistance. The analyses given only identify trait stacking across categories, which will underestimate the actual total. Out of the total of 21 464 plant trials, 6 168 (28.7%) included stacked genes in more than one trait category.

Figure 5 gives the percentage of all 28 025 trial-trait combinations of GM trials for plants by category, based on counting trait categories. The results measure research interest in specific category types. The share of herbicide tolerance out of all trials has remained at around 30% since 1990. Conversely, pest resistance trials have declined steadily from 50% of all trials in 1990 to around 10% in 2008. Over the same time period, the share of agronomic traits increased tenfold from 3% in 1990 to nearly 30%, and the share for technical traits increased five-fold from 5% to almost 25%. Product quality traits saw a large increase in interest in the early 1990s followed by a decline and a gradual increase to 2004, followed by a second decline. Overall, these results show a shift in GM crop development from a focus on first generation herbicide and pest resistance traits to second generation agronomic traits.

Figure 5. **Share of GM plant field trials by trait category (share of total trait trials)**



Source: Authors, based on UNU-MERIT (2009).

Notes: 1. See Annex A for a description of the UNU-Merit field trial database.
2. The shares exclude unknown traits (approximately 1% of the total).

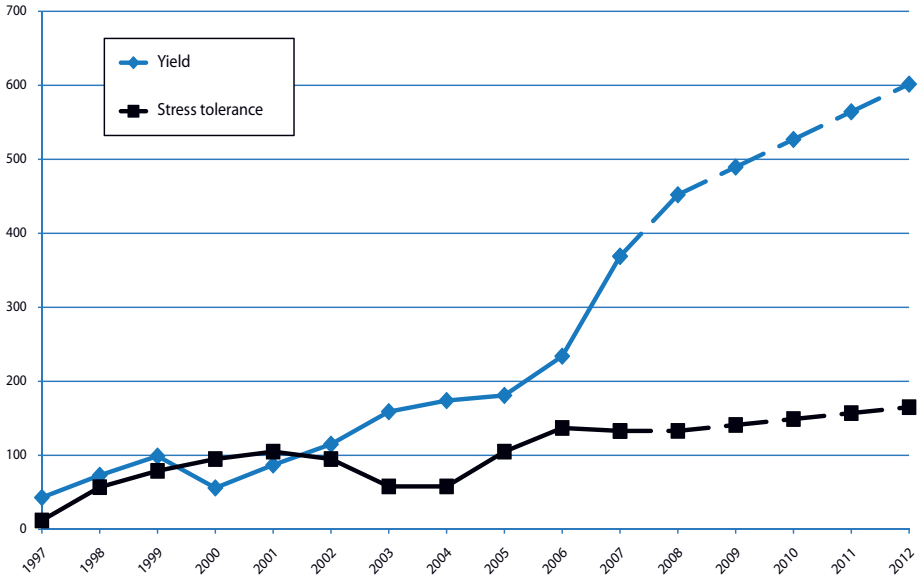
The data do not provide clear answers as to whether or not seed developers will continue to actively pursue product quality traits as a main focus of their R&D programmes. Graff *et al.* (2009) analysed 558 experiments with GM product quality traits and noted a similar decline in research interest and a shift from research into traits for consumer appeal to industrial processing traits. They suggest that one cause of the decline in interest was the European moratorium on GM crops in the late 1990s, which may have reduced consumer interest in quality traits in many other markets as well.

Field trial data do not provide accurate estimates of specific plant varieties that will reach the market over the short term future, due to the poor correlation between the number of trials and new marketed varieties. For example, there have been 921 field trials of wheat, 202 field trials of poplar, 164 field trials of melon, 97 field trials of lettuce, and 101 field trials of grape, without any GM varieties of these species given regulatory approval for commercial use in the United States as of August 2009.

Field tested varieties of GM plants can fail to proceed to market approval because of technical failures, the need for more field tests, or the firm did not apply for market approval. For example, GM wheat is ready for commercialisation, but the lack of a pending application for release is probably due to concerns over its acceptance in major export markets outside North America.[19] In addition, the number of required field trials to develop a commercial new variety is highly variable, ranging from a low of seven trials for a viral resistant plum to several hundred trials to alter the ripening characteristics of a tomato variety.

Yet even with these constraints, field trial data can provide useful insights into the focus of research programmes. This permits approximate forecasts for the types of GM plant varieties and types of traits that are likely to reach the market in the future. The time required between the first field trials and commercial approval varies depending on the maturity of the research programme, but it could range between two and ten years. Consequently, field trial data back to 1998 are used to estimate the types of product categories that could reach the market between 2007 and 2015 and data back to 2000 are used to estimate specific plant species that could reach the market.

Figure 6. **Observed (to 2007) and forecast (2008-2012) field trials by agronomic trait**



Source: Authors, based on UNU-MERIT (2009).

Notes: 1. Dotted lines give extrapolations based on the observed data series for the number trials per year. The start year for extrapolations is 1997 for stress tolerance and 2000 for yield. A total of 2685 agronomic traits were field tested from 1997 to 2007. Of these, 161 trials, or 6.0% of the total, were assigned to "other", which includes traits with an unknown agronomic purpose. No results are given for this category.

2. See Annex A for a description of the UNU-Merit field trial database.

Forecasts for agronomic traits

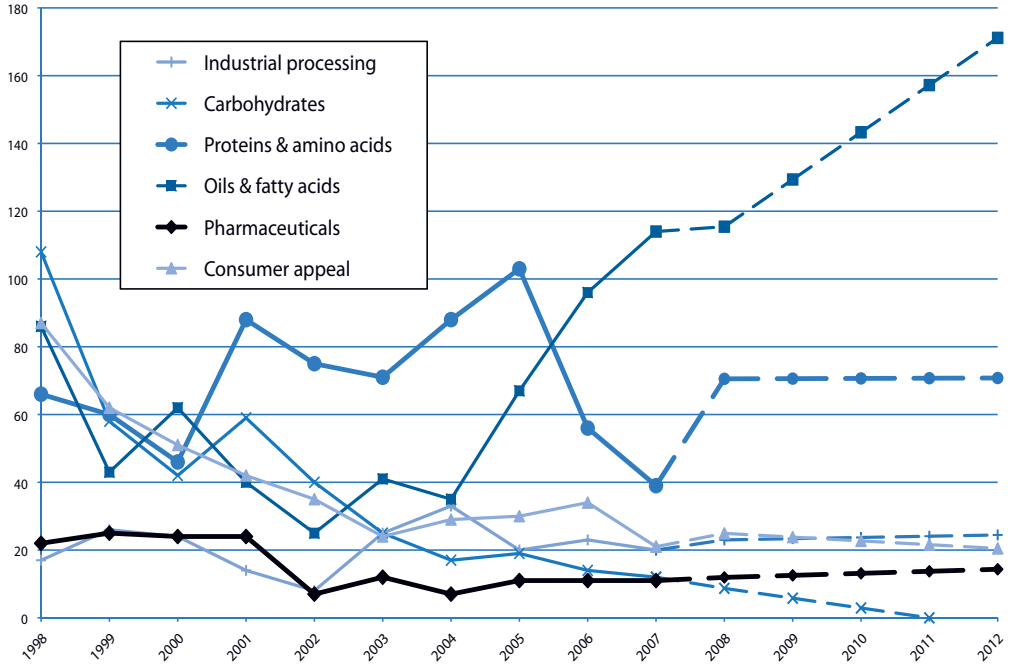
As shown in Figure 5, the focus of GM research has shifted gradually over time to second generation agronomic traits, but as of August 2009 no plant varieties with GM agronomic traits have been approved for commercial use in the United States, although two varieties are pending.

Agronomic traits are divided into two main categories: stress tolerance and yield. Figure 6 shows that there has been a constant increase since 2000 in the number of field trials for yield improvements, while the number of trials for stress tolerance has not been increasing as rapidly.

Forecasts for product quality traits

The UNU-MERIT database divides product quality traits into eight main categories, using information available from the original sources: industrial processing, improved carbohydrate content (sugar and starches), improved proteins and amino acid content, improved oils and fatty acids, the production of pharmaceutical proteins, consumer appeal (altered storage, taste, appearance or nutrition), animal feed, and an "other" category which includes trials for which insufficient information is available to assign the trait to one of the other seven categories.[20] Figure 7 gives the number of trials over time, with forecasts

Figure 7. **Observed (to 2007) and forecast (2008-2012) field trials for product quality traits**



Source: Authors, based on UNU-MERIT (2009).

Notes: 1. Dotted lines give extrapolations based on the observed number of trials per year. The start year for the extrapolations is 1998, except for carbohydrates (2003), pharmaceuticals (2002), oils and fatty acids (2001) and consumer appeal (2002). Different start dates are used for the latter three classes of product quality traits due to a shift in previous trends, such as the increase in trials of product (consumer) appeal from 2003.

2. See Annex A for a description of the UNU-Merit field trial database.

to 2012, for six of the eight product quality categories. No results are given for the "other" category and for feed, since both of these categories are infrequent, stable over time, and overlap with other categories.

Due to limited information in the original field trial data, several of the product quality categories can overlap. The category of "industrial processing" includes traits for both food product processing (starch quality of potatoes, etc.) and industrial inputs (fibre quality, lignin content, etc). However, the category of industrial processing traits could also overlap with other categories. Some of the improvements in fatty acids that are designed for industrial applications could have been assigned to "Oils and fatty acids", while some of the trials in the animal feed category could be due to improved proteins or carbohydrates.

The main focus of trials for product quality traits has been for oils and fatty acids. This category is projected to account for more than double the trials of any other type of product quality in 2012. Trials for proteins and amino acids are expected to remain around 70% per year despite the large drop off in 2006 and 2007. Consumer appeal and industrial processing applications has been comparatively steady and are expected to remain so in the future. There may also be some increased interest in pharmaceutical traits, as interest has picked up in recent years. In contrast, the number of trials for improved carbohydrates has been declining and is forecast to reach zero in 2011.

Forecasts by plant varieties from field trial data

Table 9 provides approximate estimates for when new plant varieties with specific traits could reach the market, using the field trial record.[21] The forecasts are limited to plant species with 25 or more field trials since 2000. The forecasts are subjective and also approximate. The estimated year gives an approximate date for when a new variety should reach the market: 2008/9 indicates mature research programmes for varieties that should reach the market within the next year or so, 2010 identifies varieties that will take several years longer, and 2015 is used for varieties that are farther off in time, but based on intensive research programmes. The estimated years also refer to when a research programme should be completed and not the actual year of commercialisation, which can vary because of a delay in the approval process or a decision on the part of the firm that developed the variety to delay commercialisation. The criteria for estimating the approximate year of completion for a research programme are as follows:

2008/9: Sufficient field trials over the previous seven years to have already produced a new variety. The number of "necessary" field trials is less for well-known traits for herbicide tolerance and pest resistance than for product quality and agronomic traits. In many cases the end of a research programme is also visible by a recent and marked drop in the number of trials. For example, the number of trials for herbicide tolerance in alfalfa dropped from 67 in 2005 to 13 in 2006.

2010: The annual number of trials between 2000 and 2006 is sufficient but relatively stable over all years, with no sign of the end of a research programme.

2015: Most field trials were conducted in the latter half of the 2000 to 2006 period, with no sign of a decline in the number of trials. In many cases the number of trials continues to increase over time. This is particularly common for product quality and agronomic traits.

Abandoned (a): Field trials ended by 2003 or earlier, with no request for commercialisation pending in the US.

Unknown (?): Field trials have been continuing over time, but at a low level. This could be a sign of the need for few field trials (as for the development of virus resistant plum) or a sign that the research programme has not yet fully developed, with commercialisation far off into the future.

Three main conclusions can be drawn from the results in Table 9. First, herbicide tolerance technology is well established, with 10 of the 13 plant varieties with active research programmes likely to end in a commercial product in 2008 or 2009, and the remaining three appearing by 2010. Pest resistance traits are in second place, with 11 expected by 2010, and only four research programmes possibly not reaching completion until 2015.

Table 9. **Approximate estimated date of commercialization for new GM crops by trait using field trial data for 2000 to 2006 inclusive**

	Total field trials	HT	PR	PQ	AG
Corn	4 508	2008	2008	2008	2010
Rapeseed	965	2008	2010	2008	2008
Soybean	834	2008	2008	2008	2010
Wheat	650	2008	2010	2015	2015
Cotton	608	2008	2008	2015	2015
Alfalfa	486	2008	-	2015	a
Potato	341	2010	2008	2008	2010
Rice	212	2008	2010	2008	2010
Tobacco	170	?	?	2010	?
Beet	160	2008	2010	-	-
Tomato	155	a	2010	2010	2015
Creeping bentgrass	149	2008	2008	-	2010
Safflower	73	2010	-	2010	-
Poplar	70	?	?	?	2015
Barley	68	2010	2015	2015	-
Sugarcane	60	a	2015	a	-
Kentucky bluegrass	53	2008	-	-	2015
Lettuce	50	a	a	2015	a
Eucalyptus	48	a	-	2015	2015
Pine	46	-	-	2015	2015
Flax	39	a	-	a	a
Grape	38	a	2015	a	a
Pea	36	2010	a	-	-
Petunia	33	a	-	2010	?
Apple	31	-	2015	2015	-
Lentils	26	a	-	-	-
Peanut	26	-	2010	-	-
Sunflower	26	a	a	a	a

Source: Authors, based on UNU-MERIT (2009).
HT = herbicide tolerance, PR = pest resistance, PQ = product quality, AG = agronomic.
– = no field trials for the specific trait, a = abandoned, ? = insufficient data to predict.

Notes: 1. See Table 7 for approvals pending as of 2009.
2. See Annex A for a description of the UNU-Merit field trial database.

Considerably fewer research programmes for product quality and agronomic traits are likely to be completed by 2008 or 2009, with over half estimated to reach the market in the last time period of 2015.

Second, new GM varieties are still most likely to appear in the main GM crops to date. However, GM varieties should appear by 2015 in several plants that do not yet have any commercial GM varieties on the market: safflower, poplar, barley, sugarcane, Kentucky bluegrass, lettuce, eucalyptus (one variety is already pending), pine, grapes, peas, apples, and peanuts.

Third, a large number of traits appear to have been abandoned, either due to technical failure or lack of commercial markets. In several cases the number of field trials for a specific trait, such as herbicide tolerance in grapes, suggests that the research programme was either successful or close to success. These cases may have been abandoned because of concerns that consumer opposition could have made the variety commercially unprofitable. Alternatively, a variety could be commercially unprofitable because of competitive alternative solutions to the same goal, such as managing pest infestations through pesticides or integrated pest management programmes.

Forecasting using company data

The websites of the nine largest seed firms in terms of the number of GM trials were searched in 2007 for information on their future product pipelines.[22] Four firms provide product pipeline data on their websites: Monsanto, DuPont Pioneer Hi-Bred, Syngenta, and Dow Agrosciences. These four firms account for 66.8% of all field trials of plant varieties between 2000 and 2008 inclusive. All four firms rank their pipelines by product phase, with Monsanto also giving data on the "Estimated time to Market". The information was used to develop an approximate time to market for all four firms (see Annex C for the methodology). The results are given in Table 10 for an approximate middle year of each product phase that matches the time periods used in Table 9.

The four firms report developing 112 new crop-trait combinations, 96.4% of which were in four crops: maize (42.9%), soybeans (33.0%), rapeseed (12.5%), and cotton (8%). These are the four largest GM crops to date in terms of hectares planted. They are also in the top five leading crops in terms of the number of field trials after 2000 (see Table 8). Three remaining crops in Table 10 (alfalfa, sugar beets and rice) account for 4% of the total new crop trait combinations.

Pest resistance accounts for 25 research programmes (22%) and herbicide tolerance for 24 research programmes (21%). However, the main GM firms are moving into both second generation product quality traits (34 research programmes or 30% of the total) and agronomic traits (24 research programmes or 21% of the total). There are also six research programmes under pest resistance into the more technically difficult traits for resistance to nematodes and fungi.

The expected completion dates for the research programmes corroborate the results in Table 9 based on the field trial record. An exception is pest resistance, where the company data show that almost half of the pest resistance trials (14) are not expected by be completed until the third time period, whereas the field trial record shows a peak completion time in the second time period. Conversely, the results for the other three trait categories are similar. Using both data sources, the peak time period for herbicide tolerance is in the first time period, product quality in the middle and last time periods, and agronomic traits in the last time period.

Forecasting using past GM plantings

Table 11 gives the number of hectares planted with GM varieties for each of the four main GM crops between 1996 and 2006 and the GM share of global hectares planted to each crop. Figure 8 graphically illustrates the change in GM shares over time. Data are not available for output in tonnes or USD (which would require yield data), but hectares planted provides an estimate of production and of the potential environmental benefits from reduced tillage or pesticide use.

The data from 2009 to 2015 are based on extrapolating past growth rates in the number of hectares planted to GM and the expected growth in the total number of hectares planted to each crop, based on past trends between 1995 and 2007. The forecasts assume there are no major changes in policy or regulation related to GM crops that would affect uptake.

The number of hectares planted to GM is forecast to increase for all four crops to 2015 while the GM share is forecast to continue to increase for three crops. The fastest uptake of GM technology has been for soybeans, with GM varieties accounting for just over 70% of global cultivation in 2008. This is estimated to increase to over 88.2% of all hectares planted to soybeans in 2015. This is partly driven by a large increase in soybean production

Table 10. **Estimated commercialization dates of trait categories from company website**

		Estimated commercialization date			
Crop	Trait Category	2008 (2007-2009)	2010 (2009-2012)	2015 (2012-2018)	Total
Maize	Herbicide tolerance	7	2	-	9
	Pest resistance	9	-	6	15[1]
	Product Quality	4	3	5	12
	Agronomic	-	2	10	12[2]
Soybean	Herbicide tolerance	3	1	1	5
	Pest resistance	1	3	5	9[3]
	Product Quality	4	8	4	16
	Agronomic	2	2	3	7[4]
Rapeseed	Herbicide tolerance	-	4	1	5
	Product Quality	-	4	1	5
	Agronomic	-	4	-	4[5]
Cotton	Herbicide tolerance	1	1	2	4
	Pest resistance	1	1	2	4
	Agronomic	-	-	1	1[6]
Alfalfa	Herbicide tolerance	-	-	1	1
	Product Quality	-	1	-	1
Sugar beets	Herbicide tolerance	1	-	-	1
Rice	Pest resistance	-	-	1	1
Total		*33*	*36*	*43*	*112*

Source: Authors, based on various sources.

Notes: 1. Includes two traits for fungal resistance (1 expected by 2008, 1 by 2015); others for insect resistance.
2. Includes five traits for drought resistance (1 by 2010, four by 2015), seven traits for yield/improved nitrogen efficiency (1 by 2010, 6 by 2015).
3. Includes three traits for nematode resistance (1 by 2010, 2 by 2015), 1 for fungal resistance (by 2015).
4. One trait for drought resistance by 2015, six for yield (2 by 2008, 2 by 2010, 2 by 2015).
5. All four traits for improved yield by 2010.
6. Drought resistance by 2015.
7. See Annex C for the methodology and sources.

in South America (see Annex D). GM cotton also sees a substantial increase in its global share from about 47% in 2008 to nearly 73% in 2015. Maize will increase from approximately 23% to nearly 30% by 2015. The number of hectares planted to GM rapeseed is forecast to increase from 5.9 million in 2008 to 8.7 million in 2015, but the GM share of all hectares planted to rapeseed is forecast to increase only slightly from 18.5% to 21.3%.

The lower forecasts for the share of GM rapeseed (canola) and maize are mainly due to major producing countries, such as Brazil and China, not yet planting GM varieties of these two crops.[23] 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 8. 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.

Other GM crops planted commercially during this time include alfalfa, papaya, potato, rice, squash, tobacco, and tomato. None of these crops, however, account for a significant percentage of world hectares. In addition, time series data are too limited to permit forecasting future growth rates.

Table 11. **Observed (to 2008) and forecast (2009-2015) global hectares planted with GM crops, by year**

	Soybean		Maize		Cotton		Rapeseed	
	Million of GM hectares	GM as % of hectares	Million of GM hectares	GM as % of hectares	Million of GM hectares	GM as % of hectares	Million of GM hectares	GM as % of hectares
1996	0.5	0.8%	0.3	0.2%	0.8	2.3%	0.1	0.5%
1997	5.1	7.6%	3.2	2.3%	1.4	4.2%	1.2	5.1%
1998	14.5	20.4%	8.3	6.0%	2.5	7.6%	2.4	9.3%
1999	21.6	30.0%	11.1	8.1%	3.7	11.7%	3.4	12.3%
2000	25.8	34.7%	10.3	7.5%	5.3	16.9%	2.8	10.9%
2001	33.3	43.4%	9.8	7.1%	6.8	20.1%	2.7	12.0%
2002	36.5	46.2%	12.4	9.0%	6.8	22.7%	3	13.1%
2003	41.4	49.5%	15.5	10.7%	7.2	23.3%	3.6	15.4%
2004	48.4	52.9%	19.3	13.1%	9.9	28.9%	4.3	17.1%
2005	54.4	58.9%	21.2	14.4%	9.8	29.7%	4.6	16.7%
2006	58.6	61.7%	25.2	17.0%	13.4	40.6%	4.8	17.1%
2007	58.6	65.0%	35.2	22.3%	15	45.5%	5.5	17.9%
2008	65.8	70.4%	37.3	23.3%	15.5	47.1%	5.9	18.5%
2009	73.7	76.0%	35.5	21.9%	16.3	49.5%	6.2	18.9%
2010	79.1	78.7%	38.2	23.4%	17.6	53.4%	6.6	19.4%
2011	84.6	81.1%	41.0	24.8%	18.8	57.2%	7.0	19.9%
2012	90.0	83.3%	43.8	26.2%	20.1	61.0%	7.4	20.3%
2013	95.4	85.6%	46.5	27.5%	21.3	65.0%	7.8	20.7%
2014	100.8	86.8%	49.3	28.8%	22.6	68.8%	8.2	21.0%
2015	106.3	88.2%	52.1	30.1%	23.8	72.7%	8.7	21.3%

Source: Authors, based on world hectare data from the FAO (2009) and GM plantings from James (various years).

Notes: 1. Shaded rows represent forecasts.
2. FAO data for cotton only goes to 2005, for all other crops data is for 2007.
3. Projection assumes there are no major changes in policy or regulation related to GM crops that would affect uptake.

As expected, the increase in area and the percentage of global area planted with GM crops begins to slow over the projection period. This is a result of saturation of the available market for GM crops.

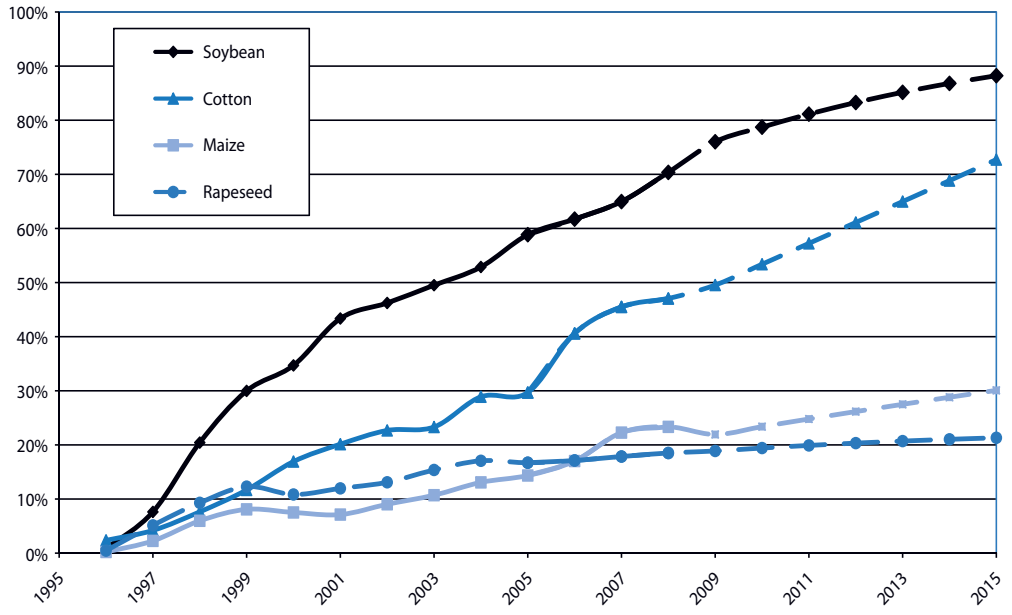
In the United States, the share of hectares planted to GM for three main crops is already close to saturation, with a GM share in 2009 for total hectares plant to each crop of 91% for soybeans, 88% for cotton, and 85% for maize (see Figure 9).[24]

Potential trends

The maximum contribution of biotechnology to the food, feed and industrial feedstock sector would be reached when 100% of crops are based on varieties developed through biotechnology. This is unlikely to occur for any crop because of demand for organic or traditional varieties, but GM varieties of soybeans could be responsible for the vast majority of total plantings by 2015. Most of the remaining new varieties of major food crops are likely to be developed using MAS and related biotechnologies.

A second estimate assumes that all crops with either GM varieties on the market or GM field trials underway will be grown using either GM or MAS varieties. The estimate gives the share of total world and OECD hectares potentially planted to "biotechnology" crop varieties and total world and OECD production prices from these varieties. The number

Figure 8. **Observed (to 2008) and forecast (2009-2015) global GM share of total hectares planted (%), by year**

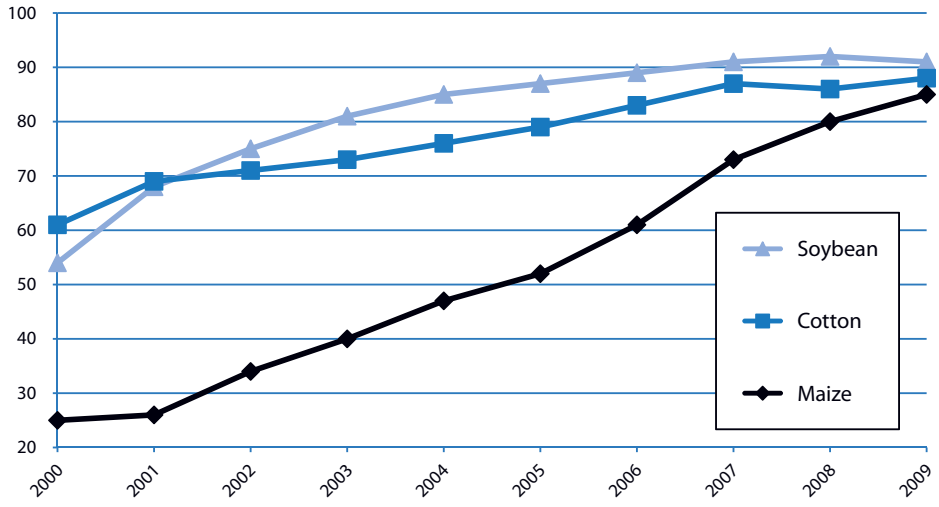


Source: Authors, based on world hectare data from the FAO (2009) and GM plantings from James (various years).

Notes: 1. FAO data for cotton only goes to 2005, for all other crops data is for 2007.

2. Projection assumes there are no major changes in policy or regulation related to GM crops that would affect uptake.

Figure 9. **Share of acreage planted to GM crop varieties in United States, by crop**



Source: Authors, based on USDA Economic Research Service (2009).

Note: Data includes insect-resistant, herbicide-tolerant, and stacked crop varieties.

of hectares planted is an indicator of potential environmental impacts. Producer prices estimate the potential economic output of biotechnology.[25] This does not take into account subsidies that may skew production prices in certain countries.

Current crop varieties based on biotechnology could potentially contribute to crops accounting for USD 164.1 billion in production prices within the OECD and USD 410.9 billion globally (see Tables 12 and 13), equivalent to 46.7% of total OECD production prices of USD 351.8 billion and 41.5% of total global production prices of USD 985.7 billion. In addition, current biotechnology crops could account for 59.2% of global crop hectares[26] and for 68.1% of crop hectares within the OECD.

The third group ("other crops" in Tables 12 and 13) consists of crops where there are no GM varieties on the market. These include many high value-added crops including vegetables, nuts, most fruits, olives and wine grapes that account for 53.4% of production prices within the OECD, although only 41.4% of hectares planted. The rate at which varieties based on biotechnology are adopted in this group will depend on the cost of GM and MAS. As many of these varieties are also sold directly to consumers, acceptance of GM could be a greater issue than for crops such as maize or soybeans that are mostly used in either processed foods (where they are less visible) or as animal feed.

Table 14 gives the yield in tonnes per hectare for each main biotechnology crop, plus the change in yield. The main biotechnological traits to date in these crops are for insect resistance and herbicide tolerance, with no agronomic traits that directly influence yields. Nevertheless, it is interesting that worldwide the yields of the four main GM crops (cotton, maize, rapeseed and soybeans) have increased at an average rate of 13.8% over the period 1995 to 2005, compared to a rate of 7.0% for the other GM crops that account for a much smaller percentage of total output of each crop. This could be due to better yields from lower insect infestations in the GM varieties or possibly because farmers growing more

Table 12. **World production of main GM and other crops (2005)**

A. WORLD	Hectares (thousand)	% of total	Production Price USD million)[5]	% of total
Main GM Target Crops				
Alfalfa	15 119	1.25%	N/A	N/A
Cottonseed	33 026	2.72%	16 950.94	1.72%
Flaxseed	2 510	0.21%	524.46	0.05%
Maize	144 990	11.94%	69 512.94	7.04%
Papaya	381	0.03%	3 056.72	0.31%
Plum1	2 343	0.19%	2 720.20	0.28%
Potatoes	18 816	1.55%	52 171.91	5.28%
Rapeseed[2]	28 261	2.33%	9 350.84	0.95%
Rice, paddy	153 860	12.67%	97 638.01	9.89%
Soybeans	92 113	7.59%	40 397.62	4.09%
Squash[3]	1 507	0.12%	2 644.83	0.27%
Sugar beet	5 456	0.45%	10 388.28	1.05%
Tobacco	3 909	0.32%	N/A	N/A
Tomatoes	4 620	0.38%	27 062.30	2.74%
Wheat	220 394	18.15%	78 464.53	7.95%
Other crops[4]	502124	41.35%	576 526.29	58.39%
Total	1 214 310	100%	985 698	100%

Source: Authors, based on FAO (2009). See table 13 for notes.

Table 13. **OECD production of main GM and other crops (2005)**

B. OECD	Hectares (thousand)	% of total	Production Price (USD million)[5]	% of total
Main GM Target Crops				
Alfalfa	11 724	4.38%	N/A	N/A
Cottonseed	7 052	2.64%	5 228.05	1.49%
Flaxseed	781	0.29%	284.66	0.08%
Maize	45 000	16.82%	35 348.07	10.05%
Papaya	20	0.01%	261.13	0.07%
Plum[1]	190	0.07%	1 225.18	0.35%
Potatoes	2 810	1.05%	16 614.62	4.72%
Rapeseed[2]	11 526	4.31%	5 313.20	1.51%
Rice	4 641	1.73%	21 571.24	6.13%
Soybeans	30 657	11.46%	18 873.37	5.36%
Squash[3]	149	0.06%	1 417.77	0.40%
Sugar beet	3 031	1.13%	8 053.85	2.29%
Tobacco	514	0.19%	N/A	N/A
Tomatoes	871	0.33%	15 500.25	4.41%
Wheat	75 128	28.07%	34 438.07	9.79%
Other crops[4]	85 233	31.85%	187 701.22	53.35%
Total	267 602	100%	351 831	100%

Source: Authors, based on FAO (2009).

Notes: 1. Plums include sloes.
2. Rapeseed includes mustard seed.
3. Squash includes pumpkins & gourds.
4. See Annex E for a list of other crops.
5. Production price data is from 2003.

Table 14. **Yield and % change (1995-2005) for world and OECD, by crop**

	Yield Rate (tonnes / hectare)			
	World		OECD	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Alfalfa	30	-2.90%	32	-2.76%
Cottonseed	1	13.47%	2	20.45%
Flaxseed	1	29.62%	2	24.35%
Maize	5	18.20%	8	18.63%
Papaya	17	5.38%	37	14.58%
Plums[2]	4	0.51%	9	21.94%
Potatoes	17	5.81%	32	15.36%
Rapeseed[3]	2	14.20%	2	14.98%
Rice, paddy	4	7.70%	7	3.26%
Soybeans	2	9.38%	3	2.75%
Squash[4]	13	2.45%	22	8.41%
Sugar beet	46	20.86%	57	11.91%
Tobacco	2	3.24%	2	-4.99%
Tomatoes	27	1.99%	50	6.82%
Wheat	3	2.74%	3	3.16%
Other crops[5]	N/A	N/A	N/A	N/A

Source: Authors, based on FAO (2009). For notes, see Table 13.

expensive GM varieties take better care of their crops. The alternative explanation is that the increase is simply part of a general trend for improved yields, with yields of conventional varieties of these four main crops also increasing rapidly.[27]

Plant diagnostics

Biotechnology can provide accurate and efficient diagnostics to identify specific plant diseases before the disease causes significant economic damage, allowing the farmer to either treat the affected crop with pesticides or to prevent the spread of disease to unaffected crops.[28] Plant pathogens can cause the loss of between 16% and 18% of the crop (Pinstrup-Andersen, 2001). Estimates of the economic losses from plant disease vary widely depending on the underlying assumptions. In the late 1980s, plant diseases were estimated to result in global crop losses of USD 8 billion in maize, USD 10 million in potatoes, USD 33 billion in rice, and USD 14 billion in wheat. Estimates for the United States vary between a total of USD 9.1 billion per year (Fermin-Munoz *et al.,* 2000) and USD 33 billion per year (Pimentel *et al.*, 2005). The developing countries suffer greater relative crop losses than developed countries, due to the economic importance of agriculture and the high cost of plant protection products.

There is a large variation in the amount of crop damage done by specific pathogens. *Fusarium* fungi species can cause crop losses of 25% to 60% for potatoes (Michigan State University, 2009) and between 18% and 95% among different lettuce varieties (ISID, 2003). Nematodes can destroy between 20% and 70% of potato crops (ISID, 2004).

As of February 2008, the American Phytopathological Society (APS) has identified 97 plant varieties suffering from 6 169 infectious diseases (APS, n.d.): 60.6% of the diseases are fungal, 15.5% are viral, 11.5% are caused by nematodes and other parasitic diseases, 5.7% are bacterial, and the balance are caused by a range of other diseases and disorders. Some pathogens are at the root of many diseases, such as the fungus *Rhizoctonia solani*, which causes 106 different diseases. New plant pathogens are continually discovered, with eight new pathogens and 10 new strains of identified pathogens identified in 2007 (ISID, 2007).

Genetic sequencing of plant pathogens permits the development of molecular diagnostics for the pathogen. As of 14 January 2008, DPVweb (2009), had catalogued the sequences of 22 542 strain of 1 185 different viruses and 672 strains of 137 fungi or protozoa. Some of these sequenced pests caused substantial crop losses. For instance, *phytophthora sojae*, which causes USD 1 billion annually in losses from stem and root rot of soybeans, was successfully sequenced in 2004 (GenomeWeb, 2004).

Current status of plant diagnostics

Two types of molecular diagnostics are widely used to detect plant pathogens: ELISA and PCR.[29] Tests are frequently carried out in the laboratory and require specific skills. Diagnostics are available for most important pathogens of developed countries (Ward, 2004). Diagnostics are available for 954 plant diseases (1,402 diagnostics are available in total). Most diagnostics either use PCR (40.4%) or ELISA (53.9%). Table 15 gives the class of pathogen targeted by diagnostics for at least 954 plant diseases. Half of the diagnostics were for the identification of viral diseases.

Forecasting for plant diagnostics

The goal for diagnostics is to develop real-time tests for multiple diseases that can be used by farmers in the field. Twenty-four real-time PCR methods are currently available,[30] but they can only detect single pathogens. An example is a test, introduced in 2007, that can identify nematodes in pine trees (INRA, 2007). Real-time PCR methods are fast but not widely used because they do not include enough assays to get a wide range of diagnoses (Ward *et al.*, 2004). The best technology is a DNA microarray that detects the genomes of plant pathogens, but none are beyond the developmental stage, such as a microarray that can test for 24 potato pathogens (EC, n.d.).[31] The method is still costly and difficult to achieve.[32]

Table 15. **Estimate of plant diagnostics by the class of plant disease tested, as of 2007**

Types of plant diseases	Number of diseases with diagnostics	Percent of total
Bacterial diseases	125	13.1
Fungal diseases	275	28.8
Miscellaneous diseases and disorders	4	0.4
Nematode and parasitic diseases	18	1.9
Phytoplasmal and spiroplasmal diseases	55	5.8
Viral and viroid diseases	477	50.0
Total	954	100.0

Source: Authors based on diagnostic from various companies.

Note: This table may not be complete, due to the difficulty in identifying all plant diagnostics.

Animal farming

Animal farming includes the breeding and raising of livestock (animal husbandry), poultry, fish and bees. It includes all biotechnology applications to farmed species in the Animalia Kingdom, consisting of heterotrophs that feed off other organisms. In addition, biotechnology has some applications to the exploitation and conservation of wild animal populations such as fish.

Livestock accounts for approximately 40% to 50% of the value of agricultural production in OECD countries. The main outputs are dairy products, eggs, meat, and fibre (wool, hair, etc). Global prices are not comparable. As an alternative, Table 16 gives the output of farmed animal products measured in tonnes. In 2005, total production of meat was 288.6 million tonnes, dairy 629.1 million tonnes, and eggs 64.0 million tonnes. The fastest growth rates for animal products between 1995 and 2005 are for poultry, eggs, and pork. Beef production grew by 3.8% globally but declined by 5.2% in the OECD.

Up to 2015, biotechnology has three main applications for livestock, poultry and aquaculture: breeding, propagation, and health (diagnostic and therapeutic) applications. The identical set of biotechnologies used in plant breeding can be applied to animal breeding, including transgenic GM, MAS, cisgenesis, and gene shuffling, etc. In addition, diagnostics can be used to identify serious inherited diseases and to remove afflicted animals from the breeding population.

Table 16. **Animal production (in thousand tonnes)**

	World		OECD	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Animal Fats	8 113	3.74%	5 368	1.59%
Bird Eggs	64 004	30.51%	18 050	10.18%
Bovine	63 982	3.81%	27 307	-5.21%
Dairy	629 053	14.94%	289 097	4.32%
Fibres[2]	3 635	-6.83%	988	-21.64%
Natural Honey	1 384	18.36%	474	8.19%
Other[3]	16 762	6.30%	6 210	-2.52%
Pig	104 630	24.23%	36 706	10.61%
Poultry[4]	82 394	38.01%	37 206	21.94%
Sheep and goat	12 768	19.23%	2 849	-8.39%

Source: Authors, based on FAO (2009).

Notes: 1. To avoid anomalies from variable growing conditions, the percent change was determined from the average production output between 1995 to 1997 and 2003 to 2005.
2. Only includes fibres of animal origin.
3. Other includes edible offal, equine meat, rabbit meat, and meat not included elsewhere.
4. Poultry includes chicken meat, turkey meat, and duck, goose, or guinea fowl.
5. See Annex F for data on the European Union, North America, and South America.

Current status of biotechnology

In contrast to plant biotechnology, there are only a few publicly available databases on animal biotechnology. These are for approved health products. There is no equivalent of the GM field trial databases for animals, nor have any GM varieties of food animals been commercially approved within the OECD.[33]

Livestock and poultry breeding

The largest current commercial application of the use of biotechnology in animal breeding is the application of MAS to conventional breeding programmes. MAS improves the accuracy and speed of breeding programmes. A study by Menrad *et al.* (2006) evaluated the use of MAS in European pig breeders and found that markers or gene assisted selection for genetic problems such as the halothane gene are already widely used to remove defective stock. MAS is not as widely used, however, to identify the presence of desirable genes, partly because of a lack of adequate knowledge of possible markers. Markers are currently available for the halothane gene plus genes linked to meat quality, intramuscular fat, tenderness, resistance to *E.coli*, appetite, growth rate, male infertility, and litter size. Menrad *et al.* (2006) estimate that "MAS contributed to the breeding of around 40% to 80% of breeding females". Similar rates for the use of MAS could apply to other valuable livestock, such as cattle and dairy cows.

Breeding in aquaculture

Table 17 gives production results for marine animals. Fish (mostly wild varieties) account for 59.7% of global production by weight, but fish catches have fallen by 5.2% over the past decade. Conversely, production of molluscs and other marine resources has grown, partly because molluscs and crustaceans are increasingly farmed. Globally, aquaculture produced 45.5 million tonnes of marine products with a market value of approximately USD 63.4 billion (FAO, 2006).

Biotechnology is used to develop improved varieties of shrimp, fish and molluscs for aquaculture. The firm Aqua Bounty, for instance, has developed a GM Atlantic salmon (AquaAdvantage™) that grows much faster than non GM salmon used in fish farming. The growth hormone gene that causes faster growth has also been included in Tilapia, trout and

Table 17. **Marine animal production (in thousand tonnes)**

	World		OECD	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Fish[2]	23 390	-5.20%	9 325	-15.19%
Molluscs[3]	4 821	14.60%	3 751	11.73%
Other[4]	10 967	2.07%	4 116	-18.69%

Source: Authors, based on FAO (2009).

Notes: 1. To avoid any anomalies due to unusual environmental conditions etc., the percent change was determined from the average quantity of the periods 1995 to 1997 and 2003 to 2005.
2. Fish includes freshwater and diadromous fish; and demersal, pelagic, and other marine fish.
3. Molluscs include clams and oysters.
4. Other includes aquatic plants, mammals, and other animals; cephalopods (squid), and crustaceans (shrimp, prawns, lobsters etc).
5. See Annex G for data on the European Union, North America, and South America.

flounder. Aqua Bounty submitted AquaAdvantage™ salmon to the US FDA for approval in 2003, but as of August 2009 the variety has not yet been approved for commercial use. Even if approved, it may not be in commercial use by 2015, due to public opposition (Mulvaney, 2007). To date, the only transgenic fish approved for use within the OECD is a fluorescent gold fish for home aquariums.

MAS has been used in breeding programmes for oysters, salmon and trout for culture. Varieties developed using MAS are estimated to account for 30% of salmon and trout breeding in the European Union, with MAS estimated to contribute to 15% of European Union fish farming turnover (Zika *et al.*, 2007).

Breeding of insects

Biotechnology has applications for reducing the viability of insect pests and for improving the health and survival of valuable insect pollinators such as honey bees. Biotechnological applications for insect pollinators and pests are only in the research stage.

Research into pests aims at reducing pest populations and infestations. This can be accomplished by developing male only strains or strains that pass a fatal genetic trait to offspring.

Research on honey bees includes developing insecticide resistant and disease resistant honey bee strains and identifying the cause of honey bee diseases or die off (Pew Initiative on Food and Biotechnology, 2004).[34] The honey bee genome was sequenced and published in October 2006 (Honeybee Genome Sequencing Consortium, 2006).

Therapeutics and diagnostics

The global market for animal heath products is estimated at approximately 3% of the market for human health products, or approximately USD 24.1 billion in 2008 (Elder, 2008), about two-thirds of which are products for farm animals and the remaining third is for companion animals (household pets).

Therapeutics

Biotechnology can be used in the development of animal therapeutics and vaccines. However, very few bio-pharmaceuticals have yet to receive approval for animal use. The FDA's Center for Veterinary Medicine publishes a list of approved drugs for animals in its Green Book.[35] The January 15, 2008 version, only listed one bio-pharmaceutical: bovine somatotropin for use in dairy cows (not approved in the EU).[36] Porcine somatotropin is approved for use in Australia, Mexico, Malaysia and Vietnam to encourage growth and lean meat in pigs. The lack of more bio-pharmaceuticals is probably due to poor cost effectiveness in livestock or a lack of applications in valuable animals such as family pets and racehorses. The most common drugs for livestock are vaccines and anti-infectives.

The only recombinant vaccine approved for the United States for livestock as of December 2006 is a vaccine for West Nile Virus (USDA, 2006), although recombinant rabies vaccines are approved for wild racoon populations and for cats. Otherwise, all vaccines use live or killed infective agents. In Europe, recombinant and live rabies vaccines have been used for the control of rabies in wild foxes. A recombinant vaccine has been available in Europe for pseudorabies (Aujeszky's Disease) which affects pigs, but this vaccine has not so far been used in the United States (Menrad *et al.*, 2006). The advantage of the recombinant vaccine over live or killed virus vaccines for this disease is that

the recombinant version permits the identification of vaccinated versus infected animals. Europe appears to lead the United States in the development of recombinant vaccines and could have additional recombinant vaccines for animal use either on the market or under development.

Diagnostics

The animal diagnostics sector largely depends on methods that have been developed for the human diagnostic industry, with minor variations. There are two main markets: companion animals (pets) and farm animals. There are two types of molecular or biotechnological tests. Genetic tests target DNA or RNA while immunological tests target protein. Table 18 gives examples of both types of animal diagnostics.

Gene based diagnostic tests for disease detection (or gene probes) permit the identification of the presence of a pathogen, rather than antibodies to a pathogen (the most common form of animal diagnostics). Genetic tests are available for swine fever, Mycobacterium paratuberculosis, and Mycoplasma gallisepticum. In addition, monoclonal antibodies are available for the detection of canine heartworm and feline leukaemia virus in household cats.

Table 18. **Types of animal diagnostics**

Type	Description	Disease target[1]
Genetic tests	Target: DNA/RNA	
Nucleic Acid Sequence Based Amplification	Method to amplify RNA sequences.	Avian influenza Foot-and-mouth disease
DNA microarray	A glass slide or bead containing microscopic DNA samples in an orderly pattern are treated with complimentary-DNA and used to detect the relative expression level of each gene.	Canine heartworm
Fluorescent In Situ Hybridization	A procedure involving the use of fluorescent DNA probes to locate in a tissue section specific regions of DNA in the chromosomes.	Pneumocystis carinii pneumonia
Polymerase Chain Reaction (PCR)	A specific sequence of nucleotides within a double-stranded DNA is amplified to test for disease and detect rare mutations.	Mycobacterium Paratuberculosis Classical Swine Fever Virus
Real-time Polymerase Chain Reaction (real-time PCR)	A laboratory technique based on polymerase chain reaction, which is used to amplify and simultaneously quantify a targeted DNA molecule. It enables both detection and quantification (as absolute number of copies or relative amount when normalized to DNA input or additional normalizing genes) of a specific sequence in a DNA sample.	bovine rotavirus Feline Leukemia Virus
Immuno-diagnostics	Target: proteins (antibody, antigens…)	
Dot Blot	Detection of organic molecules.	Canine Parvovirus Chronic Wasting Disease
Enzyme-Linked ImmunoSorbent Assay (ELISA)	The measurement of specific biochemical substances that depends upon the specificity and high affinity shown by suitable antibodies for their complimentary antigens, which are labelled with an enzyme as an indicator.	Bovine Spongiform Encephalopathy
Competitive Enzyme-Linked ImmunoSorbent Assay (competitive ELISA)	A use of ELISA through competitive binding.	Caprine Arthritis-Encephalitis Virus Bluetongue Virus
Indirect Immuno-Fluorescence Assay	An antigen or antibody is linked to a fluorescent dye that fluoresces when exposed to the complimentary antibody or antigen in a sample.	Babesia Bovis Infection

Source: Authors, definitions from a range of sources.

Notes: 1. The list is not exhaustive.
2. Not all diagnostics for each target are available on the market.

In the United States, animal diagnostic kits for veterinary use to identify diseases are under the control of the United States Department of Agriculture (USDA). This organization ensures that the tests are not harmful or dangerous.[37] In contrast, tests to diagnose genetic traits of animals are not regulated. These tests exist for companion and other animals, for example to identify purebreds, and for livestock and pet breeders (Harmon, 2007). The diagnostic market for companion animals is particularly valuable because pet owners are willing to spend more on healthcare per animal than livestock growers. In 2006, Americans spent USD 19 billion on all forms of pet healthcare (Bellingham, 2007). The time to develop an animal diagnostic (up to market entry) is estimated at half the time required for human diagnostics (Gallagher, 1998).

Estimates of the global market for animal diagnostics vary widely. One report estimated the market for animal diagnostics in 2007 at USD 474 million, (Elder, 2008) but Animal Pharma estimated the market in 2002 at USD 1 100 million (Animal Pharma Report, 2003).[38] The market is attractive for firms already involved in the development of human diagnostics.

Table 19 provides an estimate of the 2002 distribution of sales by diagnostic type. Genetic tests have a 4% market share, while immunodiagnostic tests have 40% of the market.

Table 19. **Estimate of diagnostic sales by type of product – 2002**

	2002 Sales (USD millions)	Share of total diagnostic sales
Immuno-diagnostics	440	40%
Genetic testing	44	4%
Others	616	56%
Total	1 100	100%

Source: Animal Pharma Report, 2003.

Table 20 lists companies that develop and manufacture animal diagnostics and gives the share for each company of all diagnostics that have been licensed by the USDA Center for Veterinary Biologics (2007). The top ten firms produce over 80% of the licensed products, with two firms producing more than half of all animal diagnostic products (57.5%). While not all of these diagnostic tests are biotechnology based, many are, and the table shows the level of concentration present in the animal diagnostic market.

In addition to farmed animals, biotechnological diagnostics can be used to manage wild fish, mollusc and other marine stocks. This is based on DNA fingerprinting to distinguish between different stocks of migrating fish. The technology can be used to set fishing quotas or close fisheries of endangered stocks. DNA fingerprinting can also be used to determine the factors that improve survival of wild fish species released from hatcheries (ETEPS, 2006).

Aquaculture diagnostics and therapeutics

Diagnostics in aquaculture are used to determine the health status of aquaculture species or to determine the cause of illness. Some diseases of aquatic animals can be transmitted through water, causing high infection rates in aquaculture. For example, the viral yellowhead disease in tiger prawns (Penaeus monodon) can kill up to 100% of the affected population (OIE, 2006). In Japan, economic losses due to fish diseases are estimated to

fall between USD 97 million and USD 195 million per year (The FishSite, 2005). In 2005, aquaculture production in the United States alone had a value of USD 1.1 billion, of which fish species accounted for 62% of total sales (JAVMA, 2005).

Aquatic animals can be affected by four main families of pathogens: bacteria, fungi, parasites and viruses. As shown in Table 21, there are currently 63 known pathogens that affect aquatic animals. Almost half are parasites (47.6%), one-third are viruses, 15.9% are bacteria, and 3.2% are fungi. While all aquatic species are vulnerable to disease, the vast majority of pathogens target fish. The number of known pathogens for both aquaculture and wild aquatic species is increasing over time.

Table 20. **Number of animal diagnostics, by company, licensed by the USDA (as of June 2009)**

Company	Licensed products	Share of total products (%)	Cumulative percentage (%)
IDEXX Laboratories, Inc	52	29.5%	29.5%
Synbiotics Corporation	40	22.7%	52.3%
VMRD, Inc.	14	8.0%	60.2%
Affinitech, LTD	10	5.7%	65.9%
Veterinary Diagnostic Technology, Inc.	7	4.0%	69.9%
Bio-Rad Laboratories	6	3.4%	73.3%
Intervet, Inc.	5	2.8%	76.1%
Heska Corporation	5	2.8%	79.0%
Meridian Bioscience, Inc.	4	2.3%	81.3%
Prionics USA, Inc.	3	1.7%	83.0%
Charles River Laboratories, Inc.	3	1.7%	84.7%
Trace Diagnostics, Inc.	2	1.1%	85.8%
Tetracore, Inc.	2	1.1%	86.9%
Pierce Chemical Company	2	1.1%	88.1%
Pfizer, Inc.	2	1.1%	89.2%
LMD Agro-Vet LLC	2	1.1%	90.3%
Diagnostic Chemicals Limited (USA)	2	1.1%	91.5%
Colorado Serum Company	2	1.1%	92.6%
Chembio Diagnostic Systems, Inc.	2	1.1%	93.8%
United Vaccines, Inc.	1	0.6%	94.3%
United Biomedical, Inc.	1	0.6%	94.9%
SA Scientific, Inc	1	0.6%	95.5%
Quadraspec, Inc.	1	0.6%	96.0%
Prion Developmental Laboratories, Inc.	1	0.6%	96.6%
Modern Veterinary Therapeutics, LLC	1	0.6%	97.2%
Lohmann Animal Health International	1	0.6%	97.7%
Inverness Medical Innovations	1	0.6%	98.3%
Immucell Corporation	1	0.6%	98.9%
Idetek, Inc.	1	0.6%	99.4%
Abbott Laboratories	1	0.6%	100.0%
TOTAL	176	100	---

Source: Authors, based on USDA (2009b).

Table 21. **Pathogens involved in aquatic animal diseases, by pathogen family – 2008**

	Pathogens	Share of the total
Bacteria	10	15.9
Fungus	2	3.2
Parasite	30	47.6
Virus	21	33.3
TOTAL	63	100.0

Source: Authors, based on AAPQIS (2009).

The World Organisation for Animal Health (OIE) identifies 23 notifiable diseases for aquatic animals, based on their negative economic impacts. Seven affect crustaceans (none is parasitic), nine affect fish (one is parasitic) and seven affect molluscs (all but one are parasitic) (see Table 22). According to the OIE, commercial molecular diagnostics are available for four crustacean, two fish and one mollusc disease. With the exception of a test for the parasite *Bonamia exitiosa,* all detect viruses.[39] There are no data on the exact value of the diagnostic market for aquatic animals.

Biotechnology has the potential to significantly improve aquatic animal diagnostics (McIntosh, 2004) by increasing the speed and sensitivity of diagnosis. However, very few of the currently available diagnostics for aquaculture are based on biotechnological methods such as ELISA PCR, or DNA microarrays. In Japan and in the United Kingdom, research has focused on the use of microarrays. The Japanese Fisheries Research Agency has developed a chip diagnosing 23 different bacterial infections in one test (The FishSite, 2005). A consortium of three UK universities is developing a DNA microarray for hundreds of salmon genes (University of Aberdeen, n.d.). The goal is to determine the genetic causes of poor health in salmon (Science Daily, 2006).

There is a lack of effective therapeutic products to prevent or manage aquatic animal diseases. Only two viral diseases listed by the OIE can be prevented by a vaccine: infectious haematopoietic necrosis (for which a recombinant vaccine has been developed) and red sea bream iridoviral disease. Other vaccines are available for bacterial infections, particularly for salmonid species, but none of them appear to have been developed using advanced biotechnology (Sommerset *et al.*, 2006). As of August 2009, 12 vaccines were available for use in farmed fish in the United States. Globally, five companies dominate the fish vaccine market: Intervet International, Novartis, Schering Plough, Pharmaq, and Bayer.

Propagation

The main advanced propagation biotechnology is cloning. Other propagation methods such as *in vitro* fertilisation (IVF) and embryo transfer are often included under animal biotechnology (ETEPS, 2005), but these technologies do not require genetic knowledge and have been available for decades (the first use of embryo transfer was in 1890).

Nuclear transfer (NT) cloning, based on using embryonic and somatic cells as nuclei donors, is an expensive technology that has been used commercially to reproduce high value individuals, such as breeding bulls. It is also combined with GM to produce animals that express valuable pharmaceuticals in their milk, since conventional breeding of GM stock could result in the loss of the genetic trait that produces the pharmaceutical. Although the FDA has accepted cloning in principle for food animals, cloned animals are unlikely to

directly enter the food chain in OECD countries due to their cost. Instead, the most feasible use of cloning is to produce breeding stock, with their progeny possibly entering the food supply. Even here, market opportunities are currently limited by public opposition to food products from cloned animals.[40]

Forecasting

Forecasting for breeding

Up to 2015, the most widespread application of biotechnology to animal breeding is likely to be the use of MAS and related biotechnologies in valuable commercial livestock species such as pigs, cattle, dairy cows, and sheep.

Table 22. **Notifiable OIE diseases for aquatic animals**

	Pathogen type	Molecular tests commercially available
Crustacean Diseases		
Crayfish plague (Aphanomyces astaci)	fungus	no
Infectious hypodermal and haematopoietic necrosis	virus	yes
Spherical baculovirosis (Penaeus monodon-type baculovirus)	virus	yes
Taura syndrome	virus	yes
Tetrahedral baculovirosis (Baculovirus penaei)	virus	yes
White spot disease	virus	no
Yellowhead disease	virus	no
Fish diseases		
Epizootic haematopoietic necrosis	virus	no
Epizootic ulcerative syndrome	fungus	no
Gyrodactylosis (Gyrodactylus salaris)	parasite	no
Infectious haematopoietic necrosis[1]	virus	no
Infectious salmon anaemia	virus	no
Koi herpesvirus disease	virus	yes
Red sea bream iridoviral disease[1]	virus	no
Spring viraemia of carp	virus	yes
Viral haemorrhagic septicaemia	virus	no
Mollusc diseases		
Abalone viral mortality	virus	---[2]
Infection with Bonamia exitiosa	parasite	yes
Infection with Bonamia ostreae	parasite	no
Infection with Marteilia refringens	parasite	no
Infection with Perkinsus marinus	parasite	no
Infection with Perkinsus olseni	parasite	no
Infection with Xenohaliotis californiensis	parasite	no

Source: Authors, based on OIE (2007).

Notes: 1. For those two diseases, there is a vaccine available and accepted by the OIE. For all the other diseases there is no vaccine or it has not been proven to be useful.
2. Data are not yet available for the abalone viral mortality disease.

Up to 2015, the largest potential for biotechnology in marine applications are for wild stock management, for diagnostics and therapeutics for aquaculture, and the use of MAS and related non-GM biotechnologies for breeding aquaculture fish, mollusc and crustacean varieties. Within the OECD, environmental concerns are likely to block the use of GM aquaculture in open waters, limiting this technology first to enclosed pens. Even then, firms could be reluctant to adopt GM fish and other farmed aquaculture animals due to concerns over public opposition.

The most probable developments for insects include *(1)* insecticide and pest resistance varieties of honey bees, developed using MAS or possibly GM technology (more likely to appear towards the end of the time period 2012 to 2015), and *(2)* more extensive diagnostic tests for pathogens that attack honey bee hives. The latter should appear continuously over time.

The development of GM or other modified insects that are agricultural pests is constrained by alternative technologies such as insect resistant crop varieties and insecticides. Consequently it is unclear how many modified pests will be able to successfully move from the current laboratory stage to commercial use. One exception is honey bee pests such as mites, where insecticides could kill both the pest and the honey bee.

Forecasting for diagnostics and therapeutics

Therapeutics

Research is underway to develop a few additional bio-pharmaceuticals for livestock. Examples include Babesia bovis L-lactate dehydrogenase as a potential treatment for parasitic bovine babesiosis (Bork *et al.*, 2004) and recombinant porcine interferon-alpha/gamma to treat classical swine fever (Xia *et al.*, 2005). These products could reach the market by 2015 and porcine somatotropin could be approved by 2015 for use in the United States. Otherwise, the high manufacturing costs of biopharmaceutical therapeutics severely constrain their potential use for chronic disease in livestock. Future applications are limited to three applications: growth or meat quality enhancers (bST and porcine somatotropin), economically expensive infective diseases for which other treatments are not available, and for companion animals. In the future, pharmaceutical companies that develop biotherapeutics for humans could market similar or identical products for the companion animal market (Bellingham, 2007).

Recombinant vaccines offer several advantages over conventional vaccines based on live or killed infective agents, such as improved immunity, plus the vaccinated animal will never develop the disease, which can happen following the administration of conventional vaccines in rare cases. A disadvantage is that they often require more frequent booster shots than for conventional vaccines. Additional recombinant vaccines could reach the market for livestock applications by 2015, but uptake is likely to be much slower than for human applications, where recombinant vaccines should almost entirely replace live and killed vaccines by 2015.

Diagnostics

The diagnostic market is growing rapidly. Between 2002 and 2007, 54 new animal diagnostics (most not based on biotechnology) were launched in the United States, accounting for 33.8% of the 160 diagnostics on the market in 2007 (USDA, 2007).

Over the short term, the most important application of biotechnology is likely to be for diagnostics for animal genetic conditions. This field has been growing rapidly. Some DNA-based microarrays for animal genetics are already commercially available. For example, GeneChip Porcine Genome Array, developed by Affymetrix through its expertise in similar products for the human diagnostic market, contains 20 201 genes (Affymetrix, 2009).

Genetic diagnostics for animal diseases hold great promise, but only a few are currently available. As with plant diagnostics, the goal is to develop microarrays that farmers can use in the field to detect a variety of animal pathogens. One study predicted that farmside genetic testing for disease would be widely available for livestock by 2010, but this is probably optimistic, given the small number of genetic diagnostics for disease that have reached the market so far (NZ MORST, 2005). However, this technology could be widely available by 2015.

Forecasting propagation

Due to public opposition to animal cloning, this technology is unlikely to be commercially applied to develop breeding stock for food animals within the OECD by 2015. The most probable application of animal cloning is to develop GM animals to produce high-value pharmaceuticals. The first commercial use of cloning for meat or dairy production could occur in non-OECD countries, where public opposition to meat derived from cloned animals could be less important, although this claim is based on what appear to be unverified assumptions about attitudes to animal cloning in China.

Forestry

Biotechnology applications in forestry include the use of MAS and GM in breeding programmes and new micropropagation technologies, particularly somatic embryogenesis.[41]

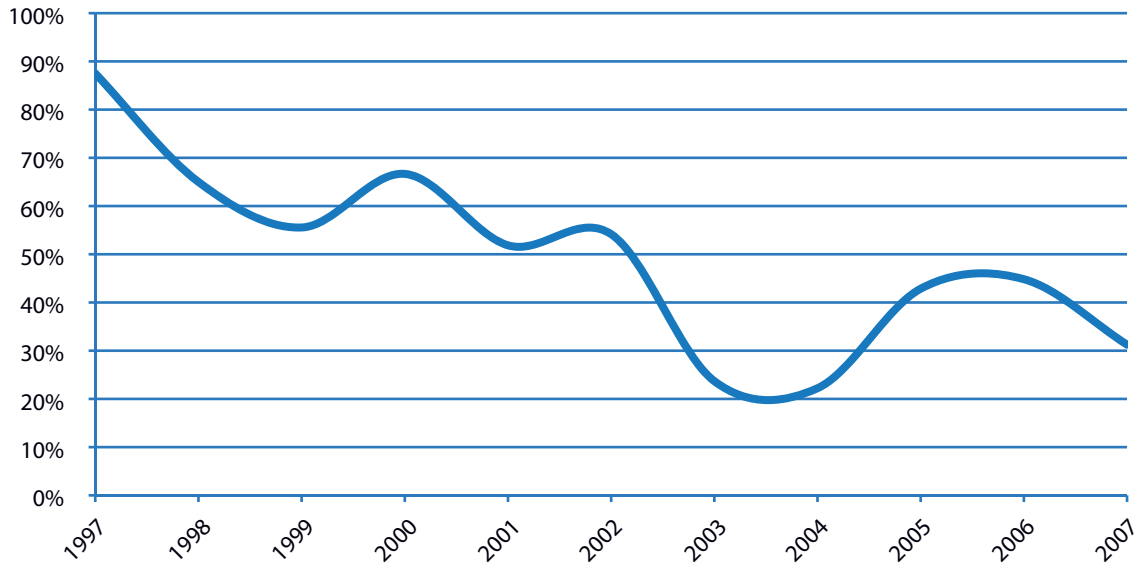
Current status of biotechnology for forestry

Biotechnology research for trees is undertaken by a mix of private and public research entities. As shown in Figure 10, the public sector conducted the majority of GM tree field trials from 1997 to 2002. In 2003, however, the number of field trials conducted by private entities surpassed public entities. This trend has continued, and the private sector conducted nearly 70% of all GM tree field trials in 2007.

Breeding

Research to develop new tree varieties covers many of the traits that are the focus of crop research: pest resistance, product quality, and agronomic traits, particularly yield. Faster growing tree species for timber, pulp and paper, and biofuel is another important goal. Product quality traits concern processing characteristics, particularly for paper production. Biotechnology

Figure 10. **Share of GM tree field trials conducted by the public sector**



Source: Authors, based on UNU-MERIT (2009).

Note: See Annex A for a description of the UNU-Merit field trial database.

can potentially reduce costs by producing tree varieties with modified lignin that is more suitable for paper manufacture, or types of wood that are suited for specialty papers, such as for high quality colour printing. An alternative is to reduce paper costs (both economic and environmental) by developing better ligninolytic enzymes to break down lignin.

Most biotechnology activity is in the research stage, such as identifying markers or sequencing the genome of a few genera such as *populus* (aspen and poplar), *pinus* (pine species), *eucalyptus* species, *betulaceae* (birch) and *picea* (spruce). Compared to breeding programmes for annual crop plants, tree breeding is in an early stage. The only commercial GM tree plantation is in China for a poplar species and one variety of GM eucalyptus is pending approval in the United States (see Table 7).

As shown in Table 23, the most frequent GM trials for tree species concern technical traits, followed by agronomic characteristics, quality applications, herbicide tolerance and pest resistance. Trials for herbicide tolerance fell after 2000, with no herbicide tolerant variety obtaining market approval. Since 2000, almost all GM trials have focused on technical traits (identification of markers), agronomic traits and product quality traits (primarily lignin content). Trials for agronomic (mostly growth) traits increased from 3 in 2001 to 77 in 2007. Based on the field trial record by species, a higher growth variety of pine and possibly poplar could be ready for commercialisation by 2012 and a reduced lignin variety of poplar for paper making (or bioethanol) by 2015.

Table 23. **GM field trials for forestry tree species by trait**

Trait	1993-1999	2000-2007	Total	Percent total
Herbicide tolerance	36	33	68	11.0%
Pest resistance	16	32	48	7.7%
Product quality	10	63	73	11.7%
Technical	24	216	240	38.4%
Agronomic	3	192	195	31.2%
Total	89	536	625	100%

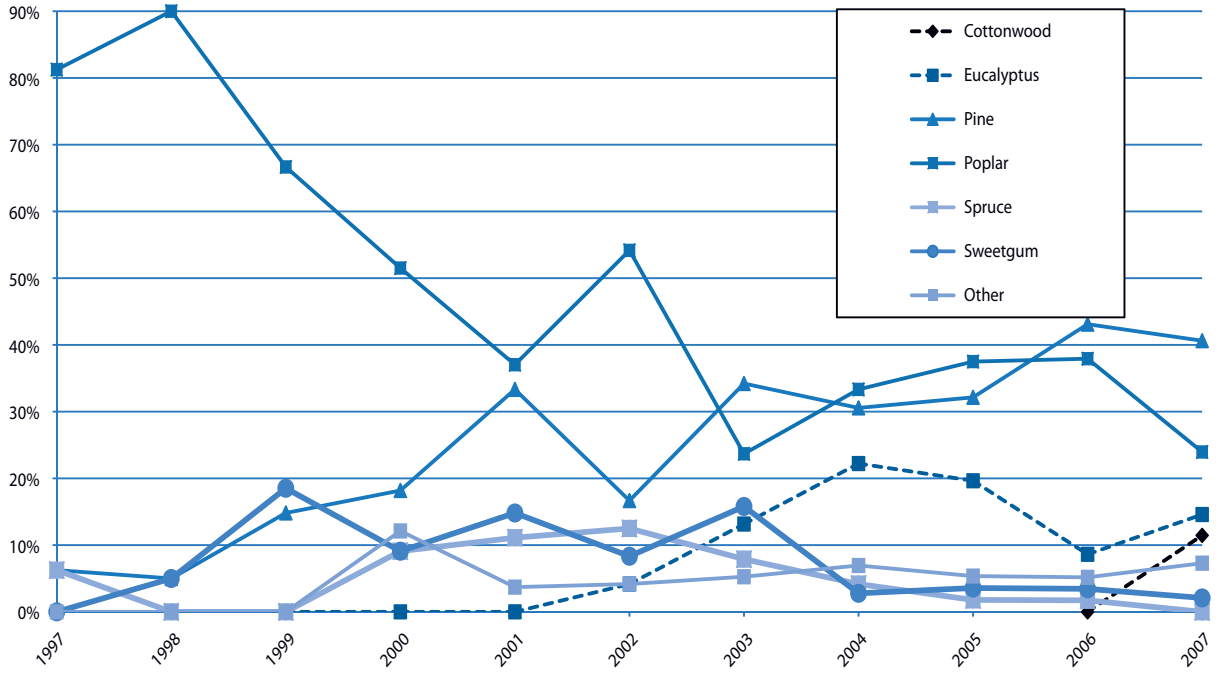
Source: Authors, based on UNU-MERIT (2009).

Notes: 1. Based on trail-trait combinations for 484 field trials conducted from 1993 to 2007.
2. See Annex A for a description of the UNU-Merit field trial database.

Although there has not been a large increase in GM research programmes in pest resistance, this is a major potential application of biotechnology to forestry, both for important wood and fibre tree varieties (pine) and in ornamentals and street trees (elms, chestnuts, California oaks) that have been damaged by introduced pests. The gene coding for *Bt* has been experimentally introduced into poplar varieties to control leaf-eating insects.

GM research has targeted a range of tree species. As shown in Figure 11, GM tree field trials were dominated by poplar species from the late 1990s through 2003. It was then surpassed by field trials for GM pine species, which in 2007 accounted for approximately 40% of all GM tree field trials. Sweetgum and spruce varieties both accounted for around 10% to 15% of all field trials from 2000 to 2003, but interest appears to have waned with no field trials for spruce and only two for sweetgum in 2007. Eucalyptus has also been the subject of field trial activity, accounting for between 10% and 20% of field trials every year since 2003. The first field trials for GM cottonwood began in 2007 and made up 11.5% of trials for that year.

Figure 11. **Share of GM tree field trials, by species**



Source: Authors, based on UNU-MERIT (2009).

Notes: 1. See Annex A for a description of the UNU-Merit field trial database.
2. Other includes American Chestnut, American Elm, Aspen, and Birch.

Micropropagation

Micropropagation covers in vitro methods of vegetative multiplication of large numbers of clones through root cuttings, organogenesis, and somatic embryogenesis. Root cutting techniques are widely used for angiosperms (broadleaf trees) but are not part of modern biotechnology. It is more difficult to use this technique for conifers. One result is that there is a greater chance of commercial success in developing new varieties of broadleaf species. An option for conifers is somatic embryogenesis (SE) which has attracted a lot of research attention as a method of propagation, although the technology has not been commercialised, since many technical problems have not been solved.

A major potential use of SE (with or without MAS) is to speed up tree breeding programmes. Tree varieties often need to be grown for six or more years before it is known if desirable traits are expressed, resulting in 15 to 20 years to develop a new variety, compared to about 8 to 12 years for an annual crop plant. At six years of age, the tree is too old for use in vegetative propagation. Different varieties developed by SE can be both grown and some clones frozen. The clones for the successful varieties can then be thawed and propagated, significantly reducing the time required to develop a new tree variety.

Trends to 2015 in forestry

As noted, two GM varieties of faster growing tree species could be ready for commercialisation by 2012 and an altered lignin variety for pulp or bioethanol production by 2015. MAS should also be widely used in breeding programmes, particularly in countries such as Canada and New Zealand where forestry is a major industry based on a limited number of tree species and active tree replacement programmes. Under these conditions, there is a large commercial potential for improved tree varieties, particularly for pest resistance.

The main growth area for wood and fibre is in humid tropical and semi-tropical regions, where biomass production is many times greater than in the temperate forest zones of the EU. As an example, one hectare of plantation in the tropics produces 40 cubic metres of wood per year, with a harvest age at six years. In contrast, a hectare of forest in Sweden produces 2 cubic metres with a harvestable age of 60 years. Not surprisingly, there is far greater interest in breeding new varieties of fast-growing short rotation trees such as pine and Eucalyptus for wood and fibre in high growth tropical and sub-tropical zones such as Florida (Sedjo, 2005). Second, many northern OECD countries have a surplus of wood. This reduces incentives to invest now in new plantations, although the balance should turn negative by 2050 due to the exploitation of northern forests for pulp and paper and for structural timber. The net result is that there has been less private sector interest for developing new wood and fibre tree varieties for temperate zones, with the exception of poplar species. It is possible that once current temperate forests have been fully exploited, most production of fibre and an increasing level of production of wood will shift to warm humid regions. Although climate change could result in a shift in the location of the best growing regions for commercial tree species, the focus of tree breeding programmes will likely remain on optimal humid and warm environments.

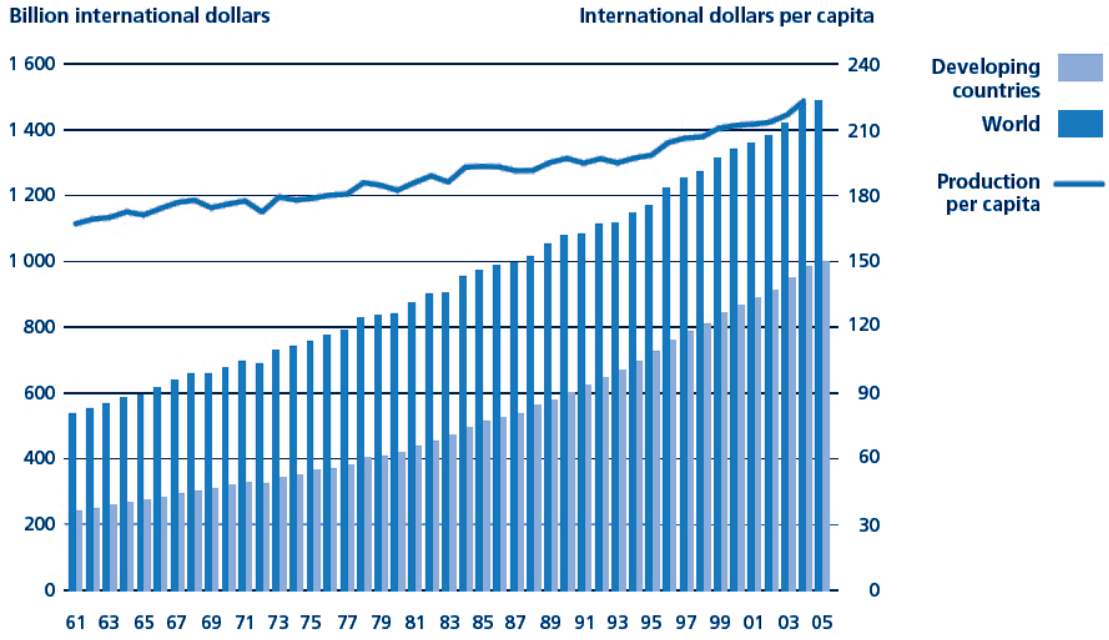
Agricultural biotechnology in developing countries

Agriculture is of vital importance to developing economies. With 80% of the world's population, these regions are the largest overall consumers of food. Hunger and malnutrition remain significant problems, and demand for agricultural products is expected to grow significantly due to increasing populations and income levels. This is likely to be particularly noticeable for animals and animal feed as meat consumption is expected to grow by nearly 1.7% per year from 2007 to 2016 after having increased by 2.7% per year over the previous decade (OECD-FAO, 2007). Meat consumption in developed countries is also expected to increase, but by only 0.7% per year.

Agriculture plays a much larger role in developing, compared with developed, economies both in terms of production and employment. The potential land area that could be dedicated to agriculture is also much larger in the developing world. Given these factors, the application of biotechnology to agriculture in the developing world could have a major impact on people, environments, and economies.

In the early 1960s, developing countries accounted for approximately 45% of global agricultural production (see Figure 12). The developing world's share has increased steadily

Figure 12. **Total and per capita agricultural production**



Source: FAO, 2007.

Note: International dollars are an international commodity price unit, average 1999-2001.

to around 70% in 2005, while at the same time, global agricultural production has risen. Agriculture accounts for an average of 13.4% of the GDP of many developing countries compared to 1.7% of GDP for developed countries. In larger developing countries the share ranges from around 5% in Brazil and Russia, to 11% and 16.6% in China and India respectively (see Table 24).

Table 24. **GDP, agricultural GDP, and agricultural labour force for selected countries and region**

	GDP[2] (billions)	Agriculture[3] (% GDP)	Agricultural Share of GDP (billions)	Agricultural Labour Force[3] (millions)
High-income countries[1]	38 081	1.7%	641	38
Argentina	245.6	6.0%	14.7	0.2
Brazil	1 269	5.1%	64.7	20
China	2 879	11.0%	316.7	345
India	894.1	16.6%	148.4	310
Russia	1 251	4.6%	57.5	6
Other, not high-income	5 740	13.4%	771	487
World Total	50 360	4.0%	2 014.4	1 206

Source: Authors, based on CIA (2008).

Notes: 1. High income countries include all OECD and EU countries. This excludes a number of other small high income countries such as, *inter alia*, Israel and Singapore that would not have a major impact on global agriculture statistics.
2. GDP is the estimated amount for 2007 and calculated using official exchange rates.
3. Data varies from 1999 to 2006.

The number of agricultural workers, which accounts for about 40% of the global labour force, is also much larger in the developing world than it is in developed countries. While high-income countries have 38 million agricultural workers (about 3.1% of the world total), developing countries have over 1.1 billion (see Table 24). Both China and India have more than 300 million workers each in agriculture, accounting for over 50% of the world's agricultural labour force.

The developing world also contains more than 70% of the world's agricultural and forest lands (see Table 25). Agricultural land, as a share of surface area, is almost identical (around 38%) for developing and developed countries, but this is strongly influenced by Russia which has a very large land area and little agricultural land. If Russia is excluded, the share of potential agricultural land in developing countries rises to 44%. The share of forest land is similar for developing and developed countries (around 29.5%). Brazil and Russia have large swathes of forest that account for approximately half of their surface area. These two countries combined account for nearly a third of the world's forests.

There are a number of social, economic, and environmental drivers that point to an increase in the application of biotechnology to agriculture in developing countries by 2015. This could lead to a massive increase in the number of workers, land area, and global agricultural production that are influenced by biotechnology. Indeed a number of developing countries have already adopted biotechnology in much of their agricultural sector. Several developing countries are also making substantial investments in biotechnology research, which should increase their future use of biotechnology.

Table 25. **Area of agricultural and forest lands for selected countries and regions**

	Surface area (1000 sq. km)	Agricultural land[2] (% of land area)	Agricultural land[2] (1000 sq. km)	Forest area[3] (% of land area)	Forest area[3] (1000 sq. km)
High-income countries[1]	35 536	37.5%	13 312	29.6%	10 534
Argentina	2 780	47.0%	1 308	11.9%	330
Brazil	8 515	31.2%	2 653	56.1%	4 777
China	9 598	59.5%	5 710	20.6%	1 973
India	3 287	60.6%	1 992	20.6%	677
Russia	17 098	13.2%	2 251	47.3%	8 088
Other, not high-income	57 027	42.2%	24 083	22.9%	13 047
World Total	13 3841	38.3%	51 309	29.5%	39 426

Source: Authors, based on World Bank (2007).

Notes: 1. High income countries include all OECD and EU countries. Although this excludes a number of small high income countries, such as Israel and Singapore, the exclusions do not have a major impact on global land area statistics.

2. The FAO defines agricultural land as "land area that is arable, under permanent crops, and under permanent pastures. Arable land includes land defined by the FAO as land under temporary crops (double-cropped areas are counted once), temporary meadows for mowing or for pasture, land under market or kitchen gardens, and land temporarily fallow. Land abandoned as a result of shifting cultivation is excluded. Land under permanent crops is land cultivated with crops that occupy the land for long periods and need not be replanted after each harvest, such as cocoa, coffee, and rubber. This category includes land under flowering shrubs, fruit trees, nut trees, and vines, but excludes land under trees grown for wood or timber. Permanent pasture is land used for five or more years for forage, including natural and cultivated crops."

3. The FAO defines forests as "land under natural or planted stands of trees, whether productive or not."

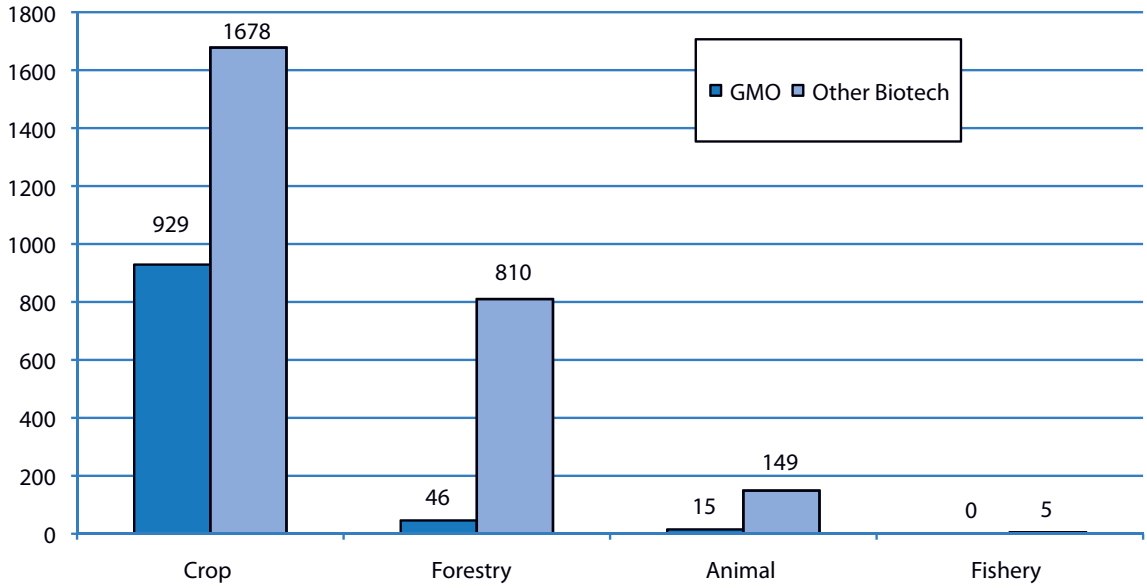
The FAO-BioDeC database, which was launched in April 2003, contains information on "state-of-the-art crop biotechnology products and techniques, which are in use, or in the pipeline in developing countries (FAO, n.d.)." There are more than 2 000 entries for 70 developing countries. They cover projects to develop biopesticides, biofertilisers, diagnostics, fermentation processes, plant breeding, micropropagation methods, other forms of propagation, and a range of other techniques. While the database is unlikely to cover all agricultural biotechnology in use or development, it provides a good indication of the location and types of biotechnology projects in developing countries. As shown in Figure 13, biotechnology in the developing world is primarily applied towards crops, followed by forestry, animal, and fishery applications. In all four application areas non-GMO techniques and products predominate.

Non-GM crop biotechnologies in developing countries

The FAO-BioDeC database contains a total of 1678 non-GM crop projects. Figure 14 shows the breakdown of these projects for three phases: experimental work, trials, and commercialisation. The distribution of each phase by region and type of technology is also shown.

Of the 1 678 projects, 142 (8.5%) have been commercialised, 313 (18.7%) are in trials, 1041 (62%) are in the experimental phase, and 182 have no status specified. Sub-Saharan Africa has commercialised 34% of the 142 projects that have reached this phase, followed by Asia and South America with 24% and 22% respectively. South America has a large majority (64%) of all trials, dominated by Venezuela with 69 trials, followed by Brazil, Chile, and Ecuador with approximately 30 each, Argentina with 18, Peru and Uruguay with 8, and Paraguay with 1. Experimental R&D is led by Asia with 30% of the total. This

Figure 13. **Number of entries in the FAO-BioDeC database**



Source: Authors, based on FAO (n.d.).

experimental research is spread widely over a number of Asian countries with no one country accounting for more than 10% of the total, except Armenia which is undertaking 18% of all experimental projects in Asia.

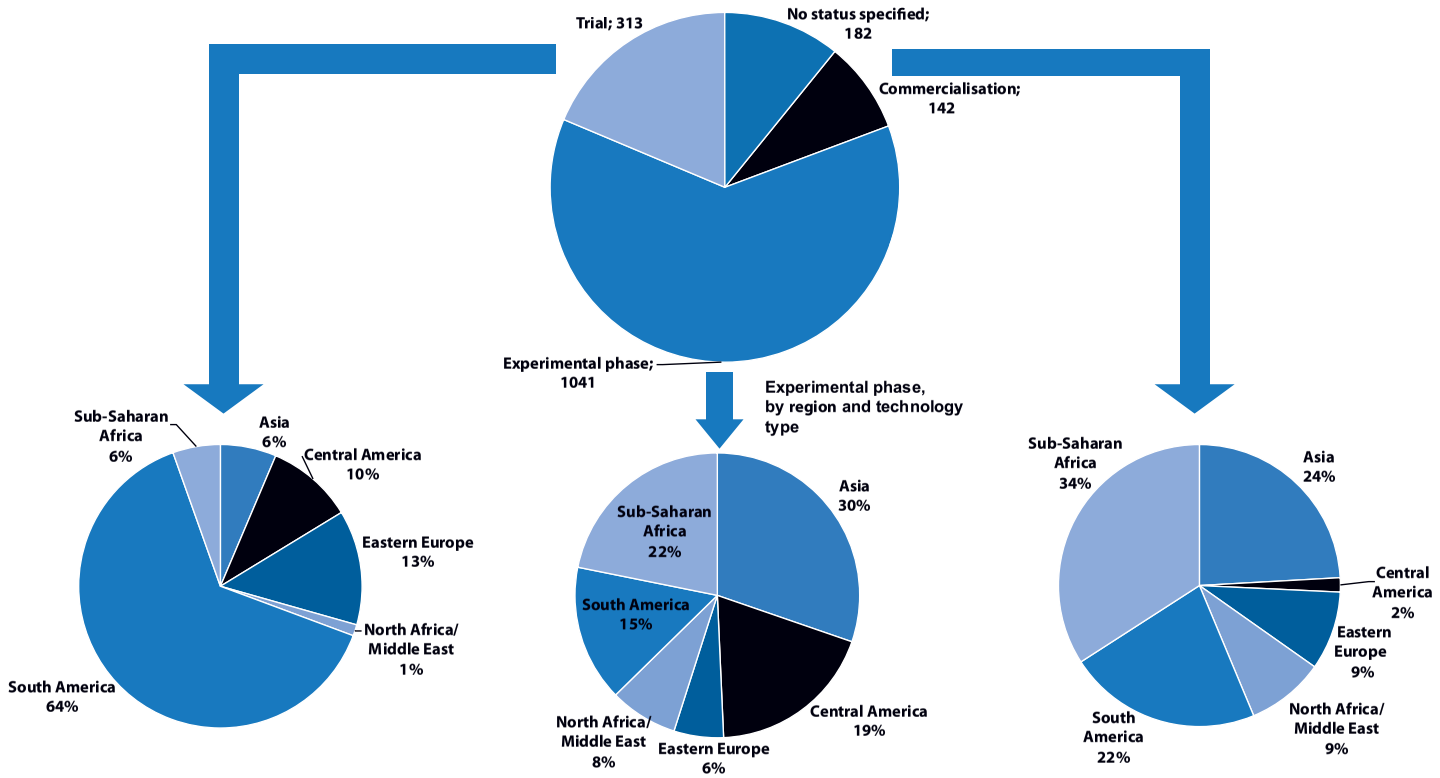
Within each project phase, the prevalence of technology categories is similar and parallels the non-GM plant biotechnology group as a whole. In all cases, plant breeding and micropropagation make up the large majority of all projects. Diagnostics and biopesticides/biofertilisers are the next most studied areas.

GM crops in developing countries

As shown in Figure 15, there are is a significant amount of GM crop activity in the developing world. The FAO-BioDeC database contains a total of 929 GM crop projects: 58 (6.2%) in the commercialization phase, 254 (27.3%) in field trials, 535 (57.6%) in the experimental phase, and the remainder (82) unspecified. In all three specified activities, the Asian region is dominant with 54% of all commercialised GM varieties, 33% of field trials, and 73% of all projects in the experimental phase. South America follows closely with 27% of field trials, but is a distant second in both commercialisation and experimental projects. Sub-Saharan Africa also contains 17% of all the commercialised GM varieties and 11% of all trials, but is only responsible for 5% of all projects in the experimental phase. Central America includes 16% of all field trials, 5% of all experimental GM varieties, and no commercialised GM crops. This large share of trials, however, is heavily influenced by the inclusion of Mexico,[42] which accounts for over 80% of all field trials in Central America.

The large share of GM projects undertaken in Asia, South America, and sub-Saharan Africa is mainly due to the contribution of a few large countries that dominate their respective regions. Table 26 shows the total number of GM projects undertaken in these regions along with the breakdown of the large regional players. In the Asian region, China, India, Indonesia and the Philippines account for more than 85% of all commercialised GM

Figure 14. **Number of non-GM applications of biotechnology to agriculture in developing countries, by phase and technology type**



Trials

Type of Technology	Number
Biopesticides/biofertilizers	22
Diagnostic	15
Fermentation, food process.	5
Other	48
Plant Breeding	113
Propagation, micro	81
Propagation, other	29

Experimental

Type of Technology	Number
Biopesticides/biofertilizers	49
Diagnostic	53
Fermentation, food process.	19
Other	235
Plant Breeding	432
Propagation, micro	247
Propagation, other	6

Commercialisation

Type of Technology	Number
Biopesticides/biofertilizers	5
Diagnostic	6
Fermentation, food process.	11
Other	8
Plant Breeding	15
Propagation, micro	97
Propagation, other	0

Source: Authors, based on FAO (n.d.).

Note: See Annex H for a list of countries by region.

varieties and field trials, and nearly 60% of all projects in the experimental phase. In South America, GM projects are even more concentrated with Argentina accounting for more than 93% of all commercialised varieties, and Argentina and Brazil undertaking more than 90% of all field trials and 40% of all experimental projects. South Africa accounts for all GM varieties commercialised in sub-Saharan Africa and more than 82% of all field trials.

Table 26. **GM projects in selected developing countries and regions, by phase**

	Commercialization	Field Trial	Experimental
Asia	31	83	390
China	10	27	28
India	8	31	114
Indonesia	0	9	54
Philippines	9	4	29
South America	15	68	57
Argentina	14	35	9
Brazil	0	27	14
Sub-Saharan Africa	10	28	25
South Africa	10	23	4

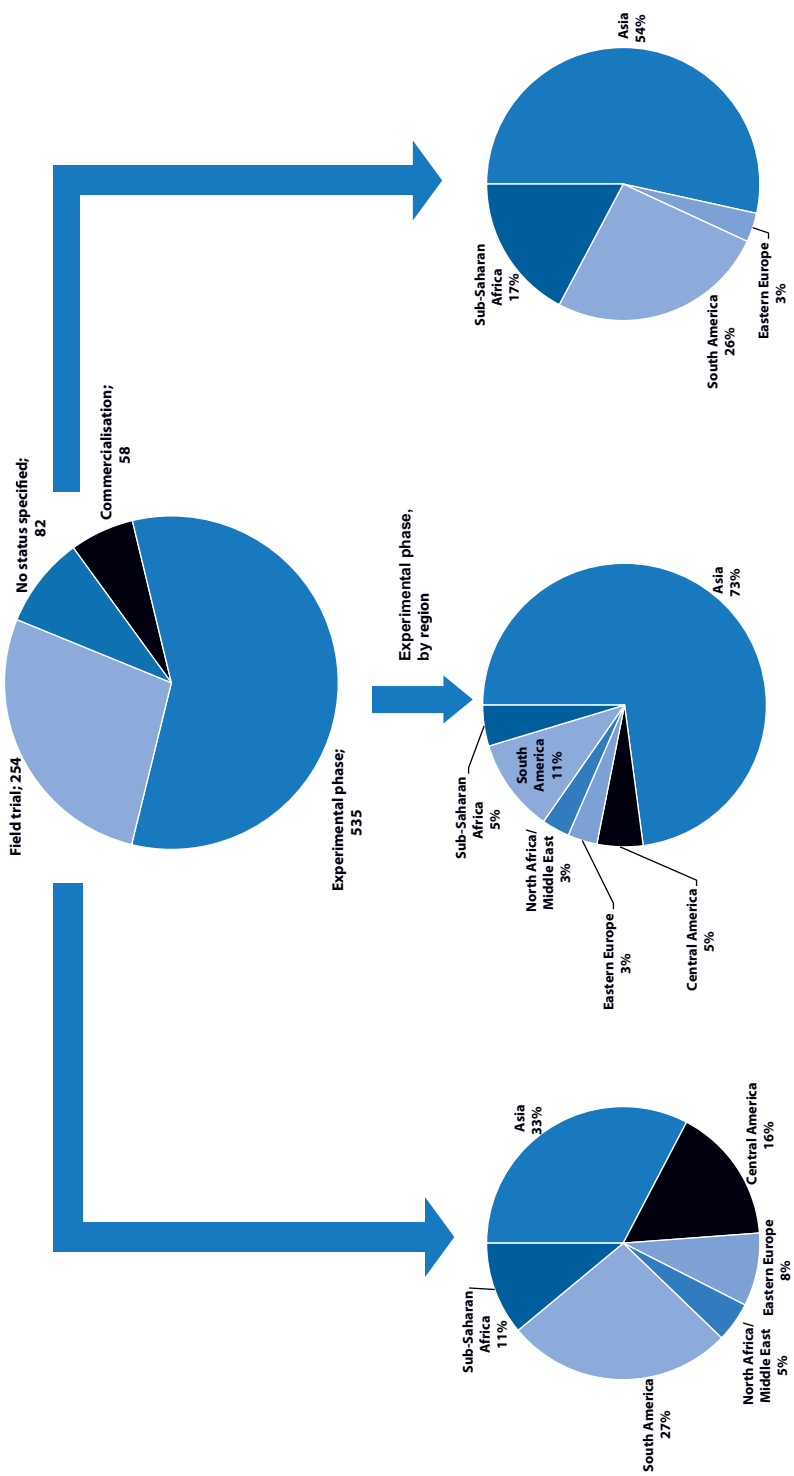
Source: Authors, based on FAO (n.d.).

Almost all of the major commercialised GM varieties and GM field trials in the developing world are for the same crops as in developed countries: cotton, maize and soybeans. In addition, a single variety of the following crops have also been commercialised: orchid, sweet pepper, petunia, green pepper, and red lettuce and field trials have been conducted for sugarcane (10 trials), sunflower (5), cauliflower (4), and cabbage (3) and in a wide variety of other plants. Roughly 60% of all GM varieties in the experimental phases target the main GM crops, while about 4% target sugarcane, and the other 40% span a wide range of plants. Some of the species receiving the most attention are barley, bananas, coffee, eggplant, oil palm, pineapple, sweet potato, and various beans and peas.

Despite the dominance of Asia in GM projects, this has not translated into an equivalent level of technology adoption. Table 27 shows commercial plantings of GM crop varieties in 14 developing countries in 2008. South America accounts for roughly 75% of all GM plantings, while Asia and Africa make up approximately 21.5% and 3.5% respectively. In addition to the plantings listed, a number of other GM crops have received regulatory approval (and are possibly being grown) in developing countries but these tend to be high value crops that are not grown over large areas. For instance, China has commercially approved GM varieties of tomato, sweet pepper and petunia (Cantley, 2006). The FAO-BioDeC database also includes a commercialized variety of GM rice in the Philippines, but there is no evidence that it is being cultivated on a large scale.

This discrepancy between the number of GM projects and adoption rates in Asia and South America could be caused by several factors. First, negative consumer opinion towards GM crops in Asia could be more prevalent that in South America. This is suggested by the adoption of GM cotton in China and India, but no GM human food crops, although pest resistant eggplant is in the final stages of market approval in India.[43] However given the large number of Asian projects for GM rice, which is the regions primary staple crop, GM rice varieties could be approved before 2015. In Asia, rice accounts

Figure 15. **Number of GMO plant variety projects in developing countries, by phase**



Source: Authors, based on FAO (n.d.).

Note: See Annex H for a list of countries by region.

Table 27. **GM plantings in developing countries, by crop for 2008**

Country	Millions Hectares Planted in 2008	Cotton	Maize	Soybean	Other
Argentina	21.0	♦	♦	♦	
Brazil	15.8	♦	♦	♦	
India	7.6	♦			
China	3.8	♦			♦[1]
Paraguay	2.7			♦	
South Africa	1.8	♦	♦	♦	
Uruguay	0.7		♦	♦	
Bolivia	0.6			♦	
Philippines	0.4		♦		
Chile	<0.1		♦	♦	♦[2]
Columbia	<0.1	♦			
Honduras	<0.1		♦		
Burkina Faso	<0.1	♦			
Egypt	<0.1		♦		

Source: Authors, based on James (2008).

Notes: 1. China also cultivates GM poplar, papaya, petunia, sweet pepper, and tomato.
2. Chile also cultivates GM rapeseed.

for 73 out of 390 (18.7%) projects in the experimental phase and for 14 of 83 (16.9%) field trials. Indeed, rice accounts for over two and a half times more experimental projects than tomatoes, which are the second most studied edible plant species in Asia. James (2006) also notes that approximately 20% of China's governmental crop biotechnology budget, or USD 24 million (USD 115 million in PPP), was devoted to rice. This makes China's investment in biotech rice, "undoubtedly … the largest in the world (James, 2006)."

Concerns regarding trade ties between these regions and important markets, such as Europe, Japan, and Korea, that have very strict regulations concerning the consumption of GM crops and adventitious presence, could also play a role in the decision to avoid GM crops. Table 28 presents mixed evidence regarding the influence of trade on the adoption of GM crops. For crops such as maize and soy that are primarily exported as animal feed, trade factors seems to have little if any effect on the decision to grow GM varieties. Between 85% and 92% of the total soy imported by the EU-15 and Switzerland, Japan, and Korea comes from Brazil and the United States, where 55% of the 2006/2007 (James, 2006), and 87% the 2005 soy crop was GM (Fernandez-Cornejo and Caswell, 2006), respectively.

The case is similar for maize, where Argentina and the United States provide over 17% of the EU-15 and Switzerland's maize imports, and the United States alone supplies more than 65% and 95% of Korea and Japan's maize imports respectively. Although the adoption rate of GM maize has been slower than that of soy, 35% of maize cultivated in the United States in 2005 (Fernandez-Cornejo and Caswell 2006) and over 65% in Argentina in 2006 was GM (James, 2006), indicating that trade concerns have not prevented plantings of GM maize.

Table 28. **Maize, rice, and soybean trade between various regions and Europe, Japan, and Korea in 2006**

	EU-15 + Switzerland (as % of total imported value[1])			Japan (as % of total imported value[1])			Korea (as % of total imported value[1])		
Exporting Country	Maize	Rice	Soy	Maize	Rice	Soy	Maize	Rice	Soy
Africa, excl. S. Africa	0.1%	6.2%	0.0%	0.0%	N/A	N/A	0.0%	N/A	N/A
Argentina	14.6%	1.3%	0.6%	0.5%	N/A	N/A	0.3%	N/A	0.0%
Brazil	11.7%	3.9%	63.4%	0.0%	N/A	8.1%	10.1%	N/A	44.4%
Canada	0.1%	0.0%	4.0%	N/A	N/A	9.2%	0.0%	N/A	N/A
China	0.0%	0.3%	0.3%	2.8%	17.8%	6.2%	22.2%	57.5%	7.4%
India[2]	0.0%	1.7%	0.0%	N/A	0.0%	N/A	0.0%	0.0%	0.0%
Indonesia	0.0%	0.0%	0.0%	0.1%	N/A	N/A	0.2%	N/A	N/A
Philippines	0.0%	0.0%	N/A	0.0%	N/A	N/A	N/A	0.2%	N/A
South Africa	0.1%	0.0%	0.0%	0.0%	N/A	N/A	0.1%	N/A	N/A
United States	3.0%	23.6%	23.1%	96.2%	52.5%	76.5%	66.3%	26.9%	48.0%

Source: Authors, based on OECD (2006).

Notes: 1. Value is measured in current USD
2. Data for India is only for Switzerland as EU-15 data was not available.
3. Shaded rows indicate countries cultivating more than 50 000 hectares of GM food/feed crops.

This may not be the case with rice. As noted in the section on "Food, feed, and industrial feedstock crops", it seems that wheat, which is primarily used as human food and widely traded, has not been commercialised despite successful R&D programs due to consumer perception concerns. This trend may also affect rice, which is a staple food for much of the world. As demonstrated, much of the rice imported to the various GM sensitive regions comes from the United States, the world's leading GM crop cultivator. However despite the development and approval of a herbicide tolerant variety of rice, it has not been adopted commercially in the United States, and there is evidence that this is due to fears of jeopardizing GM sensitive export markets.[44]

As noted, much research is going into rice and the commercialisation of a GM variety in China and/or India may significantly alter the picture. These two countries have significant internal demand for rice and make up 10% and 17%, respectively, of the value of all American rice exports.[45] However, China also has a large share of the Japanese (17.8%) and Korean (57.5%) import markets, which could influence the adoption of GM technology for this crop.

Many observers have also pointed to strict GM regulations in the European Union as hindering the uptake of GM crops in Africa due to a fear of losing export markets.[46] Yet with the exception of rice, sub-Saharan Africa is not a significant exporter of agricultural commodity products and therefore consumer opposition to GM in developed country markets is unlikely to have a significant direct effect on the decision to adopt GM. African maize, rice, and soybean exports (excluding South Africa) account for roughly 0.1%, 6.2%, and 0.0% of the total market value of imports for these products to the EU-15 plus Switzerland. The expectation of future markets could influence African countries not to permit GM crops, but Europe already imports animal feed crops from high GM regions, so it is difficult to see how future expectations could play a role. An alternative explanation is that European resistance to GM for human food could influence the policies of African Governments towards GM via professional links between politicians and regulators or by

influencing public opinion. It is also important to note that cultural, distribution, and geographic factors could hinder the adoption of GM crops in Africa.

Finally, the similarity in the types of GM crops and GM traits cultivated in North America, South America, and South Africa seems to play a role in the strong adoption of GM crops. The success of maize and soybean as GM food crops has been strongly influenced by the United States. As shown in Table 29 the United States cultivates both maize and soybean on roughly 30% of the total crop hectares planted in the country. This large reliance on these crops and the market acceptance of GM crops in the United States played an important role in the development of a large number of GM varieties available for these two crops.

The United States shares this major reliance on soybean and maize with Argentina, Brazil, and South Africa where the two crops account for well over half of all hectares planted. Argentina grows more soybeans than any other field crop and was one of the first adopters of GM soybean in 1996, followed by maize in 1998 (Argenbio, 2008). Brazil, where agriculture is also highly dependent on soybeans and maize, began planting GM soybeans in 1997 and adopted GM maize in 2008. South Africa, where maize alone accounts for more than 50% of all hectares planted, began cultivating GM maize in 2000 (Brookes and Barfoot, 2006). The approval of these GM varieties was probably heavily influenced by the availability of this technology from American seed firms.

In the major Asian countries listed, rice is the major field crop. While GM herbicide tolerant rice has been developed, other GM varieties such as *Bt* and stacked traits are not yet available for rice. Maize is a relatively important crop to China as well, but GM maize has not been adopted. Some possible reasons for this could be food security considerations (*i.e.* not wanting farmers to rely on multinational firms for seed supplies) and China's own extensive GM R&D programme. The government could be waiting for Chinese research institutes or firms to develop GM varieties.

Table 29. **Maize, rice, and soybean cultivation shares of total crop cultivation in selected countries, 2007**

Country	Total Ha Planted (1000 Ha)	Maize (% of total Ha planted)	Rice (% of total Ha planted)	Soybean (% of total Ha planted)
Argentina	32 795	9.2%	0.5%	51.7%
Brazil	61 140	22.0%	4.6%	32.9%
Canada	26 368	5.0%	0.0%	4.3%
China	164 185	17.8%	17.6%	5.4%
India	181 432	4.2%	23.5%	4.8%
Indonesia	30 575	10.3%	34.4%	1.3%
Philippines	12 717	19.8%	31.9%	0.0%
South Africa	5 996	50.8%	0.03%	3.6%
United States	99 350	35.1%	1.1%	26.1%

Source: Authors, based on FAO (n.d.).

Animal biotechnology in developing countries

Livestock and poultry

The FAO-BioDeC database contains 149 non-GM animal biotechnology projects occurring in the developing world. As shown in Table 30, a large majority of these (more than 60%) are dedicated to cattle and other large animals such as buffalos, camels, and horses. Pig and poultry account for nearly 10% of all projects and sheep and goats for about 6% each.

Table 30. **Non-GM animal biotechnology projects, by animal type**

Animal	Number	Percentage
Cattle and other large animals	90	60.4%
Pig	16	10.7%
Poultry (incl. Chicken)	14	9.4%
Sheep	10	6.7%
Goat	9	6.0%
Wildlife & game animals	2	1.3%
Domestic animals	1	0.7%
Other	7	4.7%
TOTAL	149	100.0%

Source: Authors, based on FAO (n.d.).

Nearly 80% of all projects are for animal breeding (see Table 31) while diagnostics and vaccines account for about 5% each.[47] Eighteen biotechnologies have been commercialised: seven in animal breeding (three of which are classified as artificial insemination which may not use modern biotechnology), one diagnostic, six vaccine production techniques, and four others that are mainly focused on cryopreservation. Field trials are almost exclusively being undertaken in animal breeding but there is one diagnostic being tested for Porcine Cysticercosis (Pork Tapeworm), and one hormone (somatotropin) being tested in cattle. Projects in the experimental phase are also largely dominated by animal breeding, but there are six diagnostics being developed for *E. coli*, *chlamydophila abortus*, *bovine pestvirus*, and eight other projects.

Table 31. **Type of animal biotechnologies being studied in the FAO BioDeC database, by number and share**

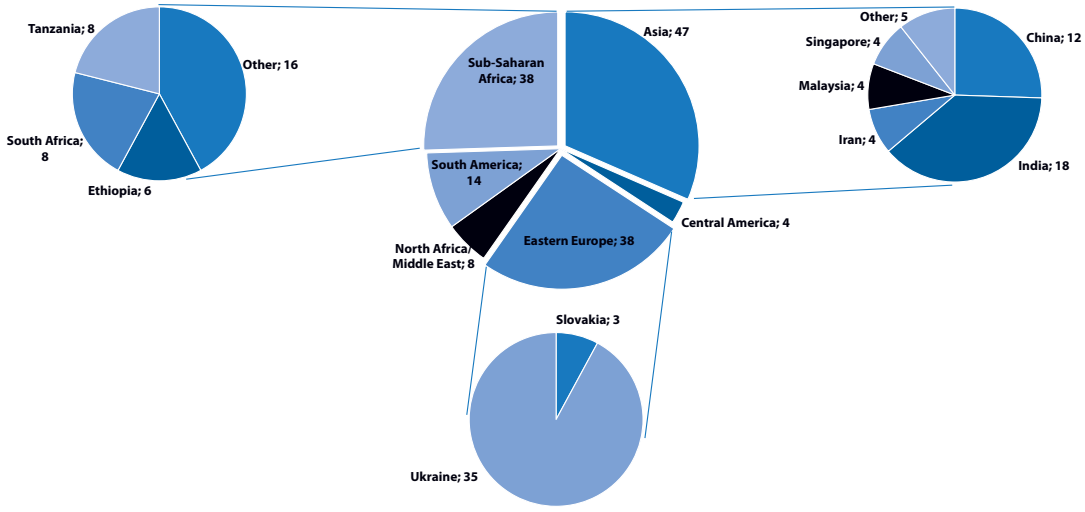
Type of Technology	Total Number	Number in Experimental Phase	Number in Field Trials	Number commercialised
Animal Breeding	118	100	11	7
Diagnostic	8	6	1	1
Vaccine production	8	0	0	6
Other	15	8	1	4
TOTAL	149	114	13	18

Source: Authors, based on FAO (n.d.).

Notes: 1. Columns may not sum to total due to projects where phase is unknown.
2. See Annex I for complete information.

As shown in Figure 16, Asia accounts for 31.5% of all non-GM animal projects and Eastern Europe and sub-Saharan Africa are both undertaking 25.5% of all projects. Within all three of these regions, a small number of countries account for a majority of projects. In Asia, China and India account for over 63% of all projects, with 12 and 18 projects respectively. Ethiopia, South Africa, and Tanzania account for more than 57% of all projects in sub-Saharan Africa.

Figure 16. **Non-GM animal biotechnology projects, by region and selected countries**



Source: Authors, based on FAO (n.d.).

The database also contains 15 projects involving GM animals. Thirteen of these are from Asia (seven in Korea, five in China, and one in Malaysia) and the other two are from Eastern Europe (one each in Slovakia and Ukraine). Ten are in the experimental phase while five are in unspecified phases. Six of these are for producing therapeutic proteins such as human lactoferrin, human granulocyte-colony stimulating factor (G-CSF), hEPO protein, h-tPA protein, and human clotting factor VIII in animals. Other projects study molecular systems and structural gene expression and one project is attempting to develop cattle resistant to mad cow disease.

Fisheries and aquaculture

The FAO-BioDeC database contains five biotechnology projects for fisheries. None of these are identified as using GM techniques. Of the five, two are taking place in Singapore (using unidentified technologies) and the remaining three, in the Ukraine, are for cytogenetic techniques, DNA markers, and isozymes.

Biotechnology could increasingly be used in developing countries to develop new aquatic animals, diagnostics and therapeutics, due to the demand for and economic importance of fisheries and aquaculture. From 1970 to 2006, average annual growth in aquaculture production has been highest in the Latin America and the Caribbean region (at 22%), followed by the Near East region (20%) and Africa (12.7%). In 2006, China alone accounted for 67% of global aquaculture production and 49% of its total value (FAO, 2008).

Forestry in developing countries

In addition to their importance as a building material, forest products are widely used as fuel in developing countries. Forestry is also a very important industry in many developing countries. As shown in Table 32, developing economies provide nearly 35% of all forestry imports to the United States and over half of all imports to the European Union-15 and Japan. Trees are also increasingly being used to solve environmental problems such as desertification.

Table 32. **2006 import value1 and share of forestry product imports to selected markets (in billion USD)**

	United States	European Union-15	Japan
High-income countries[2] (% of total)	19.49 (65.6%)	11.83 (44.0%)	6.00 (43.5%)
Non high-income countries (% of total)	10.21 (34.4%)	15.08 (56.0%)	7.78 (56.5%)

Source: Authors, based on OECD (2006).

Notes: 1. Value is measured in current USD
2. High income countries include all OECD and EU countries. This excludes a number of other small high income countries such as Israel and Singapore that would not have a major impact on forestry statistics.

Non-GM forestry biotechnologies

Developing countries are undertaking a lot of projects to apply biotechnology to forestry. The FAO-BioDeC database contains 810 non-GM forestry projects. As shown in Table 33, micro-propagation is the most used technology, followed by biotechnology based plant breeding, biopesticides and biofertilisers, and diagnostics.

Table 33. **Number of non-GM forestry projects**

Type of Technology	Number
Biopesticides/biofertilisers	42
Diagnostic	15
Other	70
Plant Breeding	267
Propagation, micro	413
Propagation, other	3

Source: Authors, based on FAO (n.d.).

Research is concentrated on a few tree species. The top ten studied tree varieties make up about 54% of all projects underway, while the top five varieties (acacia, eucalyptus, populus, pinus, and mahogany) make up more than 43% (see Table 34). The remaining projects are in a variety of other trees, many of which are region specific.

Only five non-GM forestry biotechnologies have been commercialised in the developing world: two in Malaysia and one each in Nepal, Tunisia, and Burundi. Of these, detailed information is available for four, all of which use micro-propagation. Two of these are for *Acacia* species and promote auxiliary budding and the other two are for *Prunus* and mulberry. There are also 67 forestry products in field trials, 34 of which are in Asia, followed by 23 in South America, 7 in Eastern Europe, 2 in sub-Saharan Africa, and one in Central America. India, Argentina, Chile, and Bangladesh are the leading countries with 20, 11, 7, and 6 field trials respectively. Surprisingly, China, despite a large share of experimental projects (see Figure 17), does not have any reported field trials.

Table 34. **Number and share of non-GM biotech projects, by tree type**

Tree type	Number of Non-GM Biotech Projects	Percent of Total Non-GM Biotech Projects
Acacia (*thorntree, wattle*)	96	11.9%
Eucalyptus	89	11.0%
Populus (*poplar, aspen*)	76	9.4%
Pinus	62	7.7%
Mahogany	28	3.5%
Teak	24	3.0%
Quercus (*Oak*)	22	2.7%
Picea (*Spruce*)	15	1.9%
Ulmus (*Elm*)	13	1.6%
Dalbergia (*sheoak, beefwood*)	12	1.5%

Source: Authors, based on FAO (n.d.).

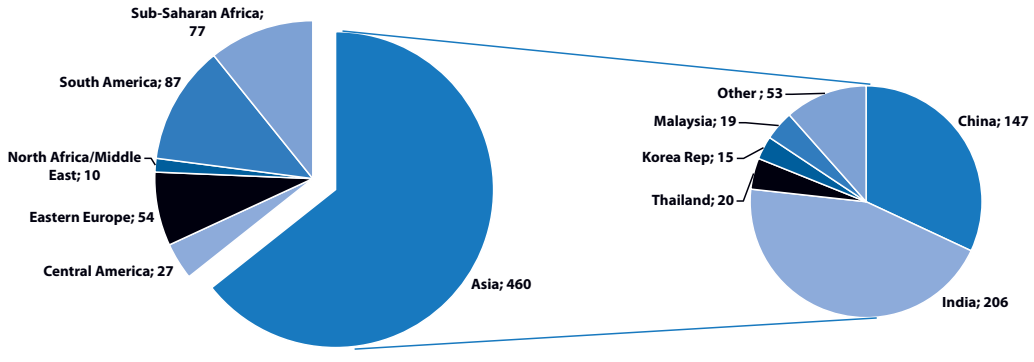
Note: Italics represent commonly known species within the tree genus.

715 of the 810 non-GM forestry projects in the FAO database are in the experimental phase and nearly 65% of those are in Asia (see Figure 17). In Asia, India and China are very dominant with 206 (45% of Asian experimental projects and 28% of the total) in India and 147 (32% of Asian experimental R&D and 20.5% of total). South America has 87 experimental forestry projects with the majority in Brazil (49), Argentina (19), and Chile (16). Sub-Saharan Africa also has a lot of experimental forestry activity (77 total projects) with South Africa under taking 23 of these projects, nearly four times as many as the next largest sub-Saharan African country.

GM forestry biotechnologies

The FAO-BioDeC database also contains 46 GM projects related to forestry. As shown in Table 35, over 50% of these are focused on poplar species, 10% on Eucalyptus and teak, nearly 9% on pine, and the remainder on cocoa, birch, walnut, mulberry, and several other unspecified varieties. A large majority of all projects (over 80%) are in the experimental phase, but there are four poplar, two eucalyptus, and one birch variety in field trials.

Figure 17. **Non-GM forestry projects in the experimental phase, by region (and country for Asia)**



Source: Authors, based on FAO (n.d.).

Table 35. **Number and share of GM biotech projects, by tree type**

Tree type	Number of GM Biotech Projects	Percent of Total GM Biotech Projects	Number in Experimental Phase	Number in Field Trials
Populus (*poplar, aspen*)	25	54.3%	20	4
Eucalyptus	5	10.9%	3	2
Teak	5	10.9%	5	0
Pinus	4	8.7%	4	0
Other	7	15.2%	5	1

Source: Authors, based on FAO (n.d.).

Notes: 1. Italics represent commonly known species within the tree genus.
2. Number of experimental projects and field trials do not sum to total for populus and other because of a project with unspecified status.

Table 36 provides the type of traits being researched in forestry. Over 41% of all GM projects are for insect resistance, followed by 13% for bacterial and fungal resistance, nearly 11% for salinity tolerance, and 4% each for male sterility and wood quality/lignin content.

Table 36. **GM forestry projects, by trait**

Trait	Number of GM Biotech Projects	Percent of Total GM Biotech Projects
Insects resistance	19	41.3%
Bacterial/fungal resistance	6	13.0%
Salinity resistance	5	10.9%
Male sterility	4	8.7%
Wood quality/lignin content	4	8.7%
Other or not specified	8	17.4%

Source: Authors, based on FAO (n.d.).

Forecasting for developing countries

About 97% of global population growth to 2030 is expected in developing countries (UN, 2006). This population growth, coupled with rising income levels and the associated demand for animal products, will have a massive impact on global agriculture in the coming years.

Though developing countries are increasing their investment in R&D for agriculture and related biotechnologies, it is very unlikely that their R&D capacity will equal that of the developed world by 2015. Therefore, as was the case with GM maize and soybeans, the uptake of agricultural biotechnologies in developing regions will probably continue to be influenced by the development of biotechnology in OECD countries. For example, agronomic traits such as drought and salinity tolerance, which are the focus of several research programmes within the OECD, could have a major beneficial impact on large areas of the developing world. If robust strains of important local crops are developed with these traits, adoption is likely if the benefits outweigh the extra cost of GM seed. As long as regulatory conditions and consumer acceptance are favourable, the sheer size of the agricultural

market in Brazil, China, India, Argentina and other developing countries will continue to attract the interest of seed firms based in OECD countries.

Conversely, the development of crop varieties with improved micronutrient levels to address chronic malnutrition in some developing regions is unlikely to attract the interest of seed firms based in OECD countries, due to the inability of poor farmers to pay for new seed varieties. The development of nutrient-enhanced varieties of crops such as sorghum or rice is likely to depend on investment by the public sector in developing countries (OECD, 2009).

Many observers have also pointed to non-technological reasons for the slow adoption of GM food crops in some developing countries such as India, China and sub-Saharan Africa. These include weak regulatory capacity, high regulatory costs, consumer mistrust or opposition, persistent fears of a negative effect on export markets, and inadequate public funds for agricultural biotechnology research. Efforts to address these problems could significantly improve the adoption of biotechnology in developing countries.

Without solid data for developing regions on the average time spent in various development phases and average success rates, it is impossible to accurately predict the types of crop and tree species that will come out of the R&D pipelines in developing countries pipelines by 2015. There are however a very large number of crop and forestry projects (both GM and non-GM) in the experimental phase and some in field trials. This indicates that a significant number of these technologies could be commercialised by 2015, including GM rice and poplar varieties and non-GM varieties of aquatic animals for aquaculture.

Conclusions

Table 37 summarizes the main developments in biotechnology for agriculture, fishing and forestry that are expected to be ready for commercialisation by 2015. Of note, there is a marked shift in GM research since 2000 towards agronomic traits, especially for increased yield. Research into product quality traits also appears to be achieving results. Seed firms extensively discussed these developments in the late 1990s, but there was no data at that time to back up this shift. Today, both the field trial results and company data confirm the move away from a focus on herbicide tolerance and pest resistance (based on the *Bt* gene) towards environmentally beneficial stress tolerance and higher value-added quality traits. In addition, GM crops with improved fungal and nematode resistance should appear on the market by 2015.

The short-term trends covered in this article also highlight the impact of public opposition to GM products. This is by no means limited to Europe. Concern over a lack of markets in many OECD countries, including the United States, could be reducing private sector investment in developing GM varieties of fish, forest trees, honey bees, and food animals. In crops, the main application of GM technology has been for animal feed crops and for crops that are used in food processing. Neither produce agricultural products that are directly eaten by consumers. The number of apparently abandoned GM research programmes for crops such as grapes, plus the decision of Monsanto not to commercialise GM wheat in Canada and the United States (due to opposition of wheat farmers concerned about export markets), suggests that GM still faces a difficult future in many markets.

Two issues for the future are the role of MAS and other non-transgene biotechnologies in breeding programmes and public acceptance of these technologies. Continued opposition to GM could shift breeding methods to non-transgene technology. The extent of any such shift will also depend on the relative cost of GM versus alternatives such as MAS and gene shuffling. To date, the public does not appear to be concerned about the use of MAS or gene shuffling, but this could be based on ignorance about their use. Greater public awareness could lead to a negative association between MAS and GM. Alternatively, greater awareness could lead to a decline in opposition to GM, since the boundaries of technologies such as gene shuffling or cisgenesis overlap with that of GM. For example, cisgenesis uses the same technology as GM, but transfers genes between two plant varieties that could interbreed under normal conditions. If the public accepts cisgenesis, they might be increasingly likely to accept GM technology. How public opinion develops on this issue is clearly of importance to agricultural, forestry, and fisheries policy.[48]

Developing countries have become heavily involved in the use and development of agricultural biotechnologies. This is driven to a large extent by the economic importance of agriculture to their economies (in terms of share of GDP and employment) and by increasing demand from growing populations and incomes. Although this initial wave of agricultural biotechnology uptake in the developing world was mainly driven by technologies developed in OECD countries, developing countries are increasingly conducting their own research using biotechnology. The emergence of major agricultural biotechnology research programmes in developing countries could also have a major impact on future technology developments.

Two major impacts are likely. First, R&D programmes in developing countries are likely to focus on new varieties of local crops and crops that are adapted to local conditions, which would extend the range of crops affected by biotechnology. Second, competition from developing countries could serve to reduce some of the extreme concentration that has caused a large reduction in the number of firms active in agricultural biotechnology. This "competition" could also push governments in developed countries to boost investment in agricultural R&D.

Table 37. **Indicative short-term trends in biotechnology for agriculture and related natural resources**

	Expected by 2010-2012	Expected by 2015
Food, feed & industrial feedstock crops	Almost all varieties of major crops such as maize, cotton, rapeseed and soybeans in OECD countries developed using some form of biotechnology (GM, MAS, etc).	Almost all varieties of alfalfa, potatoes, sugar beet, tomatoes, rice, wheat, barley, rye and oats in OECD countries developed using some form of biotechnology (GM, MAS, etc).
		GM varieties of safflower, poplar, barley sugarcane, Kentucky bluegrass, lettuce, grapes, peas, apples and peanuts become available.
	Some agronomic GM traits available for stress resistance and improved yield available for rapeseed, maize, soybean, potato, rice, and turf grasses.	Some agronomic GM traits available for wheat, cotton, tomato, poplar, many traits for maize, and a few additional traits for soybeans.
	Some product quality GM traits available for tomatoes, rapeseed and safflower.	Large increase in product quality GM traits, with traits available for the main GM target crops.
	New forms of GM pest resistance that are not based on bT in maize, rapeseed, soybeans, potatoes, wheat, sugar beets and tomatoes.	A few major crop varieties with GM resistance to nematodes and fungi.
		Worldwide, GM varieties account for 88% of all soybean plantings, 73% of cotton, 30% of maize, and 21% of rapeseed.
Animals	Commercial use of GM cloned animals that express valuable pharmaceuticals in their milk.	Cloned food animals in non-OECD countries.
	MAS used in OECD countries in all major breeding programmes for pigs, cattle, dairy cows, and sheep.	
	Increase in recombinant vaccines, particularly in Europe.	A few new therapeutic bio-pharmaceuticals for livestock for economically expensive and infective diseases.
	New diagnostics for undesirable genetic conditions.	New genetic diagnostic products for livestock diseases.
Fish, molluscs, crustaceans	New genetic diagnostic and therapeutic products for diseases.	
	Expansion of use of DNA fingerprinting to manage wild fish stocks.	
	Widespread use of MAS in breeding programmes for aquaculture.	GM fish in aquaculture in non-OECD countries.
Forestry	Widespread use of MAS in breeding programmes.	
	Use of GM varieties of pine, eucalyptus and other broadleaf varieties in sub-tropical and tropical plantations for paper and timber.	MAS combined with somatic embryogenesis for cool climate conifers.
Insects	New diagnostics for pests that attack honey bees	Insecticide and pest resistance strains of honey bees, developed using GM or MAS

Notes

1. The figure uses the United Nations median variant.
2. The FAOSTAT database shows that globally there were 1 280 780 hectares of arable land in 1961 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".
3. 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).
4. Many forms of plant tissue culture are not part of advanced biotechnology.
5. The field trial database used in this report is constructed from publicly available information, in English. It does not contain GM field trial results for Korea, Norway and Turkey. This may be because no GM field trials have been conducted in these two OECD countries, or because their field trial data are not publicly available in English. See Annex A for more information.
6. All analyses of the patent data are by the authors.
7. The two main industrial classifications systems are NACE (used in Europe) and ISIC (International). The NAFTA countries use NAICS, but the three systems are generally comparable for the ANR sectors. For both NACE and ISIC (3rd revision), the ANR sectors are covered under sections A and B (at the NACE two-digit level, sectors 01, 02, and 05).
8. Total gross value-added (GVA) is similar to GDP and equals output values minus subsidies and input costs (at producer or purchaser prices). GVA at the sector level is intended to measure the sector contribution to GDP. National differences in the method of calculating sector value added can introduce variability of 5% to 10% in the estimate of the sector contribution to total GDP. See *www.oecd.org/dataoecd/53/21/34464010.doc*.
9. OECD estimate excludes Iceland, Luxembourg, and Norway.
10. Monsanto, Syngenta, and Bayer CropScience reported over 15 000 employees in 2006, but this included employees active in plant protection divisions that manufacture pesticides.
11. The number of patent applicants will underestimate the number of firms using biotechnology in plant breeding. Although the USPTO and the EPO receive many applications from firms based in other OECD countries, the number of applicants from Japan, Korea or Australia is likely to be smaller than the number of firms in these countries that use biotechnology. Firms can also use biotechnology without applying for a plant patent. Conversely, some firms that apply for a plant patent are not involved in plant breeding.
12. A complete patent application record for the USPTO is not available because the USPTO did not start publishing patent applications until 2001. This explains why the USPTO data are for grants until 2004, followed by patent applications.
13. The share of field trials attributed to a firm includes wholly owned subsidiaries plus purchases of other firms. Field trials by a purchased firm are assigned to the new owner from the year after the purchase. For example, Monsanto's share during 1995 to 1999 includes field trials registered to firms purchased by Monsanto, including Agracetus and Asgrow. Since it is difficult retrospectively to identify all subsidiaries, the concentration measures are probably underestimated.

14. Field trials are assigned by the location of the firm's head office and not by the location of the field trial. For example, field trials conducted by European firms such as Syngenta, Bayer CropScience or their subsidiaries in the United States are assigned to Europe.

15. Although some public sector institutions in non-OECD countries apply for an EPO plant patent or received a USPTO plant patent grant, they only accounted for 4.3% of EPO and 5.9% of USPTO patents.

16. See pages 119 – 122 of Menrad *et al*. (2006).

17. Analyses by the authors. The names of all 41 firms were searched in the UNU-MERIT field trial database, with 25 listed as applying for one or more GM field trials.

18. The FAOSTAT database shows that globally 1 214 310 000 hectares were planted in 2006. Data for 2008 were not available at the time of writing.

19. There is more concern over public acceptance for crops used as human feed than for animal feed. More than 80% of wheat is used as human food in OECD countries. In 2009, Monsanto announced that, despite opposition, it would refocus attention on developing GM wheat (Gillam, 2009).

20. A total of 2853 product quality traits were field tested from 1998 to 2007. Of these the feed category accounts for 4 trials (less than 0.1% of total) and the "other" category accounts for 376 trials (13.3% of total). Data for 2008 are not used in the trends because it may be incomplete.

21. The field trial data are not useful for estimating the commercialisation date of high value crops that could be grown entirely in enclosed greenhouses, such as plants to produce pharmaceuticals.

22. The firms include Monsanto, Bayer Crop Science, Du Pont Pioneer Hi-Bred, Syngenta, Targeted Growth, Dow Agrosciences, Scotts, ArborGen and BASF. The websites for major subsidiaries were also checked: Plant Genetics (part of Bayer) and Seminis, Calgene and Asgrow (part of Monsanto).

23. 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.

24. The United States is not a major producer of rapeseed, accounting for only 1.5% of global hectares planted in 2007 (FAO, 2009).

25. Value added data are not available. Producer prices cover costs from pesticides, fertilizers, seeds, etc.

26. When permanent crops are included, total world arable land increases to 1.54 billion hectares, of which biotechnology varieties could account for 46.1%.

27. A recent comprehensive review of GM crops and yield (Brookes and Barfoot, 2006) reports no effect on yield from the GM trait for herbicide tolerance, but in most countries (with the exception of Australia) GM crop varieties with insect resistance traits increased yields by over 5% in corn and over 3% in cotton.

28. There are approximately 50 000 plant pathogens in the United States, although many cause little economic damage (Pimentel *et al*., 2004).

29. Some variants of these methods are also used. For example, the Reverse Transcription-PCR (RT-PRC) method, or the Double-Antibody Sandwich-ELISA (or DAS-ELISA) method are used to detect the Verticillium sp. pathogen (van de Koppel and Sebots, 1995).

30. An example is a diagnostic for nematodes in potatoes (Bates *et al*., 2002). FLASHKIT tests developed by the firm Agdia are ELISA-based and can be performed in the field. Most identify viruses, but a few tests can identify bacteria.

31. There are 15 viruses and virus-like organisms, six nematodes, one fungus and two bacterial diseases (EC, n.d.).

32. The European Commission has launched the Diag Chip project to develop a chip that can recognize 275 harmful pathogens. These pathogens are listed in the EU directive 77/93/EEC.

33. GM laboratory animals for research, primarily mice, are widely used.

34. Possible viral and pathogen causes of the 2006-2007 "colony collapse disorder" have been identified using high throughput screening for viruses (Science Daily, 2007).

35. The Green Book list of approved products is available at *www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/ucm042847.htm*. In the EU, the EMEA's Committee for Veterinary Medicinal Products approved recombinant interferon-omega in 2001 for the treatment of canine parvovirosis in dogs and cats in 2004.

36. The green book includes biologics such as porcine insulin, chorionic gonadotropin, follicle stimulating hormone, polysulfated glycosaminoglycan and serum gonadotropin. These are obtained from biologic extracts from animals or humans. Some can also be produced using recombinant technology, but none of the examples in the Green Book appear to be recombinant versions.

37. The control applies to diagnostics which are produced in the United States and for imports.

38. According to Arundel and Sawaya (2009), the total in vitro diagnostic market for humans was estimated at 27.6 billion USD. The market for animal diagnostics is therefore approximately 2% to 4% of the human diagnostic market.

39. The company AquaBounty markets diagnostic systems using PCR that identify five shrimp and salmon viruses (SybrShrimp and SybrSalmon), see *www.aquabounty.com*. Aquatic diagnostics have also been used as a research tool (McIntosh, 2004).

40. In many countries, public opinion surveys have found the lowest level of support for cloned animal food products out of all agricultural biotechnology applications. This has been found as recently as 2007 for Australia (Eureka, 2007), consistently for Europe (Gaskell, 2000), and also in the United States, where a 2006 survey found that 64% of Americans were 'uncomfortable with animal cloning' (Mellman Group, 2006). Less is known about public attitudes in Asia. A survey in Zheijiang Province found a generally utilitarian and positive attitude to agricultural biotechnology, although there were no specific questions reported for animal cloning (Lu, 2007).

41. See Forest Resources Development Service (2004) and Mccord and Gartland (2003).

42. While Mexico is included in the FAO-BioDeC database, it has been excluded from the developing country category throughout the rest of the report.

43. Approval was expected by the end of 2009 (*http://gmopundit.blogspot.com/2008/06/gm-brinjal-moves-forward-in-india.html*). If approved, this would be the first GM crop for human consumption approved in India.

44. See *http://calriceproducers.org/BCI_executive_summary.pdf.*

45. The 2006 value of all rice imports to the United States was USD 368.3 million of which China and India accounted for USD 37.9 million and USD 62.8 million respectively.

46. For examples see *www.nuffieldbioethics.org/fileLibrary/pdf/gm_crops_summary.pdf* and *www.goldenrice.org/Content4-Info/Info10_GM+development.html*.

47. There are no data on whether or not these vaccines and diagnostics are based on advanced biotechnology.

48. As of October 2009, cisgenesis is regulated in Europe as transgenic crops, but the status of cisgenesis has been under review.

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Annex A

Description of the UNU-Merit field trial database

In most OECD countries, field trials of new GM plant varieties are registered and the data are publicly available. Field trials cover a comparatively late stage of the development of GM varieties, as they do not include greenhouse and laboratory trials. Consequently, field trials provide evidence of relatively late stage research into new plant varieties that could be ready for commercialization within two to six years. The field trial database is updated annually and currently covers 1987 to December 31, 2008.

Field trial data have many of the advantages and limitations of patents. Both provide a measure of investment in particular lines of research by firms and public sector institutions to develop new plant varieties (field trials) or inventions (patents), but in both cases there is no direct relationship between the number of trials or patents and the outcome in terms of commercialised GM varieties or inventions. A series of trials can be abandoned, with no commercialisation of the GM variety, and there is large range in the number of field trials required to develop a GM variety. For example, several hundred field trials were conducted in the United States to alter the ripening characteristics of a tomato variety whereas only 15 trials were required to develop a virus resistant papaya variety. Furthermore, field trials are not fully comparable across countries, as they can vary by size (number of hectares) and by the number of years for which they are valid. In Canada, the number of field trials is increased by regulatory limits on the size of each individual trial, while in New Zealand a field trial can last for multiple years.

In the United States, field tests of GM varieties that have already received approval do not need to be registered, which decreases the comparability between Europe and the United States. The UNU-MERIT GM Field trials database used here includes American data for both releases and notifications (an expedited type of release permit). For all countries, the results given in this article exclude non-plant field tests, such as for bacterial pathogens and animals.

The United States provides ten identifiers for the purpose of each trait. These identifiers were used by UNU-MERIT to identify field trials of specific traits for herbicide tolerance, pest resistance, product quality, agronomic characteristics, and other types of traits. Other countries provide information on the trait but do not include an identifier. UNU-MERIT used the data from the United States and other sources to assign each trait in these countries to one of the five main categories. This classification system contains an unknown but small amount of error because some genetic traits can be used for different purposes. In a small number of trials insufficient detail is provided to accurately determine the purpose of a trial. These are assigned to an “other” category.

Ownership is based on the country of the head office of the organisation performing the field trial in the year in which the trial is conducted. Ownership is revised annually to take account of mergers and acquisitions.

All field trials are assigned to either the private sector, public research institutions (universities and research institutes), and to private non-profit research institutes. The public sector is defined as public research institutes and private non-profit institutions. Trials conducted jointly by the private sector and the public sector are assigned to the public sector. There is a small degree of error in the assignment of trials to the public and private sector (estimated at well under 1%), due to a lack of information on the applicant for some trials conducted by Eastern European and Japanese organisations.

Annex B

Definition of plant patents

Patents are assigned by the patent examiner to one or more International Patent Codes (IPC). A single patent can be assigned dozens of IPC codes, depending on the patent claims. In respect to agriculture, the EPO 2004 patent application by Abbot Laboratories for "control of plant cell proliferation and growth" was given 18 IPC codes and covered four major classes: A01H, A01N, C07K, C12N15, of which two (A01H and C12N15) are plant patents.

A plant patent is defined as including at least one of the following IPC classes:

1. **A01H1 to A01H4**: includes processes for modifying genotypes and phenotypes, plus plant reproduction by tissue culture techniques.
2. **A01H5 to A01H17**: includes product patents for varieties of flowering plants, conifers, mosses, algae, fungi, lichens, and symbiotic or parasitic combinations. Many of the patents for plant species other than flowering plants (A01H5) and conifers (A01H7) (with forestry applications could be for uses other than agriculture or other forms of primary production.
3. **C12N15/82, /83 and /84**: includes recombinant DNA or RNA and other technologies, such as vectors, that are part of the genetic modification of plants.

This article excludes patents that are *only* assigned to product IPC classes (group 1 above). Only results for plant patents with an IPC code in either group 1 or group 3 above are included. These are patents for processes or for recombinant technology. Of note, these two groups overlap, since many patents assigned to genetic modification are also assigned to process patents. Consequently, it is not possible to sum different subgroups of plant patents.

Annex C

R&D pipeline review methodology

A web search was conducted of the following firms active in agricultural biotechnology:

- Monsanto
- Bayer Crop Science
- Du Pont Pioneer
- Syngenta
- Targeted Growth, Inc. (private firm)
- Dow Agrosciences
- Scotts
- ArborGen
- BASF

In addition, the websites for five subsidiaries were also checked:

- Plant Genetic Systems (now part of Bayer)
- Novartis (ag-bio now under Syngenta)
- Seminis (now a seed company of Monsanto)
- Calgene (now part of Monsanto)
- Àsgrow (now a seed company of Monsanto)

Of those surveyed, 4 companies had sufficient data to be included in a timeline of what biotechnologies are coming through the pipelines to 2015:

1. DOW Agrosciences
2. Monsanto
3. DuPont Pioneer
4. Syngenta

The companies provide information regarding what products they are developing, and where the products are in their development pipelines. The different products were classified as follows:

- Agronomic
  - Drought
  - Stress resistance
  - Yield
  - Nitrogen efficiency

- Product quality
- Pest resistance
  - Insect
  - Virus
  - Nematodes
  - Fungi
  - Bacteria
- Herbicide tolerance

Each trait was counted as a single instance so that products which stacked two traits, *e.g.* pest resistance and herbicide tolerance, were counted twice.

Some companies also gave an indication of when they believe the product would come to market. When this information was not given, it was either estimated from other company literature or from similar data provided by other companies.

A list of methods by each company is below:

1. **DOW Agrosciences** – Estimated by comparison with Monsanto's pipeline "Estimated Time to Market" (ETM) data.
2. **Monsanto** – Product "phase" data was given in a company pipeline document. In the same document, the ETM is given in ranges. Both high and low limits were taken for each phase.
3. **DuPont Pioneer** – Product "phase" data was given in a company pipeline document. ETM is given for some products, and for those where it was not, ETM is estimated from the other company phase data.
4. **Syngenta** – Product "phase" data and ETM was given in a company pipeline document. This included information about the percentage completed within each phase. The ETM given was a single year, so a (+/-) 1 year buffer was used. The percentage developed, which was provided by the company, was taken into account when classifying into the "OECD phases", which are discussed later.

Given the difficulties in comparing the different research phases of each company, an "OECD classification for use in agriculture projections" was developed to facilitate comparison.

Once the products were classified, they were placed into Table 10.

Table 38. **Description of OECD agricultural biotechnology development phases**

OECD Phase	Estimated Time to Market	Description
Discovery	8 to 12 years	Key Activities: High-throughput screening; Model crop testing Research Focus: grain yield, environmental stress tolerance, pest control, herbicide tolerance, disease resistance, lipid enhancements (increased oil, improved fatty-acid balance), protein enhancements (improved amino-acid balance), carbohydrate enhancements, & bioactive compounds.
I	6 to 8 years	Key Activities: Gene optimization; Crop transformation
II	3 to 6 years	Key Activities: Trait development; Pre-regulatory data; Large-scale transformation
III	1 to 3 years	Key Activities: Trait integration; Fixed testing; Regulatory data generation, Regulatory submission; Seed bulk-up; Pre-marketing

Source: Adapted from the "Monsanto 2007 R&D Pipeline at a glance", and their phases III & IV were combined.

Annex D

Crop production data

Table 39. **Number of hectares planted and % change (1995-2005) for world and major region, by crop (in thousands of hectares)**

	World		OECD		European Union[2]		North America[3]		South America[4]	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Alfalfa	15 119	-4.65%	11 724	-4.06%	2 099	-13.62%	9 421	-3.71%	1 801	0.85%
Cottonseed	33 026	-6.11%	7 052	-14.43%	451	-7.08%	5 688	-14.29%	818	-52.86%
Flaxseed	2 510	-19.00%	781	-7.76%	187	-33.01%	589	0.84%	14	-82.72%
Maize	144 990	4.05%	45 000	4.58%	8 924	3.80%	38 102	3.12%	17 486	-5.83%
Papaya	381	28.47%	20	31.47%	0	0.00%	20	30.97%	68	9.60%
Plums[5]	2 343	31.64%	190	-33.97%	211	-27.09%	59	-13.12%	36	1.91%
Potatoes	18 816	2.17%	2 810	-28.77%	2 254	-32.97%	657	-7.26%	848	-12.64%
Rapeseed[6]	28 261	7.70%	11 526	13.35%	4 901	22.69%	5 962	2.32%	64	91.39%
Rice, paddy	153 860	0.41%	4 641	-9.58%	413	1.21%	1 419	-0.28%	6 111	0.52%
Soybeans	92 113	35.97%	30 657	9.53%	418	-8.77%	30 094	9.93%	40 238	91.87%
Squash[7]	1 507	25.54%	149	-6.58%	41	-20.75%	50	-24.98%	56	-5.53%
Sugar beet	5 456	-25.55%	3 031	-20.66%	2 159	-26.31%	515	-10.01%	32	-38.02%
Tobacco	3 909	-19.67%	514	-35.82%	186	-13.76%	145	-51.53%	602	33.01%
Tomatoes	4 620	34.13%	871	7.50%	343	-5.72%	294	-7.60%	142	-8.34%
Wheat	220 394	-0.30%	75 128	0.14%	26 196	-2.88%	30 811	-7.79%	14 076	51.32%
Total GM Target	727 304	N/A	194 093	N/A	48 784	N/A	123 825	N/A	82 392	N/A
Other crops[8]	502 124	3.00%	85 233	-4.75%	42 996	-7.98%	26 382	-3.26%	33 938	2.49%

Source: Authors, based on FAO (2009).

Notes: See notes at end of Annex D.

Table 40. **Number of tonnes produced and % change (1995-2005) for world and major region, by crop (in thousands of tonnes)**

	World		OECD		European Union[2]		North America[3]		South America[4]	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Alfalfa	454 635	-7.45%	372 842	-6.77%	66 790	-18.24%	296 106	-5.47%	47 839	1.31%
Cottonseed	39 133	6.63%	10 766	3.86%	871	3.24%	7 927	6.77%	230	-42.17%
Flaxseed	2 878	5.28%	1 784	11.96%	194	-34.04%	1 582	22.82%	47	-72.08%
Maize	709 366	22.94%	364 497	23.80%	62 685	3.65%	309 784	26.27%	65 150	26.67%
Papaya	6 614	35.82%	730	51.73%	0	0.00%	724	52.09%	2 212	44.80%
Plums[5]	9 252	32.23%	1 748	-19.24%	1 548	5.09%	491	-23.10%	426	78.37%
Potatoes	316 166	8.08%	88 769	-17.90%	59 488	-24.87%	25 112	2.06%	13 012	-1.93%
Rapeseed[6]	49 477	23.62%	271 59	30.82%	15 656	28.34%	10 596	30.64%	129	111.59%
Rice, paddy	628 198	8.16%	31 709	-6.57%	2 687	10.12%	10 416	16.06%	24 241	23.25%
Soybeans	212 577	48.62%	88 049	12.15%	1 188	-26.08%	86 688	13.11%	95 766	129.26%
Squash[7]	20 212	28.61%	3 319	1.21%	1 206	6.89%	1 011	-17.33%	699	-13.03%
Sugar beet	250 884	-9.83%	171 956	-11.31%	129 182	-15.32%	25 696	-0.21%	2 823	-22.57%
Tobacco	6 572	-17.54%	886	-38.92%	417	-6.47%	349	-51.05%	1 136	41.17%
Tomatoes	122 880	36.74%	43 297	14.90%	17 967	16.83%	14 683	-0.40%	6 367	14.78%
Wheat	622 561	2.44%	255 287	3.36%	133 330	-0.89%	87 070	-3.37%	20 470	29.51%
Total GM Target	3 451 405	N/A	1 462 798	N/A	493 206	N/A	878 236	N/A	280 546	N/A
Other crops[8]	3 583 342	18.61%	544 231	-0.21%	217 521	-4.48%	203 791	0.28%	673 543	22.36%

Source: Authors, based on FAO (2009).

Notes: See notes at end of Annex D.

Table 41. **Yield and % change (1995-2005) for major regions, by crop (in tonnes/ha)**

	European Union[2]		North America[3]		South America[4]	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Alfalfa	32	-5.28%	31	-1.75%	27	0.47%
Cottonseed	2	10.78%	1	23.00%	0	8.15%
Flaxseed	1	-1.05%	3	24.81%	3	135.48%
Maize	7	0.72%	8	22.67%	4	34.41%
Papaya	0	0.00%	37	15.24%	33	32.22%
Plums5	7	43.37%	8	-12.02%	12	73.38%
Potatoes	26	12.16%	38	10.18%	15	12.30%
Rapeseed[6]	3	3.79%	2	26.99%	2	9.26%
Rice, paddy	6	9.20%	7	16.41%	4	21.70%
Soybeans	3	-18.37%	3	3.25%	2	20.37%
Squash[7]	29	40.38%	20	10.01%	13	-7.82%
Sugar beet	60	15.02%	50	10.83%	89	25.17%
Tobacco	2	8.42%	2	2.01%	2	6.19%
Tomatoes	52	23.84%	50	8.17%	45	25.22%
Wheat	5	1.83%	3	3.96%	1	-8.71%
Total GM Target	N/A	N/A	N/A	N/A	N/A	N/A
Other crops[8]	N/A	N/A	N/A	N/A	N/A	N/A

Source: Authors, based on FAO (2009).

Notes: See notes at end of Annex D.

Table 42. **2003 production price for world and major region, by crop (in USD millions, 2003 production price)**

Commodity	European Union[2]	North America[3]	South America[4]
Alfalfa	N/A	N/A	N/A
Cottonseed	560.22	3 316.42	362.82
Flaxseed	47.75	238.07	4.07
Maize	7 911.83	28 749.20	5 458.51
Papaya	0.00	254.66	2 009.74
Plums[5]	946.41	278.58	86.88
Potatoes	10 964.77	4 152.12	2 045.94
Rapeseed[6]	2 931.58	1 915.35	15.45
Rice, paddy	762.29	1 493.18	2 522.59
Soybeans	192.24	18 314.96	14 098.65
Squash[7]	678.97	190.71	131.20
Sugar beet	5 675.80	1 139.40	100.82
Tobacco	N/A	N/A	N/A
Tomatoes	9 244.44	2 300.36	1 361.96
Wheat	14 624.39	10 538.49	2 951.05
Total GM Target	N/A	N/A	N/A
Other crops[8]	N/A	N/A	N/A

Source: Authors, based on FAO (2009).

Notes apply to Tables 39 to 42:

1. To avoid any anomalies due to environmental conditions etc. the percent change was determined from the average quantity from the periods 1995 to 1997 and 2003 to 2005.
2. The European Union includes Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, & the United Kingdom
3. North America includes Canada, Mexico, and the USA
4. South America includes Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, & Venezuela
5. Plums include sloes.
6. Rapeseed includes mustard seed.
7. Squash includes pumpkins & gourds.
8. Other crops include nuts, tree fruits (except plums), vine fruits (including grapes), vegetables, other root crops (cassava, sweet potatoes, yams), other cereals (barely, oats, sorghum, millet), legumes, spices, plantains, etc. See Annex E for a complete list.

Annex E

Crops included in world acreage total

Almonds; anise, badian, fennel, corian; apples; apricots; artichokes; asparagus; avocados; bananas; barley; beans (including string b.), green; beans (including cow peas), dry; broad beans, horse beans, dry; cabbages and other brassicas; carrots and turnips; cashew nuts; cassava (fresh and dried); cauliflowers and broccoli; cereals, nec; cherries (including sour cherries); chestnuts; chick peas; chillies and peppers, dry; chillies and peppers, green; cinnamon (canella); citrus fruit, nec; cloves; cocoa beans; coconuts (including copra); coffee, green; cranberries, blueberries; cucumbers and gherkins; currants and gooseberries; dates; eggplants (aubergines); figs; fruit, nec (including persimm.); garlic; ginger; grapefruit and pomelo; grapes; groundnuts; guavas, mangoes, mangosteens; hazelnuts; kiwi fruit; leeks, other alliaceous vegeta; legum. veg., nec; lemons and limes; lentils; lettuce and chicory; millet; mushrooms and truffles; natural honey; nutmeg, mace and cardamoms; nuts, nec; oats; oilseeds, nec; olives; onions (including shallots); oranges; other melons (including cantaloupes); palm nuts-kernels (nut equiv.); peaches and nectarines; pears and quinces; peas, dry; peas, green; pepper (piper spp.); pineapples; pistachios; plantains; pulses, nec; raspberries and other berries; rye; sesame seed; sorghum; spices, nec; spinach; starchy roots, nec; strawberries; sugar cane and sugar crops, nec; sunflower seed; sweet potatoes; tangerines, mandarins, clem.; tea and maté; vanilla; vegetables, nec (including okra); walnuts; watermelons; yams.

Annex F

Animal production data

Table 43. **Land animal production data, by region (in thousand tonnes)**

	European Union		North America		South America	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Animal Fats	1 513	-9.09%	3 373	6.01%	1 026	10.27%
Bird Eggs	6 505	-2.46%	8 005	27.69%	3 089	14.10%
Bovine	8 649	-19.07%	14 817	2.62%	13 509	7.65%
Dairy	150 491	-2.44%	98 397	11.80%	48 400	16.90%
Fibres[2]	195	-9.77%	23	-28.81%	158	-29.40%
Natural Honey	199	18.60%	166	-2.60%	133	21.68%
Other[3]	3 093	-9.44%	2 160	2.58%	2 673	25.59%
Pig	21 253	1.80%	13 113	24.04%	4 426	20.84%
Poultry[4]	11 762	11.24%	22 144	27.26%	12 989	70.93%
Sheep and goat	1 204	-11.48%	196	-12.84%	338	-5.98%

Source: Authors, based on FAO (2009).

Notes: 1. To avoid any anomalies due to unusual environmental conditions etc., the percent change was determined from the average quantity of the periods 1995 to 1997 and 2003 to 2005.
2. Only includes fibres of animal origin.
3. Other includes edible offal, equine meat, rabbit meat, and meat not included elsewhere.
4. Poultry includes chicken meat, turkey meat, and duck, goose, or guinea fowl.

Annex G

Marine production data

Table 44. **Marine animal production data, by region (in thousand tonnes)**

	European Union		North America		South America	
Commodity	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)	Total (2005)	% change[1] (1995-2005)
Fish[2]	2 035	-37.66%	2 893	-1.96%	1 733	-18.38%
Molluscs[3]	1 106	4.46%	1 091	26.20%	302	57.13%
Other[4]	460	-19.92%	1 100	0.23%	1 173	15.97%

Source: Authors, based on FAO (2009).

Notes: 1. To avoid any anomalies due to unusual environmental conditions etc., the percent change was determined from the average quantity of the periods 1995 to 1997 and 2003 to 2005.
2. Fish includes freshwater and diadromous fish; and demersal, pelagic, and other marine fish.
3. Molluscs exclude cephalopods.
4. Other includes aquatic plants, mammals, and other animals; cephalopods, and crustaceans.

Annex H

Developing countries, by region

Asia: Afghanistan, Armenia, Azerbaijan, Bangladesh, China, Georgia, India, Indonesia, Iran, Korea Rep, Malaysia, Mongolia, Myanmar, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Thailand and Vietnam.

Central America: Bahamas, Barbados, Belize, Costa Rica, Cuba, Grenada, Guadeloupe, Guatemala, Honduras, Jamaica, Mexico, Netherlands Antilles and Puerto Rico.

Eastern Europe: Albania, Bosnia Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Lithuania, Macedonia, Moldova Rep, Poland, Romania, Serbia and Montenegro, Slovakia and Ukraine

Middle East/North Africa: Algeria, Egypt, Iraq, Jordan, Kuwait, Morocco, Syria, Tunisia and United Arab Emirates

South America: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Uruguay and Venezuela.

Sub-Saharan Africa: Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Congo, Côte d'Ivoire, Ethiopia, Gabon, Ghana, Kenya, Madagascar, Malawi, Mali, Mauritius, Namibia, Niger, Nigeria, Rwanda, Senegal, South Africa, Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia and Zimbabwe

Annex I

Non-GM biotechnologies in FAO Bio-DeC

Table 45. **Non-GM crop biotechnologies in the FAO Bio-DeC database**

Technology	Type of Technology	Number	Percentage
AFLP	Plant Breeding	71	4.23%
Anther culture	Plant Breeding	78	4.65%
Bioprospecting	Other	1	0.06%
Bios-pesticide	Biopesticides/biofertilizers	11	0.66%
Design-delivery biocontrol agents	Biopesticides/biofertilizers	33	1.97%
Design-delivery of biofertilizers	Biopesticides/biofertilizers	35	2.09%
ELISA	Diagnostic	69	4.11%
Embryo rescue	Plant Breeding	37	2.21%
Fermentation, food processing	Fermentation, food process.	35	2.09%
Gene cloning	Plant Breeding	4	0.24%
Gene discovery	Plant Breeding	1	0.06%
Genetic engineering	Plant Breeding	2	0.12%
Genetic Transformation	Plant Breeding	11	0.66%
Genome sequencing	Plant Breeding	9	0.54%
In vitro germplasm conservation & exchange	Other	43	2.56%
In vitro regeneration	Propagation, other	35	2.09%
Isozymes	Plant Breeding	8	0.48%
MAS – Marker Assisted Selection	Plant Breeding	19	1.13%
Micropropagation	Propagation, micro	485	28.90%
Microsatellite markers	Plant Breeding	78	4.65%
Monoclonal antibodies	Diagnostic	9	0.54%
Nucleic acid probes	Plant Breeding	1	0.06%
Other – cell biology	Other	94	5.60%
Other or not specified	Other	185	11.03%
PCR	Plant Breeding	51	3.04%
Protoplast fusion and culture	Plant Breeding	23	1.37%
RAPD	Plant Breeding	169	10.07%
RFLP	Plant Breeding	64	3.81%
Somaclonal variation	Plant Breeding	12	0.72%
Somatic hybridisation	Plant Breeding	5	0.30%
TOTAL		1 678	100.00%

Source: Authors, based on FAO (n.d.).

Table 46. **Non-GM animal biotechnologies in the FAO Bio-DeC database**

Technology	Type of Technology	Number	Percentage
AFLP	Animal Breeding	2	1.3%
Artificial insemination	Animal Breeding	3	2.0%
Biochemical markers	Animal Breeding	4	2.7%
Blood protein markers	Animal Breeding	4	2.7%
Cell culture	Other	1	0.7%
Cryopreservation	Other	5	3.4%
Cytogenetics Techniques	Other	4	2.7%
DNA markers – unspecified	Animal Breeding	6	4.0%
DNA probes	Diagnostic	5	3.4%
DNA sequencing	Animal Breeding	3	2.0%
ELISA	Diagnostic	3	2.0%
Embryo transfer	Animal Breeding	7	4.7%
Enzymes	Other	1	0.7%
Gene cloning and characterisation	Animal Breeding	1	0.7%
Gene expression	Animal Breeding	2	1.3%
Genome sequencing	Animal Breeding	3	2.0%
Genotyping	Animal Breeding	6	4.0%
Hormones	Other	1	0.7%
in vitro fertilisation	Animal Breeding	3	2.0%
Isozymes	Animal Breeding	3	2.0%
Marker assisted breeding	Animal Breeding	1	0.7%
Microsatellites	Animal Breeding	10	6.7%
Mitochondrial DNA	Animal Breeding	3	2.0%
Other or unspecified	Other	3	2.0%
PCR	Animal Breeding	37	24.8%
PCR – RFLP	Animal Breeding	5	3.4%
RAPD	Animal Breeding	1	0.7%
RFLP	Animal Breeding	1	0.7%
Ribosomal DNA ITS	Animal Breeding	1	0.7%
RT – PCR	Animal Breeding	8	5.4%
RT – PCR & Sequencing	Animal Breeding	4	2.7%
Vaccine production	Vaccine	8	5.4%
Grand Total		149	100.0%

Source: Authors, based on FAO (n.d.).

Table 47. **Non-GM forestry biotechnologies in the FAO Bio-DeC database**

Technology	Type of Technology	Number	Percentage
AFLP	Plant Breeding	18	2.22%
Agrobacterium mediated transformation	Plant Breeding	12	1.48%
Anther and pollen culture	Plant Breeding	2	0.25%
Biofertilizers	Biopesticides/biofertilizers	41	5.06%
Biopesticides	Biopesticides/biofertilizers	1	0.12%
Chloroplast DNA markers	Plant Breeding	11	1.36%
DNA based	Plant Breeding	2	0.25%
DNA chip	Diagnostic	14	1.73%
ELISA	Diagnostic	1	0.12%
Embryo rescue	Plant Breeding	4	0.49%
Expressed Sequence Tags (EST)	Plant Breeding	1	0.12%
Gene expression	Plant Breeding	12	1.48%
Genetic markers techniques	Plant Breeding	4	0.49%
Genetic variation	Plant Breeding	7	0.86%
In vitro germplasm cons. and cryopreservation	Other	9	1.11%
In vitro regeneration	Propagation, other	3	0.37%
Isozymes	Plant Breeding	52	6.42%
MAS – Marker Assisted Selection	Plant Breeding	17	2.10%
Micropropagation	Propagation, micro	413	50.99%
Other or not specified	Other	61	7.53%
PCR	Plant Breeding	2	0.25%
Polyploid induction	Plant Breeding	3	0.37%
Protoplast culture	Plant Breeding	2	0.25%
RAPD	Plant Breeding	79	9.75%
rDNA – ribosomal DNA sequences	Plant Breeding	4	0.49%
RFLP	Plant Breeding	9	1.11%
Sequencing	Plant Breeding	1	0.12%
Microsatellites or SSRs	Plant Breeding	20	2.47%
Transformation	Plant Breeding	5	0.62%
TOTAL		810	100.00%

Source: Authors, based on FAO (n.d.).

Human Health Biotechnologies to 2015

Anthony Arundel

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*This article provides an overview of the current use of biotechnology to produce human health products and short-term estimates of the number and types of these products that are likely to reach the market by 2015. Relevant health products include biopharmaceuticals, experimental therapies (*e.g. *cell/tissue engineering and gene therapy), small molecule therapeutics, diagnostics, bioinformatics (including DNA sequencing and pharmacogenetics), functional food and nutraceuticals, and medical devices. The analysis of current use is based on regulatory approval data and the current literature and includes a comparison of the additional therapeutic value of biopharmaceuticals compared to small molecule pharmaceuticals. The short-term estimates of the number and types of products that are likely to reach the market by 2015 are based, where possible, on an analysis of quantitative data on clinical trials. For several other products, including functional foods and nutraceuticals, it is not possible to make short-term estimates due to a lack of reliable data.*

While the biopharmaceutical share of all pharmaceuticals reaching the market is expected to remain very close to historical levels, biotechnology is expected to be used in the discovery, development, manufacturing, and/or prescribing of nearly all *new drugs by 2015. In addition, the use of biotech based diagnostics (especially genetic testing), bioinformatics, and pharmacogenetics is likely to increase. In some cases, these technologies will be used to improve the safety and efficacy of clinical trials, to personalise prescribing practises, and to reduce adverse drug reactions.*

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Abbreviations

ADR	Adverse drug reaction
AIDS	Acquired immune deficiency syndrome
DBF	Dedicated biotechnology firm
DDBJ	DNA Data Bank of Japan
DNA	Deoxyribonucleic acid
EMBL	European Molecular Biology Laboratory
EMEA	European Agency for the Evaluation of Medicinal Products
EPO	European Patent Office
EU	European Union
FDA	Food and Drugs Administration (United States)
FFN	Functional Food and Nutraceuticals
GDP	Gross domestic product
GM	Genetic Modification or Genetically Modified
HAS	La Haute Autorité de santé (France)
HIV	Human Immunodeficiency Virus
ICH	The International Conference on Harmonisation
IMF	International Monetary Fund
IVD	*in-vitro* diagnostics
JPO	Japan Patent Office
mAbs	Monoclonal antibodies
NME	New molecular entity
OECD	Organisation for Economic Cooperation and Development
PCR	Polymerase chain reaction
PCT	Patent Cooperation Treaty
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interference
SFDA	State Food and Drug Administration (China)
SM	Small Molecule
UNU-MERIT	United Nations University – Merit
USPTO	United States Patent and Trademark Office

Executive summary

This article provides short-term estimates of the number and types of human health products based on biotechnology that are likely to reach the market by 2012-2015. This includes biopharmaceuticals, experimental therapies (*e.g.* cell/tissue engineering and gene therapy), small molecule therapeutics, diagnostics, bioinformatics (including DNA sequencing and pharmacogenetics), functional food and nutraceuticals, and medical devices.

Data are obtained from publicly available sources such as the Organisation for Economic Cooperation and Development (OECD), the United States Food and Drugs Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMEA), the published literature, as well as proprietary data sources such as Pharmaprojects and Pharmapredict.

The direct economic effects of the health applications of biotechnology occur in the pharmaceutical manufacturing sector and from biotechnology firms active in the R&D services sector. Secondary effects occur in the health care services sector, for example if new therapies based on biotechnology increase or decrease total health care costs.

This article does not estimate the biotechnology share of value added or employment in the pharmaceutical manufacturing sector. However, the share of pharmaceuticals in gross domestic product (GDP) and employment gives an indication of the maximum possible contribution of biotechnology to this sector. This would be reached if biotechnology contributed to 100% of all new therapeutics, vaccines, and diagnostics. In this case, the direct economic impact of health biotechnology would approach the current share of pharmaceuticals in GDP of 1.24% in the United States and 0.66% of GDP in the European Union, although these percentages could continue to decline, as they have over the past decade. Biotechnology is unlikely to reach this maximum share of pharmaceutical GDP by 2015, but its increasing use in the development of small molecule therapeutics suggests that close to all value added in the pharmaceutical sector will be partly dependent on biotechnological knowledge by 2030. The main area that is unlikely to be affected is the manufacture of small molecule generics developed before 2000.

The biopharmaceutical sector is dominated by 45 American firms that account for 65% of the 155 biopharmaceuticals that have received market approval, anywhere in the world. Almost all of the remaining biopharmaceuticals have been developed by firms based in other OECD countries, with the exception of seven biopharmaceuticals: three developed in China, three in Cuba, and one in Israel.

The share of biopharmaceuticals out of all pharmaceuticals increased rapidly between 1989 and 1998 and then remained relatively stable at between 12% and 14% between 1999 and 2007, with the exception of an increase to 16% in 2003.

Biopharmaceuticals offer a greater therapeutic advance, in comparison to existing treatments, than small molecule pharmaceuticals. An analysis of therapeutic evaluations

by France's Haute Autorité de Santé (HAS) for 53 biopharmaceuticals and 1 476 small molecule drugs shows that 47.6% of biopharmaceuticals provide a "moderate" therapeutic advance or better over existing treatments. In comparison, only 12.4% of all other drugs provide a moderate therapeutic advance or better. An identical analysis of 68 evaluations of biopharmaceuticals 1 915 evaluations of other types of pharmaceuticals from the journal *Prescrire* produced comparable results.

The factors that support the development of therapeutically valuable biopharmaceuticals are of relevance to both policy and the design of future business models. An important question is who develops therapeutically valuable drugs: small dedicated biotechnology firms (DBFs) or large established pharmaceutical firms? The data from HAS and *Prescrire* were combined with data on the firm that developed each biopharmaceutical to answer this question. Using the HAS data, 65.4% of biopharmaceuticals developed by DBFs received an evaluation of a "moderate" advance or better, compared to only 28.6% of the biopharmaceuticals developed by large firms. The pattern is similar using the Prescrire data, with over double the share of biopharmaceuticals developed by DBFs receiving an evaluation of "some" advance or higher compared to large established pharmaceutical firms (38.7% versus 14.3%). The better performance of DBFs could be due to closer linkages with university researchers that discover new modes of action, or their ability to obtain venture capital financing could allow them to work on riskier projects, rather than concentrating on "me-too" drugs.

Forecasting for health therapies

The proprietary databases Pharmaprojects and Pharmapredict were used to estimate the number of biopharmaceuticals that are expected to obtain marketing approval by 2015. The databases cover preclinical studies, clinical trials, and pre-registrations for most countries in the world. Pharmapredict estimates the probability of compounds in each development stage to reach market registration. These success rates are based on historical data for similar compounds. At the time of writing, success rates were not available for new product categories where only a few products had obtained market approval by the end of 2007.

In total, 25 countries have one or more bio-new molecular entities (bio-NMEs) in clinical trials: seven non-OECD countries, the United States, and 17 other OECD countries. Of interest, there are fewer Phase I than Phase II trials, suggesting a dip in the future supply of biopharmaceuticals. This may not be long lasting, since there are a large number of preclinical trials underway.

The United States' share of biopharmaceuticals is estimated to decline slightly from approximately 60% of market approvals for new biopharmaceuticals between 2000 and 2007 to 54% between 2008 and 2015.

The major disease targets for the clinical trials consist of cancer (258 trials), infections (135 trials), cardiovascular diseases (57 trials), arthritis (28 trials), diabetes (18 trials) and asthma (11 trials). Monoclonal antibodies (mAbs) account for 25.1% of the total clinical trials, followed by recombinant vaccines (18.6%) and recombinant therapeutics (15.6%). The remaining four types account for 40.7% of the total, but few, if any, of these types of bio-NMEs have received market approval, with most of the compounds in Phase II (57%) or Phase I (28%) trials. This shows that there is a very strong biotechnology pipeline for these unproven or "experimental" therapies.

Research on experimental therapies is largely undertaken by small DBFs, with few large established pharmaceutical firms active in this area. One possible explanation is

that access to ample venture capital or other "high risk" capital could explain this pattern. However, this may not be the main cause, as there was no relationship between the availability of venture capital by country and the national share of clinical trials of NMEs due to experimental therapies.

Of 648 biotechnology compounds in clinical trials, there was sufficient data for 399 (61.6% of total) to estimate the number of expected new registrations between 2008 and 2018. The estimate is that roughly 13 biopharmaceuticals will be registered per year from 2008-2015. This is higher than the average of 8 biopharmaceuticals per year between 2000 and 2007 inclusive, but within the historical range of the number of bio-NMEs approved annually. For example, twelve bio-NMEs were registered in 1998, 2001, and 2006.

This does not translate into a significantly increased percentage of biopharmaceuticals as a share of all pharmaceuticals. Between 2000 and 2007, biopharmaceuticals accounted for slightly more than 12% of all new pharmaceutical registrations. An analysis of current clinical trials shows that biotechnology's share of all drugs to reach the market between 2008 and 2015 will increase to around 18% until 2012, but then will probably decrease to approximately 15%. These results provide no evidence for a large surge in biotechnology drugs, or in the share of biotechnology drugs out of all drugs in the coming 5 to 10 years.

Although the share of biopharmaceuticals will not substantially increase in the foreseeable future, the real variable of interest is the effect of future biopharmaceuticals on public health. The evaluation of therapeutic value shows that biopharmaceuticals offer greater therapeutic value than other pharmaceuticals. The large number of experimental biopharmaceuticals, offering new modes of action, also suggests that the future stream of biopharmaceuticals should provide substantial therapeutic advantages over existing therapies.

Experimental therapies include cell and tissue engineering, stem cells, gene therapies, antisense (ribonucleic acid interference) RNAi, nanobiotechnology (drug delivery) and synthetic biology. Several new tissue engineering products are expected to reach the market by 2015, but only a few other experimental therapies are likely reach the market by this date.

By 2015 the large majority of small molecule drugs in development are likely to partly depend on the use of biotechnology, for instance in the discovery phase (particularly for target identification), to improve the efficiency of clinical trials (application of pharmacogenetics for safety), or to improve prescribing practices. At some point in the near future, the current division between biotechnology firms and biotechnology drugs, and other firms and other types of drugs, is likely to become meaningless, with biotechnology playing a significant role in the development of all drugs.

Forecasting for diagnostics and bioinformatics

The importance of biotechnology based diagnostic tests is likely to continue to increase to 2015. This is particularly the case for *in-vitro* diagnostics which are likely to see much stronger product development to 2015 than *in-vivo* diagnostics. The number of diagnostic tests produced could be strongly influenced by the increased use of pharmacogenetics and preventive medicine.

The continued creation, population, and maintenance of complex health databases will continue to be an important application of bioinformatics to 2015. The variety of information stored in large genetic databases and the number of individuals included in these databases will expand as the price of genome sequencing continues to fall. These trends will support an increase in pharmacogenetic studies and the identification of new gene-drug

links, as well as an increase in the number of drugs for which prescribing practice will depend on genetic tests to identify clinical response or the probability of an adverse drug reaction (ADR). However, widespread use of pharmacogenetics to identify respondent and non respondent subgroups in clinical trials is unlikely before 2015.

Functional foods and nutraceuticals

Functional foods and nutraceuticals (FFN) are products, meant for consumption, that provide physiological benefit or provide protection against chronic disease. In theory, modern biotechnologies could be applied to the production of FFN, but to date, few biotech based FFN applications are on the market. Even by 2015, biotechnology is unlikely to play a large role in the FFN sector.

Conclusions

The number of biopharmaceuticals expected to reach the market to 2015 is somewhat higher than in the past and biotechnology will play a role (at some point) in the development and use of nearly *all* large and small molecule therapeutics by 2015. While these developments will contribute to improved health outcomes, the promise of biotechnology in health is much greater than simply adding new drugs to a doctor's existing arsenal.

Experimental therapies of the kind described in this article and a shift to personalised medicine, through the application of pharmacogenetics, have the potential to drastically improve health by preventing disease before its onset and, in some cases, curing rather than treating debilitating illnesses. Achieving the full potential of these technologies will require appropriate business models and policies.

Introduction

The future of biotechnology in health has been the subject of intensive speculation since the first biopharmaceutical obtained marketing approval in 1982,[1] and more recently following the sequencing of the human genome in 2003. While there is little doubt that biotechnology has contributed to health care by providing new and effective therapeutic treatments, the full potential of biotechnology in health is still far off. Many technological and social questions remain to be solved before biotechnology can fulfil its promise to improve health outcomes, provide cures instead of long-term treatment, reduce unwanted side effects from treatment, and increase the efficiency of R&D.

This article identifies the current uses of biotechnology in health care and the types of products that could reach the market by 2015. The focus is on OECD countries, which have dominated health care research to date, but biotechnological research in developing countries has also produced new therapies. This introduction provides a brief overview of the economic context for the use of biotechnology in health, describes the data sources used in this article, and evaluates the potential economic contribution of health biotechnology. The other chapters examine specific applications of biotechnological knowledge to health.

The use of biotechnology in health

The health sector is undergoing a long-term increase in demand, driven by increasing incomes in developing countries and demographic change in developed countries. At the same time, the efficiency of pharmaceutical pipelines has been declining, in terms of the number of new drugs (new molecular entities or NMEs) developed per unit of research expenditures. To date, the use of biotechnology in health research may have contributed to the decline in research efficiency by opening up new modes of action that are poorly understood, requiring greater research investments (Hopkins *et al*., 2007). Future applications could be even more expensive, requiring a convergence in biotechnological advances in a range of disciplines, including gene sequencing, personalised medicine, bioinformatics, protein and cell metabolism, and pharmacogenetics.

The efficiency of pharmaceutical R&D has been declining for some time. In November 2006, the United States' Government Accountability Office (US GAO) reported that, "the overall number of [new drug applications] – and new molecular entities (NME) in particular – approved annually has generally been declining since 1996", although longer-term trends show that the number of new applications increased slightly after 1996 compared to the previous decade (Cockburn, 2006). Yet over the same period, R&D expenditures nearly doubled. In addition, between 1993 and 2004, the therapeutic advance offered by new drugs was generally low, with 60% of new drug applications submitted to the United States' FDA in the lowest class for therapeutic advance, while only 12% received the highest rating.[2]

These stark statistics showing a decline in both therapeutic value and the efficiency of R&D pose a serious challenge for both public health and for the pharmaceutical industry.

Between now and 2030, health care expenditures as a percentage of GDP, in both OECD and non-OECD countries, are likely to increase significantly. After rapid growth in the early 1970s, health care expenditure levelled through the 1980s. However in the early 1990s, the cost of health care began to rise steeply again and has continued unabated. New health technologies have played a major role in this increase. An OECD working paper (2006a) noted that, "given that 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."

Furthermore, technology is expected to drive health care costs into the future. OECD projections of health care expenditure to 2050 separated total health spending into health care expenditure and long-term care. The 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 indeed are the most important driver of the increase in [future, non-long-term] health-care expenditure."

In addition, rising income levels around the globe are likely to exacerbate spending concerns. "Technical progress can be cost-saving and reduce the relative price of health products and services, but its impact on expenditure will depend on the price elasticity of the demand for health care. If it is high, a fall in prices will induce a more than proportionate rise in demand, increasing expenditures. Even if prices do not fall, new technologies may increase demand by increasing the variety and quality of products."

The trend toward constantly increasing costs as a share of GDP has led many OECD Governments to actively search for methods to contain costs, including limiting the cost of prescription drugs. This could lead governments (through their substantial investments in medical research) and firms to search for methods to improve the efficiency of pharmaceutical research. Many experts believe that recent developments in biotechnology could help to reduce drug development costs. For example, knowledge of effective biomarkers could lead to quicker drug identification, while the use of pharmacogenetics to identify respondent and non-respondent patients could reduce clinical trial costs and drug failure rates.

Alternatively, society may be willing to pay for higher health care costs *if* improvements in health outcomes are commensurate with costs. This would require a significant increase in the therapeutic advance offered by new drugs. Biotechnology, by opening up new modes of action for drug treatment and by improving prescribing practices, could help to improve the efficacy of health treatments.

Estimating the use of biotechnology for health applications

Health biotechnology is defined here as the use of knowledge on cell functions and genetics at the molecular level, including an understanding of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins and enzymes, to develop new therapeutics and diagnostics. Researchers also use bioinformatics to analyse genomes, proteins, and population health databases (NZ MoRST, 2005).

A brief description of the two main biotechnologies in health is as follows:

- **Biotechnology therapies:** Compounds and treatments that are produced using modern biotechnology techniques. There are three main categories:
  - **Biopharmaceuticals**: Large molecule therapeutic compounds, usually proteins with molecular weights in the tens of thousands of Daltons, which are produced

by using monoclonal antibodies (mAbs) or recombinant technology. In the latter case, a gene that codes for the target molecule is inserted into the DNA of a host species, which in turn produces the molecule. The host species can be a micro-organism, plant, or animal. Recombinant technology can produce proteins, amino acid chains, mAbs, vaccines, enzymes, and hormones. Some biopharmaceuticals can be produced without using recombinant technology, such as using pigs to produce porcine insulin. These "biologics" are not covered in this paper.

- **Experimental treatments**: This includes a disparate group of biotechnologies that currently have relatively small markets compared to biopharmaceuticals: tissue engineering, stem cell research, and gene therapy. Tissue engineering is based on knowledge about the growth of cells and includes bone and skin scaffolds and potentially the engineering of other organ complexes. Stem cell research could lead to the production of entire organs. Gene therapy involves the insertion of genes into living cells.
- **Small molecule therapeutics**: Small molecules are usually produced through chemical synthesis. Biotechnology can be used to identify new therapeutic targets or to improve clinical trials or prescribing practice. In some cases recombinant technology is used to manufacture small molecule precursors or chiral molecules.

• **Bioinformatics and diagnostics**:[3] Bioinformatics cover the manipulation and analysis of large datasets of genetic and health information. This article includes several technological fields such as pharmacogenetics and gene sequencing under bioinformatics. The analysis of genetic data, combined with large public databases on health outcomes, prescriptions and treatments could have far reaching implications for health care and delivery systems. To date, most research has used either pharmacogenetic data or large public health databases.[4]

Many diagnostics are based on compounds produced through biotechnology, such as mAbs, or are directed towards identifying genes or alleles associated with disease. A developing area is the identification of protein biomarkers. Diagnostics can be either *in-vivo* (*i.e.* invasive), in which case they are closely regulated, as with therapeutics, or *in-vitro* (*i.e.* non-invasive) in which case the regulatory requirements are considerably less demanding.

In addition to the above categories, there are several miscellaneous areas where biotechnology could have applications for health. One is functional foods and nutraceuticals (FFN). These are only part of biotechnology if the source material, such as vitamin enriched cereals or foods containing phytosterol or stanols, are produced from plants or micro-organisms that have been altered using biotechnology. Another area is medical devices. Several medical device technologies, such as tissue engineering and diagnostics, are included above, but there are a few additional areas where biotechnology could have applications.

This article provides brief descriptions of the types of biotechnologies of relevance to health applications, data on biotechnology products that are already on the market, and forecast estimates of the number of new products which might reach the market by 2015. The quality of the forecasts varies substantially by product field, depending on data availability. Table 1 gives available data sources for estimating trends in the use of biotechnologies to 2015. The best coverage is for biopharmaceuticals, with several sources of high quality quantitative data. The poorest coverage is for small molecule therapeutics and bioinformatics.

Table 1. **Data availability for human health biotechnology**

Biotechnologies	Data sources
1. Biotechnology therapies	
• Proven treatments - Biotherapeutics - Biovaccines - mAbs	UNU-MERIT database of biopharmaceuticals Pharmaprojects (clinical trials and approved drugs) Pharmapredict (clinical trials and approved drugs) Regulatory websites (FDA, EMEA) HAS and Prescrire evaluations of therapeutic value Data on the size of the potential target population
• Experimental treatments - Tissue engineering - Stem cells - Gene therapy - Synthetic biology	Literature, FDA/EMEA, clinical trials
• Small molecule therapeutics	German survey Literature
2. Diagnostic tests • *in-vivo*/molecular imaging • *in-vitro*	*In-vivo* & *in-vitro*: Literature *In-vivo*: FDA/EMEA, clinical trials
3. Bioinformatics	Literature, PharmGKB database
4. Miscellaneous	Literature

Maximum potential impact of biotechnology in health

Most of the direct economic effects of the health applications of biotechnology occur in two sectors: the pharmaceutical manufacturing sector and the R&D services sector.[5] The latter includes the activities of biotechnology start-ups that do not have products on the market.[6] Secondary effects can also occur in the health care services sector, for example if new therapies based on biotechnology decrease the time spent in hospitals (potentially decreasing health care costs) or significantly increase life spans (potentially increasing health care costs).

Data on the value added produced by biotechnology firms in the R&D services sector are not available for any country, since it is not possible to separate firms active in biotechnology research from firms active in other research activities, such as ICT or engineering. It is also not possible to identify the biotechnology component of the value added produced by the pharmaceutical manufacturing sector. However, data on the share of pharmaceuticals in GDP gives an indication of the maximum possible contribution of biotechnology to this sector, if biotechnology contributed to the development of all pharmaceutical products, including small molecule therapeutics.

Table 2 gives the share of the pharmaceutical manufacturing sector in total value added for the EU-25 countries, the United States, Canada, Mexico, and Norway. No comparable data are available for the share of pharmaceuticals in global value added or GDP. The pharmaceutical sector accounts for 1.24% of total value added in the United States in 2004. The share of the pharmaceutical sector in the EU-25 is almost half that for the United States, at 0.66% of total value-added. Between 1999 and 2004, the share of the pharmaceutical sector in total value added has been growing in the European Union (EU), by an average of 1.43% per year and declining by an average of 1.89% per year in the United States.[7] In 2004, the value added of the pharmaceutical sector was USD 135.7 billion in the United States and USD 82.9 billion in the EU-25.[8] For comparison, IMS Health (2007) estimated the global sales of pharmaceutical products to be USD 643 billion in 2006, or roughly twice

the value added of the pharmaceutical sector. Approximately 10% of the sales market is from biopharmaceuticals.

The employment share of the pharmaceutical manufacturing sector is highest in the United States at 0.44% of total employment. In both the EU-25 and the United States the pharmaceutical share of total employment has been declining, with an average annual decline of 0.01% in the EU-25 and 0.13% in the United States. The total hours worked in pharmaceutical manufacturing declined between 1999 and 2004 by 4.6% in the EU-25 and by 16.1% in the United States. However, this does not account for gains or losses in employment in the R&D services sector, where many dedicated biotechnology firms are active.

The maximum contribution of biotechnology to the pharmaceutical sector would be reached if biotechnology contributed to 100% of all new therapeutics, vaccines, and diagnostics. In this case, the direct economic impact of health biotechnology would approach 1.24% of GDP in the United States and 0.66% of GDP in the EU-25, although the actual impact in the United States could be smaller, due to the decline of the share of pharmaceuticals over time in the United States' GDP. This also assumes that the share of the pharmaceutical sector does not increase over time, due to population ageing or rapid growth in the pharmaceutical share of total health care expenditures. To put these data in perspective, the maximum potential contribution of biotechnology to the agriculture and related natural resource sectors (ANR) is approximately 2% of GDP within the OECD countries (Arundel and Sawaya, 2009).

The maximum contribution of health biotechnology to employment is more difficult to estimate. The pharmaceutical sector accounts for 1.437 million employees, or 0.31% of total employment in the OECD countries listed in Table 3 (excluding Mexico and Turkey), but there is also extensive biotechnology-related employment in the public research sector

Table 2. **Basic economic indicators for pharmaceutical manufacturing (PM) sector: 2004 or nearest available year**

	GDP (USD billion)	PM share of total value-added (%)	Average annual change in PM share of total value added (%)	Total employment (000)	PM share (%) of total employment	Average annual change in PM share of total employment (%)
EU-25	13 100	0.66	1.43	202 760	0.27	-0.01
United States	11 712	1.24	-1.89	149 512	0.44	-0.13
Australia	645		-	9 207	-	-
Canada	1 089	0.36	-	15 314	0.19	1.15
Iceland	14	-	-	0.159	-	-
Japan	4 911	-	-	66 222	0.18	0.34
Korea	897	-	-	21 557	-	-
Mexico	742	0.73	-	-	-	-
New Zealand	99	-	-	1 443	-	-
Norway	262	0.23	-	2 310	-	-

Source: EU KLEMS database (2007) for the EU-25 and the United States; OECD STAN Structural Analysis Databases (2007a) for all other countries. The two databases are not fully comparable.

Note: 1. Value-added data and Employment are for 2004, except for Canada (2002 for value added and 2003 for employment), Mexico (2003 for value added), Norway (2002 for value added) and Japan (2003 for employment).

2. Average annual change in Pharmaceutical manufacturing share of total GDP and of total employment are for 1995-2004 or 1995 to 2003, as relevant.

and in the R&D services sector. Conversely, an unknown share of current pharmaceutical manufacturing is for small molecule generics and patented drugs that will still be in use in 2015 or even in 2030. Therefore, the maximum potential estimate of 0.31% of total employment in the OECD from a biotechnology pharmaceutical sector is unlikely to be achieved by 2015, but biotechnology is increasingly being used to develop small molecule therapeutics. Consequently, the percentage of pharmaceutical employment and value added that is partly or entirely dependent on biotechnology is likely to rise rapidly and approach 100% by 2030.

Table 3 gives basic economic data for the entire health care services sector for 2007. All health care expenditures account for 9.1% of GDP in the European Union (based on data for 19 countries that account for 98% of European Union GDP) and for 16% of GDP in the United States. Health care expenditures as a share of GDP between 2000 and 2007 grew in all OECD countries, with the exception of Iceland. The largest increase was in the United States where healthcare expenditures increased from 13.6% of GDP in 2000 to 16% in 2007.

Biotechnology will also contribute to health care services, for example by replacing hospital stays with new therapeutic treatments, or by altering the type of medical intervention, for instance by replacing long-term drug therapies with cures due to gene or stem cell therapy. This will affect the share of pharmaceutical costs in health care spending and the total share of health care services in GDP. The former is influenced not only by drug costs themselves, but also by all other health care costs. One consequence is that pharmaceutical costs are a smaller share of total health care costs in the United States than in Europe, even though pharmaceutical costs are higher in the United States than in Europe as a share of total GDP.

The pharmaceutical share of all health care expenditures varies substantially, from a low of 8.0% in Norway to 24% or more in Mexico, Turkey and Korea. It is also higher, at 14.6%, in the European Union than in the United States, at 12.0%. The pharmaceutical share of all health care costs is shown in column D of Table 3, and the change in that share from 2000 to 2007 is shown in column E. The pharmaceutical share of healthcare costs increased by 1.1% in the EU-19, 0.7% in the United States, 0.9% in Japan, and 4.6% in Mexico from 2000 to 2007. The share has fallen in Australia, Iceland, Korea, New Zealand, Norway, and Switzerland.

Many of the effects of biotechnology could improve cost-benefit ratios of treatment or potentially reduce or increase the health care share of GDP. However, at this time not enough data are available to estimate the non-pharmaceutical effects of biotechnology in health care value-added. However, treatments based on biotechnology will never approach 100% of health care costs by 2015 or even 2030, due to the large share of health care services from long-term chronic care for the elderly.

Table 3. **Basic economic indicators for the health care sector (HC) sector: 2007 or nearest available year**

	A	B	C	D	E	F
	2007 GDP (USD billions, current prices, PPP)	2007 HC share of GDP (%)	Change in HC share of GDP (%) 2000-2007	Pharmaceutical share of HC expenditures	Change in pharmaceutical share of total HC expenditures (%) 2000-2007	Average life expectancy at birth
EU-19[1]	12 868	9.1	0.6	14.6	1.1	79.0[2]
United States	13 742	16.0	2.4	12.0	0.7	78.1[2]
Australia	795	8.7[2]	0.4[2]	13.7[2]	-1.0	81.4
Canada	1 270	10.1	1.3	17.7	1.8	80.7[2]
Iceland	11	9.3	-0.2	13.5	-1.0	81.2
Japan	4 296	8.1[2]	0.4[2]	19.6[2]	0.9	82.6
Korea	1 202	6.8	1.9	24.7	-1.6	79.4
Mexico	1 480	5.9	0.8	24.0	4.6	75.0
New Zealand	115	9.2	1.5	9.6	-1.5	80.2
Norway	252	8.9	0.5	8.0	-1.5	80.6[2]
Switzerland	309	10.8	0.6	10.3	-0.5	81.7[2]
Turkey	960	5.7[3]	0.8[3]	24.8[4]	N/A	71.8

Source: Authors, based on OECD (2009a), with GDP from OECD (2008).

Notes: 1. Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands, Poland, Portugal, Slovak Republic, Spain, Sweden, United Kingdom.
2. Data for 2006, or change in share is the average from 2000 to 2006.
3. Data for 2005, or change in share is the average from 2000 to 2005.
4. Data for 2000.

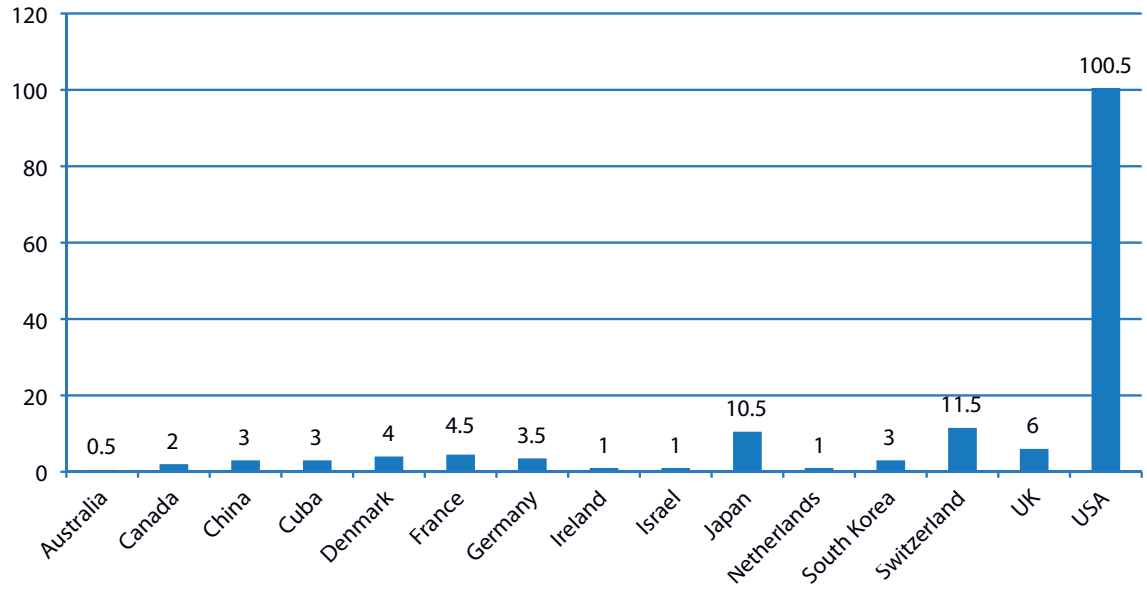
Health therapies

This section looks at the use of biotechnology to develop therapies to treat disease. These include biotechnologies with products on the market (proven biopharmaceuticals), experimental therapies with products in clinical trials but with very few if any products yet on the market, and small molecule pharmaceuticals in which biotechnology is used during manufacturing or in the drug development process. This article defines a new molecular entity (NME) as a biopharmaceutical or small molecule therapeutic) that is still in development or clinical trials, while a pharmaceutical has obtained marketing approval by a regulatory agency somewhere in the world.

Current status of proven biopharmaceuticals

The development of biopharmaceuticals is dominated by American firms, both in terms of the number of firms that developed at least one new biopharmaceutical that has received market approval and in terms of the total number of biopharmaceuticals.

Figure 1. **Number of biopharmaceuticals by nationality of the developer firm, Jan 1989-Jan 2009**



Source: Authors, based on data from Informa (2007a), EMEA, and FDA.

Notes: 1. Biopharmaceuticals are limited to NMEs and exclude biosimilars. See Annex A, Table 27 for a list of the 155 biopharmaceuticals.

2. A rating of 0.5 is given when development was jointly shared by firms in two different countries.

3. Biopharmaceuticals include therapeutics, vaccines, in vivo diagnostics, and experimental therapies.

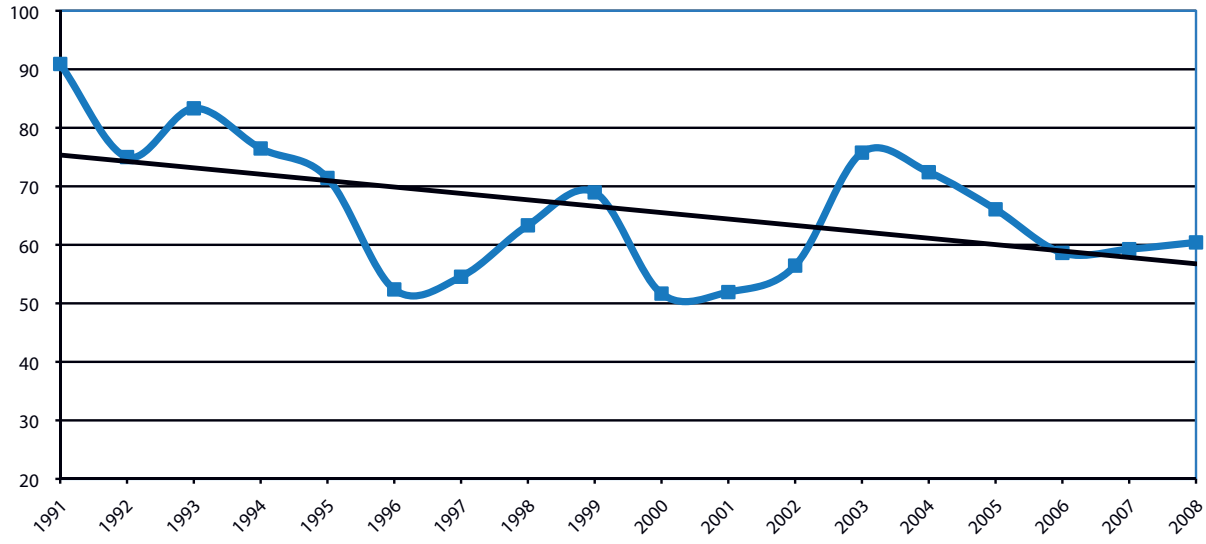
Between January 1989 and January 2009, 155 biopharmaceuticals, including therapeutics, recombinant vaccines, *in-vivo* diagnostics and a few experimental therapies, received marketing approval. Figure 1 gives the number of biopharmaceuticals by the head office country of the developer firm. For approximately 40% of approved biopharmaceuticals, the firm that developed the drug did not take it all the way through clinical trials and apply for marketing approval. Instead, the developer was purchased by another firm before marketing approval or the drug was licensed to another firm. For a few biopharmaceuticals, development was jointly shared by firms in two countries. In this case each head office country is given a rating of 0.5. Firms based in the United States developed 100.5 (64.8%) of the 155 biopharmaceuticals, while European firms account for 32 biopharmaceuticals (20.6%) and Japanese firms for 10.5 biopharmaceuticals (6.8%).

The share of biopharmaceuticals developed by American firms has declined from over 75% before 1995 to approximately 60% after 2006 (see Figure 2). Almost all of the remaining biopharmaceuticals have been developed in other OECD countries, with the exception of three developed in China, three in Cuba, and two in Israel.

Additional therapeutic value of biopharmaceuticals

An important measure of the impact of new drug approvals on public health is their therapeutic value. This concept refers to the effectiveness of new drugs, compared to existing therapies, for treating disease. For example, a new drug that has a similar effect to an existing drug already on the market provides little additional therapeutic value to available treatments. 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. Although effective, they offer no therapeutic advance over existing drugs. Since the early

Figure 2. **Share of biopharmaceuticals (3-year running average) developed by US firms, by year of market approval: Jan 1989-Dec 2008**



Source: Authors, based on data from Informa (2007a), FDA, EMEA

Notes: 1. See Annex A, Table 27 for a list of all biopharmaceuticals.

2. Data series begins in 1991 with the average for three years: 1989, 1990 and 1991.

1980s, approximately two-thirds of new drugs have been "me too" drugs (US GAO, 2006). An important goal for policy and for pharmaceutical firms is to improve the share of new drugs that offer a therapeutic advance over existing treatments.

Many biopharmaceuticals are based on a new technology with new modes of action (Ashton, 2001). In this respect biopharmaceuticals display some of the characteristics of an emerging technology, in contrast with the "mature" technology characteristics of many classes of small molecule drugs. Consequently, we would expect biopharmaceuticals to offer a greater therapeutic advance, on average, compared to other small molecule pharmaceuticals.

To test this assumption, the therapeutic value of biopharmaceuticals was compared against other types of drugs, using two separate data sources: France's Haute Autorité de Santé and the physician-funded organisation *Prescrire*. The data were used to compare the therapeutic value ratings for small molecule pharmaceuticals and biopharmaceutical. Both sets of data produced similar results and confirm the hypothesis that biopharmaceuticals, on average, offer greater therapeutic advance than other small molecule pharmaceuticals. The analyses do, however, raise some concerns.

Both analyses indicate that the therapeutic advance of biopharmaceuticals is declining over time as the class takes on the characteristics of a mature technology. The decline in therapeutic advance is partly due to the diffusion of the technology to an increasing number of firms, with competitors bringing comparable biopharmaceuticals onto the market. A good example is interferon, with many different versions currently available.

Analysis of therapeutic value using HAS and Prescrire data

HAS was set up by the French government in August 2004 as an independent, financially autonomous body. It is tasked with using scientific data to assess the therapeutic value of drugs, medical devices, and procedures. As of the end of 2007, the organisation has evaluated 53 biopharmaceuticals approved for use in the European Union, and 1 476 other drugs.[9] The evaluations are based on indications,[10] which are the approved use of the drug to treat specific diseases. A single drug can be approved for multiple indications. For example, HAS evaluated 53 biopharmaceuticals for 102 different indications. The results

Table 4. **HAS evaluations of the therapeutic value of biopharmaceuticals and all other drugs (January 2001-December 2007)**

	Biopharmaceuticals				All other drugs	
	Highest rating		All indications		All indications	
Evaluation Class	N	%	N	%	N	%
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%	102	100%	1 476	100%

Source: Authors, based on HAS (2008).

Note: For a full definition of each evaluation category, see the notes to Annex B, Table 31, which also lists each evaluated biopharmaceutical, the HAS evaluation, and the indication that received the highest evaluation.

are given in Table 4. Results are only given for therapeutics, with *in vivo* diagnostics and vaccines excluded to improve comparability.

Based on the results for all indications, a higher percentage of biotechnology than all other drugs provide a "moderate improvement" or higher: 47.6% versus 12.4% of all other drugs. In addition, only 39.2% of biopharmaceuticals are rated as offering no therapeutic advance over existing drugs on the market, versus 77.2% of all other drugs.

The data suggest that the therapeutic advance of biopharmaceuticals as a class is declining over time. The share of biopharmaceutical indications offering some therapeutic advance or greater 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 time period, the percentage of "me too" indications also increased from 25.0% to 50.9%. In absolute terms, however, the number of biopharmaceuticals per year offering a "moderate improvement" or greater has not changed, with an average of 0.5 per year between 2001 and 2007.

Prescrire is an independent French organization that is supported entirely by doctor subscriptions for its journal. *Prescrire* only evaluates drugs after marketing approval, using all available clinical trial results. It uses a similar evaluation class structure as HAS, except that it has one additional class of "not acceptable" for drugs that the evaluators believed should not have obtained marketing approval. Compared to the HAS results, the distribution of *Prescrire* evaluations above the category of a "minimal" advance are shifted downwards. For example, HAS gives 8.8% of biopharmaceuticals an indication of "major therapeutic progress" whereas *Prescrire* gives none of the evaluated biopharmaceuticals its highest rating of a "major advance". These differences are not important here, as the main purpose of the analyses is to compare the distribution of evaluations for biopharmaceutical and small molecule drugs, rather than the absolute rankings.

Table 5. ***Prescrire* evaluations of the therapeutic value of biopharmaceuticals and all other drugs (Jan 1986-April 2008)**

	Biopharmaceuticals				All other drugs	
	Highest rating		All indications		All indications	
Evaluation Class	N	%	N	%	N	%
Major advance	0	0.0%	0	0.0%	8	0.4%
Important advance	5	7.4%	7	5.1%	57	3.0%
Some advance	14	20.6%	21	15.2%	196	10.2%
Minimal advance	20	29.4%	41	29.7%	449	23.4%
No advance (me too)	19	27.9%	39	28.3%	964	50.3%
Not acceptable	8	11.8%	13	9.4%	127	6.6%
Judgment reserved	2	2.9%	17	12.3%	114	6.0%
Total	68	100%	138	100%	1 915	100%

Source: Authors, based on data from Prescrire issues between January 1986 and February 2008. All other drugs: 1986 – 2000 data on page 59, Prescrire Jan 2001, 2000 – 2007 data on page 136, Prescrire, Feb 2008; data for 2008 from individual Prescrire issues.

Notes: 1. The evaluations for biopharmaceuticals were subtracted from the totals for all drugs.
2. For a full definition of each evaluation category, see Annex C, Table 33 gives each evaluated biopharmaceutical, the highest Prescrire evaluation and the indication that received the highest evaluation.
3. After 1996, Prescrire separated the therapeutic value of biopharmaceuticals and all other drugs from generic equivalents. In this table, generics are excluded.

As of the end of April 2008, *Prescrire* had evaluated 138 indications for 68 biopharmaceuticals approved for use in the European Union, and 1 915 other (small molecule) drugs. The results, given in Table 5, only cover therapeutics and exclude diagnostics and vaccines. A full description of each drug evaluation class is given in Annex C.

The second column of Table 5 provides the highest rating given to biopharmaceuticals. *Prescrire* updates evaluations when new information becomes available, so the highest rating for a biopharmaceutical could be due to either a revised rating for the same indication or to a new indication. The "all indications" column includes all ratings, whether revised or not, in order to maintain comparability with the results for all other drugs, given in the last two columns of Table 5.

Based on the results for all indications, a higher percentage of biotechnology than all other drugs provide "some advance" or higher: 20.3% versus 13.6% of all other drugs. In addition, only 28.3% of biopharmaceutical indications are rated as offering no therapeutic advance over existing drugs on the market, versus 50.3% of all other drugs.

Of note, the results in Table 5 raise a few concerns. The two categories of "not acceptable" and "judgment reserved" refer to drugs that the evaluators believed should not have received marketing approval, either because the drug is deemed to be more harmful than alternatives or because the available data are insufficient for assessing drug safety and efficacy. Slightly more than one-fifth of biopharmaceutical indications fall in this group, compared to 12.6% for all other drugs.

Limited to the highest rating, the share of biopharmaceuticals that offer some therapeutic advance or greater declined from 50.0% of 22 indications evaluated between 1986 and 2000 inclusive, to 22.7% of 22 indications evaluated between 2001 and 2004 and to 21.1% of 24 indications evaluated after 2004.[11] A comparison of the time periods before and after 2001 shows that the percentage of the highest indications receiving a "me too" rating increased from 18.1% to 37.0% (there was no substantive difference in the two time periods 2001 to 2004 and after 2004). It is important to note that in absolute terms the number of biopharmaceuticals per year offering some therapeutic advance or greater almost doubled, from 0.7 per year between 1986 and 1999 to 1.3 per year between 2000 and 2006.

Firm type and therapeutic value

The factors that support the development of therapeutically valuable biopharmaceuticals are of relevance to both policy and the design of future business models. One possibility is that small DBFs could be more likely than large established firms to develop biopharmaceuticals that offer a therapeutic advance over existing treatments. This could occur either because DBFs have closer linkages with university researchers that discover new modes of action or business models that accept riskier projects. The latter could include close ties with venture capitalists or a goal to license promising drugs at the clinical trial stage.

An analysis was undertaken to determine whether there was a correlation between the type of firm that developed the biopharmaceutical and the therapeutic value of the drugs being developed. Data from HAS and *Prescrire* were used. In both analyses, small biotech firms had a substantially higher share of drugs providing "some" therapeutic advance or better. Conversely, larger firms had a much higher share than large established firms of biopharmaceuticals that were rated as a "minimal" advance, or which provided no advance ("me too" drugs).[12] In addition, the analysis of *Prescrire* data shows that the share of drugs developed by mid-size biotech firms that were deemed "not acceptable" was almost double that of small biotech firms.[13]

Table 6. **Therapeutic value of biopharmaceuticals by the type of firm that developed the drug, using data from the *Haute Autorité de Santé* (*HAS*)**

		Therapeutic advance over previous treatments			
Firm type	Number of biopharmaceuticals	Major advance, important or moderate advance	Minimal or no advance	Judgment reserved	Total
Small biotech	26	65.4%	26.9%	7.7%	100%
Established biotech	13	69.2%	23.1%	7.7%	100%
Large / established	14	28.6%	64.3%	7.1%	100%
Total	53	57.7%	36.5%	5.8%	

Source: Authors, based on HAS (2008) for therapeutic value data and publicly available data on firm size.

Notes: 1. Excludes vaccines and diagnostics.
2. For a full definition of each evaluation category, see the notes to Annex B, Table 31.

Table 6 gives the distribution of the HAS evaluations of 53 biopharmaceuticals by the type of firm that developed the drug. For example, HAS evaluated 26 biopharmaceuticals that were developed by small dedicated biotech firms. Since their establishment, three dedicated biotechnology firms (Amgen, Genzyme and Genentech) have developed into established biopharmaceutical firms that are much larger and successful than the small biotech firms. Drugs developed by these firms and which received marketing approval 20 years after the establishment date of the firm are assigned to the "established biotech" category.[14] Large firms consist of pharmaceutical firms that were established before the biotechnology revolution in 1974. Most had over 20 000 employees in 2008. Compared to large established firms, a higher share of biopharmaceuticals developed by small biotech firms received an evaluation of "some" advance or better (65.4% versus 28.6%). Conversely, compared to both the small biotech firms and the mid-size firms, large firms had over double the share of biopharmaceuticals that were rated as a "minimal" advance, or which provided no advance ("me too" drugs).

Table 7 gives the distribution of *Prescrire* evaluations for 68 biopharmaceuticals by the type of the firm that developed the drug. A higher share of biopharmaceuticals developed by small firms received an evaluation of "some" advance or better (38.7% versus 25.0% for

Table 7. **Therapeutic value of biopharmaceuticals by the type of firm that developed the drug, using data from *Prescrire***

		Therapeutic advance over previous treatments			
Firm type	Number of biopharmaceuticals	Important or some advance	Minimal or no advance	Not acceptable or judgment reserved	Total
Small biotech	31	38.7%	45.2%	16.1%	100%
Established biotech	16	25.0%	43.8%	31.3%	100%
Large / established	21	14.3%	85.7%	0.0%	100%
Total	68	28.4%	58.2%	13.4%	

Source: Authors, based on *Prescrire* (various) for therapeutic value data and publicly available data on firm size.

Notes: 1. For a definition of each evaluation category, see Annex C, Table 33.
2. Small biotech firms were established after 1974 specifically to develop biotechnological applications in health. Established biotech firms primarily consist of Amgen, Genzyme, and Genentech that were originally small dedicated biotech firms. They are assigned to the mid-size firms 20 years after the year of establishment. Elan and Organon are also assigned to this category (1 drug each). Large firms either have over 20 000 employees in 2007 or were multi-product chemical and pharmaceutical firms established before the advent of biotechnology in 1974.

mid-size firms and 14.3% for large firms. Large established firms developed the highest share of biopharmaceuticals with a therapeutic value rating of "minimal advance" or "no advance" (85.7%). The established biotech firms developed the highest share of biopharmaceuticals that were rated as "not acceptable" or "judgement reserved" (31.3%).

Conclusions for therapeutic value

The analyses of the HAS and Prescrire data consistently show that biopharmaceuticals offer a notable "therapeutic advantage" over small molecule pharmaceuticals, although the level of the advantage has been declining over time. DBFs have also been the major contributor for therapeutically valuable new biopharmaceuticals. The decline in the therapeutic advantage over time could be reversed in the future, if research into experimental therapies results in clinically successful new drugs (see below).

Current status of experimental therapies

In addition to the biopharmaceuticals that have entered the market over the last two decades, many new experimental biotechnologies are being developed. These have the potential to produce new treatments that could treat or cure diseases or improve the quality of life. At present, there are only a few relevant products on the market, mostly outside the OECD countries. Research and development is ongoing however and there are products in all phases of clinical trials. Some have completed phase III clinical trials and are in the pre-registration phase.

American firms account for 119 of 197 clinical trials or pre-registrations of experimental therapies, as shown in Table 8. Table 29 provides results by country for the number of clinical trials in Phases I, II and III.

Table 9 presents the experimental therapies by clinical trials phase. There are 55 and 112 experimental trials in Phase I and Phase II, respectively. This represents approximately 85% of all experimental therapy trials. While this indicates a very robust pipeline, many of the experimental therapies have performed poorly in clinical trials and will have success rates far below that of traditional biotherapeutic products.

Table 8. **Experimental therapies in clinical trials or pre-registration, by country: as of March 2008**

Therapy Type	Australia	Austria	Belgium	Brazil	Canada	China	Denmark	France	Germany	Israel	Italy	Japan	Malta	Netherlands	South Korea	Spain	Sweden	United Kingdom	United States	TOTAL
Antisense	2	0	0	0	6	0	2	0	1	0	0	0	0	1	0	0	1	2	19	34
Cell & tissue, non stem cell	2	0	1	1	1	0	2	3	2	0	1	1	0	2	1	1	0	6	32	57[1]
Stem cell	1	0	0	0	0	0	0	0	3	2	0	0	0	0	2	0	0	0	15	23
Gene therapy	0	1	0	0	1	1	1	5	1	2	3	1	1	1	5	0	0	6	49	78
RNA interference	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	6
TOTAL	5	1	1	1	8	1	5	8	7	4	4	2	1	4	8	1	1	16	119	197

Source: Authors, based on data from Informa (2007a).

Note: 1. There was one cell therapy for which the country was not specified.

Table 9. **Experimental therapies in clinical trials or pre-registration, by phase: as of March 2008**

Therapy Type	Phase I	Phase II	Phase III	Pre-registration	Total
Antisense	10	21	2	1	34
Cell & tissue, non stem cell	11	37	6	2	57
Stem cell	12	7	4	0	23
Gene therapy	20	44	12	2	78
RNA interference	2	3	1	0	6
TOTAL	55	112	25	5	197

Source: Authors, based on data from Informa (2007a).

The following sections summarize the current state of activity in cell and tissue engineering (including stem cells), gene related therapies (including gene therapy, antisense and RNAi), and synthetic biology and give some examples of potential applications for the health sector.

Cell and tissue engineering

These technologies involve techniques that replace or act directly on cells and tissues in the body.

Cell and tissue engineering

In general, cell therapies replace, "diseased or dysfunctional cells with healthy, functioning ones (MedicineNet, 2001)." This refers to the replacement of individual cells with new, living cells. In comparison, tissue engineering develops "biological substitutes to restore, maintain and improve [human] tissue functions (NSF, 2007)." This can include new living tissues attached to inert substrates.

A review for the European Commission reports that approximately 40 tissue engineering products are on the market, "mainly autologous[15] skin replacements, cartilage, and bone products, generating sales of about EUR 60 million/year (JRC, 2007)." Most of these however, do not require intensive clinical trials due to their non-invasive nature (*e.g.* – wound coverings). Several tissue engineering products for the treatment of diabetic and other skin ulcers have been available in several OECD countries for a decade. Examples include Apligraf™ and Dermagraft™.

Presently, 57 cellular therapies are currently in clinical trials including 12 in phase I, 37 in phase II, 6 in phase III and 2 in pre-registration. Thirty are for treating cancer and 30 use autologous (usually dendritic) cells. Eleven use a single cell type to replace or improve existing tissue: heart muscle, blood vessels, cartilage, diabetes islet cells, etc. All of these, with the exception of porcine diabetes islet cells, use autologous cells. There are also nine engineered tissues (mostly skin tissue, mostly not autologous), as well as three trials for immune disorders (alopecia, rheumatoid arthritis, MS), two for incontinence (anal and urinary), one for Parkinson's disease and one for ocular disorder. Except for the nine engineered tissues, all use a single cell type. Even for the engineered tissues, only a few use more than one living cell type (keratinocytes and fibroblasts).

Stem cell therapy

Stem cells in particular have garnered a lot of attention as a form of cell therapy. A stem cell can make exact copies of itself indefinitely and is generic, with the ability to produce specialized cells for various tissues in the body, such as heart muscle, brain tissue, and liver tissue. There are two basic types of stem cells. The first type is the embryonic stem cell, which is obtained from either aborted foetuses or fertilized eggs that are left over from in vitro fertilization. Embryonic stem cells are useful for medical and research purposes because they can produce cells for almost every tissue in the body, but ethical concerns have placed legal or financial limitations on research using them. The second type is the adult stem cell, which is not as versatile for research purposes because it is specific to certain cell types, such as blood, intestines, skin, and muscle (eJournalUSA, 2005).

Bone marrow transplants, which have been practiced for 40 years, are a type of stem cell treatment. The only more advanced treatment that has received marketing approval to date is OTI-050, which entered the United States' market in 2005, and is used to regenerate bone before dental implantation. The process uses stem cells but the principle is similar to the other cellular therapies described above.

Currently 23 (twelve in phase I, seven in phase II and four in phase III) stem cell therapies are in clinical trials (see Table 9). Four target myocardial infarction, four target ischaemia, three are focused on regeneration and transplantation, and the rest target a variety of other diseases. The vast majority of all clinical trials underway are focused on adult stem cells.

The future promise of stem cells is based on the ability to produce more complex structures, such as teeth, complex tissues, or organs, that are not possible to produce with other cellular therapies. The New Zealand Ministry of Research Science and Technology has identified several technical bottlenecks for stem cell development as an advanced treatment option:

- "Understanding the mechanisms regulating stem cell growth and differentiation into tissue;
- Eliminating the risk of stem cell differentiation into cancer cells; and
- Overcoming the risk of immune rejection which may arise when a patient is receiving stem cells from a donor – as would be the case with embryonic stem cell derivation (NZ MoRST, 2005)."

Gene-related therapies

These technologies either use or act directly on nucleic acids, which are the molecules that serve as the building blocks for DNA and RNA.

Gene therapy

Gene therapy is "[t]he insertion of normal or genetically altered genes into cells, usually to replace defective genes especially in the treatment of genetic disorders (IFOPA, 2007)." Although clinical trials began in 1990, there are still no gene therapies approved by the FDA or EMEA, although, as of March 2006, two have been approved in China (Jia, 2006).[16] Gene therapy still faces technical difficulties, as shown by serious side effects, including the deaths of several patients in clinical trials (Edelstein, Abedi, Wixon, 2007).

The US Human Genome Program has identified four primary reasons that gene therapy has not become a successful treatment option:

- **Short-lived nature of gene therapy:** Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits.
- **Immune response:** Since gene therapy introduces a foreign object into human tissues, the immune system is stimulated in a way that can reduce gene therapy effectiveness. Furthermore, the immune system's enhanced response to known invaders makes it difficult for gene therapy to be repeated in patients.
- **Problems with viral vectors:** Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient: toxicity, immune and inflammatory responses, and gene control and targeting issues.
- **Multigene disorders:** The best candidates for gene therapy are mutations due to single gene, whereas most conditions are multigene disorders (US DOE, 2007).

Despite these hurdles, research is ongoing and a total of 78 gene therapies are in clinical trials or pre-registration: 20 in phase I, 44 in phase II, 12 in phase III, and two in pre-registration (see Table 9). Of these clinical trials, 44 target cancer, 13 target cardiovascular diseases, seven target peripheral vascular disease, four target Parkinson's disease, and all the remaining gene therapies focus on individual indications.

Antisense therapy

Antisense therapy is, "[t]he *in vivo* treatment of a genetic disease by blocking translation of a protein with a DNA or an RNA sequence (an oligonucleotide) that is complementary to a specific mRNA (FAO, 1999)." There is currently one antisense therapy (fomivirsen sodium) that received regulatory approval in 1998 in the United States. Developed by Isis Pharmaceuticals, the drug, administered via injection into the eyeball, was used to treat CMV retinitis which can cause blindness in people with impaired immune systems such as those with acquired immune deficiency syndrome (AIDS). The market is very small. The drug was approved for use in the European Union in 1999, but withdrawn from the market in 2002.

Antisense therapy faces several technical difficulties. As with gene therapy, the immune system can react to the introduction of a foreign antisense oligonucleotide into the body. In addition, antisense faces several other technical challenges, "including, oligonucleotide stability versus binding affinity, [and] delivery of oligonucleotides to the target cells (Tamm, Dörken, and Hartmann, 2001)." One of the reasons that formiversen may be an early entrant on the market is that delivery to the target cells was straightforward, due to direct injection into the eye.

There are currently 34 anti-sense therapies in clinical trials: ten in Phase I, 21 in Phase II, two in Phase III and one in pre-registration (see Table 9). Fourteen of the antisense therapies target cancer, five target cardiovascular diseases, three target restenosis, two target diabetes, two target human immunodeficiency virus (HIV)/AIDS and the rest target other individual indications.

RNA interference

RNA interference (also known as RNAi, small interference RNA, or siRNA) is a, "gene-silencing process in which double-stranded RNAs trigger the destruction of specific RNAs (National Institute of General Medical Sciences, 2006)." There are currently no RNAi therapies that are approved for sale and only six RNAi drugs in clinical trials: two in Phase I, three in Phase II, and one in Phase III (see Table 9). Three RNAi therapies are aimed at treating macular degeneration, two are indicated for the treatment of infections (respiratory and hepatitis B) and one targets renal failure disease.

Though the RNAi process was only described in 1998, research on the topic has flourished (Howard, 2003). It also appears that many large pharmaceutical companies are betting that RNAi will lead to new discoveries and large pay-offs, as both Roche and Merck recently completed acquisitions and licensing agreements with specialty RNAi firms that could reach over USD 1 billion (IHT, 2007).

Nanobiotechnology

Nanotechnology is the manipulation and design of particles at the nanoscale. While there are myriad potential uses of nanotechnology in medicine, known as nanomedicine, this section refers to a subset of these health technologies, dubbed nanobiotechnology, dealing with the convergence of nanotechnology and biotechnology. Definitions in this area can be unclear, but generally nanobiotechnology is used for drug delivery and regenerative medicine. In addition, as discussed in the sections on diagnostics, some biotechnology diagnostics use nanotechnology to detect DNA sequences, proteins, etc.

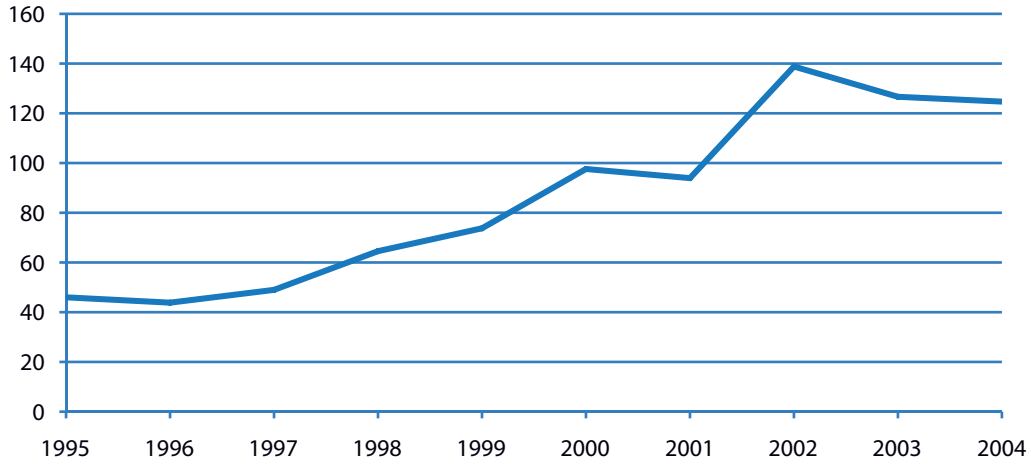
Nanotechnology holds a great deal of promise as a novel drug delivery technology. This is attractive for small molecule therapeutics because it can provide more targeted distribution of active compounds, particularly in oncology, as well as solving some solubility and metabolism issues of drugs inside the body. There is also an advantage for drug developers in that a nano-formulation may extend the patent life of a drug.

These delivery technologies can also be applied to biotherapeutics and particularly some experimental therapies such as gene, anti-sense, and RNAi therapies. As noted previously, one of the challenges facing the exploitation of these experimental therapies is the immune system response to the delivery vector. Experts believe that nanoparticles may not induce such a strong immune reaction and that the minute particles may better penetrate cell walls. However despite the promise, it is not clear that nano-delivery systems will be more effective for experimental therapies than traditional delivery vectors. Furthermore, given different material properties at the nano-scale, there remain unanswered questions about potential toxicity of certain nano-materials in the body.

Due to the structural and self organising properties of some nanoparticles, in the future there may also be nano-applications for cell and tissue engineering. For example, nanobiotechnology could produce tissue scaffolds to facilitate blood flow in the body and replace failing cardiovascular tissue (NZ MoRST, 2005).

There is evidence that nanobiotechnology research is producing results. As shown in Figure 3, the number of nanotechnology patents filed for "medicine and biotechnology" applications has increased nearly 3 fold between 1995 and 2004. While it is not possible to identify the percentage of patents for nano*bio*technology applications, it seems reasonable, given known activities in the area, that the number of those patents has also increased (though perhaps not at the same rate) over the same period.

Figure 3. **Number of nanotechnology patents in "medicine and biotechnology", by year**



Source: Authors, based on OECD (2007b) Patent Database.

Notes: 1. Nanotechnology patents identified by tag Y01N in the European Patent Office (EPO) database EPODOC; see Scheu *et al*. (2006).

2. Patent applications filed under the Patent Cooperation Treaty (PCT), at international phase, designating the EPO.

3. The graph only covers countries/economies with more than 250 patents filed under PCT for the period 2002-04.

While patents are a good indicator of research activity, they do not necessarily translate into products. It is not clear if there are any nanobiotechnology products on the market to date, including therapeutics, cell or tissue engineering products that use nanotechnology. Some analysts include PEGylated biotherapeutics, involving the attachment of Polyethylene glycol strands to proteins in order to increase the metabolic half-life, under nanobiotechnology. However, including PEGylated molecules as nanotherapy products would suggest that any method to reformulate molecules to enhance their activity in the body would count as nanobiotechnology.

There is some measurable nanobiotechnology activity in the clinical trial pipeline. The Pharmaprojects database contains 66 active nanoparticle formulation drugs.[17] Of these, seven are nano-formulations of biotechnology therapeutics: four are in preclinical testing, two in Phase I trials, and one in Phase II. It is not possible to determine if there are new (*i.e.* non-formulation) bionano-therapeutics under development.

Synthetic biology

Synthetic Biology is "the design and construction of new biological parts, devices and systems that do not exist in the natural world and also the redesign of existing biological systems to perform specific tasks (ETC Group, 2007)". Though still in its infancy, synthetic biology has caused quite a stir, with many claiming that it is the future of biotechnology and even life itself. At present, synthetic biology is confined to the research stage, with no products near the market.

Drew Endy, a leading synthetic biology researcher, has identified four challenges that presently limit the engineering of biology:

- "an inability to avoid or manage biological complexity"
- "the tedious and unreliable construction and characterization of synthetic biological systems"
- "the apparent spontaneous physical variation of biological system behaviour"
- "evolution" (Endy, 2005)

Craig Venter, well known for his role in deciphering the human genome, is expected in the near future to announce the creation of the world's first artificial life form. Using lab-made chemicals, Venter and a team of scientists have synthetically constructed a chromosome that will be inserted into a living bacterial cell and in the final stage of the process it is expected to take control of the cell and in effect become a new life form. The new organism will depend upon the existing cell for functions such as metabolism and reproduction, but the DNA will be artificial (The Guardian, 2007).

Some synthetic biologists are also working to transform biology into a traditional engineering design discipline by standardizing biological "parts" in much the same way that transistors and capacitors have been standardized for electrical and computer design. MIT has begun a library of several hundred standard biological parts (called *BioBricks*) that can be assembled into various biological devices (iGEM, 2007a). 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.

These *BioBricks* facilitate the International Genetically Engineered Machine (iGEM) competition which is an arena where student teams compete to design and assemble engineered machines using advanced genetic components and technologies. Contest participants have produced systems ranging from biological thermometers and timers to photographic biofilm and biological sketch pads to bacteria that smell like wintergreen or bananas. They have also used engineered cells to intercept the body's excessive response to infection, which can lead to a fatal inflammation condition called sepsis (iGEM, 2006a, 2006b, 2007b; ScienceDaily, 2006).

The use of synthetic biology has many applications in health, notably in the areas of drug production and therapeutics.

By redesigning cells to produce various compounds, synthetic biology could lead to a way to economically mass produce drugs. The method is an advance over recombinant technology, as it redesigns a specific gene rather than transposing existing genes across species. The Bill & Melinda Gates Foundation recently granted USD 42.6 million to the Institute for OneWorld Health (in partnership with the University of California, Berkeley, and Amyris Biotechnologies), to develop a more affordable cure for malaria. The project aims to create a new enzyme to produce artemisinin (Institute for OneWorld Health, 2004) (also see the section on "Manufacturing"). The team of scientists are working to have artemisinin ready for mass distribution in late 2009 or early 2010 (Zimmer, 2006). Other drugs, derived from expensive or limited natural sources, such as taxol (anti-cancer) and prostratin (anti-HIV) could be produced in the same manner.

Researchers are also examining the use of synthetic biological devices that can communicate with cells inside the body, detect diseases, and produce the compounds necessary to treat the sickness. This would act as, "a kind of autonomous, molecular-scale "physician"

that can combat disease at a very early stage in its development (EC, 2005)." Similar techniques could be applied to repairing genes and tissues in the body. Furthermore, synthetic viruses could be developed that lead to treatments or cures for many diseases.

Despite the promise, it is unlikely that there will be any synthetic biology therapeutic products on the market before 2015, as the field is still in the early research stage.

Current status of small molecule therapeutics

Small molecule drugs, usually of less than 500 Daltons in weight (Cheng *et al*., 2007), account for approximately 86% of all NMEs approved since 1999 and for approximately 90% of global sales of prescription drugs in 2006 (578 billion out of total sales of USD 643 billion) (IMS Health, 2007). Even with the predicted increase in large molecule biopharmaceuticals up to 2015, small molecule drugs will account for over 80% of NMEs.

The number of small molecule drugs reaching the market, based on US FDA approvals, has increased slightly since the 1980s, but R&D expenditures have increased far more rapidly, creating a fall in R&D productivity.[18] This has been a frequent outcome for successive waves of new drug development techniques, such as the decline in the 1960s in the productivity of screening molecules produced by synthetic chemistry or extracted from natural products. Biotechnology was believed to provide new methods of drug development that would overcome the decline in R&D productivity, but this has not happened to the extent that was originally expected with the advent of recombinant DNA drugs and mAbs (Pisano, 2006).

Biotechnological knowledge can also be applied to develop, produce, test, and manage the use of small molecule drugs. This creates opportunities to improve the productivity of small drug development. Currently, there are four relevant application areas of biotechnology for small molecules: manufacturing, drug discovery, clinical trials, and patient care.

Manufacturing

In order to be financially viable, the manufacturing costs for small molecule drugs must match market requirements. For example, production costs for a mass market drug must be low enough for the drug to be marketed at a price that will maximize sales.[19] For some drugs, such as Tamiflu and the anti-malarial artemisinin, the cost of producing precursors derived from plant sources has been unacceptably high. Recombinant micro-organisms have been developed to produce shikimic acid, a precursor derived from star anise for Tamiflu, and artemisinic acid, a precursor for artemisinin derived from the leaves of Artemisia annua (Ro *et al*., 2006) (a relative of sagebrush and wormwood). Other small molecule drugs have been produced using recombinant micro-organisms to obtain chiral forms, although chiral molecules can also be synthesized. Genetically modified (GM) bacteria have also been used to improve the characteristics of drug candidates. An example is the kinase inhibitor rapamycin. Recombinant bacteria were used to increase the potency and improve the metabolic stability of this drug candidate (GEBN, 2006).

Drug discovery

One of the most important applications of biotechnology to small molecule drugs is in the drug discovery process, particularly the identification of drug targets. The number of identified drug targets, largely due to the application of biotechnology, increased from approximately 500 in the mid 1990s to about 1 500 today (Hopkins *et al*., 2007).

One relevant application of biotechnology to small molecule drug discovery is the use of genomics and genetic databases, plus analytical methods such as gene transfer, gene expression profiling, and gene knock-out techniques such as RNAi, to identify human drug targets (Pisano, 2006; Hopkins *et al*., 2007). The same methods are also used to understand the genetics of infectious micro-organisms and parasites that cause disease, in order to identify targets for drugs to attack the organism. In addition, rDNA techniques are used to synthesize target receptors and enzymes that are used in models to search for new drugs.

Table 10 give several examples of the use of biotechnology in the discovery process for small molecule drugs.

Table 10. **Use of biotechnology in small molecule (SM) drug development and therapy**

Main Biotechnology	Other technologies	Purpose	Effect on SM
Genomics	Genome mapping, mapping human genetic variation, genome sequence analysis	Identify genes and variations in populations	Identify drug targets
Gene expression profiling, comparative and genetic studies of model organisms	Interference with gene expression, adding genes of unknown function	Identify genes involved in disease pathways	Identify drug targets
Human clinical association studies	Bioinformatics, gene based diagnostics	Correlation of genomic markers with clinical phenotypes	Identify drug targets
Toxicogenomics	In vitro pharmacogenetic studies	Study relationship between genetic variation and drug response	Improve clinical trials and prescribing practice
Pharmacogenetics	Clinical association studies	Study relationship between genetic variation and drug response	Improve clinical trials and prescribing practice
Gene-based diagnostics		Identify population sub-groups that respond differently to drug therapy	Improve clinical trials and prescribing practice

Source: Adapted from Martin, Hopkins and Nightingale (2008).

Clinical trials

Biotechnological knowledge, such as pharmacogenetics, toxicogenomics and gene-based diagnoses (see Table 10) have many applications to improve the safety and efficacy of drug development and clinical trials.

Toxicogenomics is used in pre-clinical research to identify possible safety problems and consequently improve the selection of drug candidates. Pharmacogenetics can be used to stratify patients for clinical trials, with the method applied both to patients and, for infectious diseases, to the type of organism. For example, patients with a specific strain of HIV virus may not respond to drug A, but research could find that drug B will work. Pharmacogenetics applied to the patients can identify genetic differences that influence whether or not patients will respond positively to a specific drug, if they have an increased risk of adverse reactions,[20] or if they metabolize drugs at a rate that requires an adjustment to the dose.

The benefits of pharmacogenetics to clinical trials are currently limited by a lack of validated genes and protein or metabolic biomarkers that can be used to identify "responding" versus "non responding" patient groups. Part of the challenge is to identify genetic factors that can accurately differentiate between responders and non-responders.

An example is Astra Zeneca's lung cancer drug candidate Iressa (a kinase inhibitor), which failed to receive marketing approval due to a lack of effectiveness. Astra Zeneca tried to use pharmacogenetics to identify genetic factors that could identify respondent patients, but was unsuccessful. Generally, kinase inhibitors only work in a small percentage of people because of the large number of potential kinase pathways, which are also influenced by the type of tumour. In order to identify respondent patients, pharmaceutical firms need to profile both the patient and the tumours to find out which kinase pathways are active. This will require validated biomarkers (Bogdanovic and Langlands, 2006).

A second application of pharmacogenetics is to improve safety by reducing the incidence of serious adverse effects from specific drugs. This requires identifying genetic risk factors for adverse reactions.

Prescribing practices

The same uses of biotechnology to improve clinical trials also apply to post marketing-approval prescribing practices. Regulators can restrict or recommend the market approval of a specific drug for patients that have identified genes or alleles. Examples include warfarin, with the recommended dose depending on genetic differences in drug metabolism rates, the use of Herceptin (trastuzumab) to treat breast cancer (effectiveness depends on the presence of a gene to overexpress the HER2 protein), and carbamazepine, where the presence of the allele HLA-B*1502 increases the risk of serious side effects.

Convergence

The value of biotechnology for drug discovery and clinical trials for both small molecule drugs and biopharmaceuticals is leading to a convergence in the research strategies adopted by both large pharmaceutical firms such as GSK, Roche and Novartis (Emerton and Belsey, 2006), with traditional strengths in small molecule drugs, and in biotechnology firms such as Amgen and Genentech, both of which have formed alliances to improve small molecule drug discovery and development (Jarvis, 2007).

The convergence is due to synergies in the drug development process for related drug targets. For example, Genenetech developed trastuzumab (a biopharmaceutical) to target the HER2 receptor, but GSK has been able to develop a small molecule drug, Tykerb (lapatinib), that acts on the same metabolic pathway (FDA, 2007). The modes of action are not identical, as trastuzumab works on the cell wall while Tykerb works within the cell, and Tykerb has so far only been approved for women which do not respond to trastuzumab. Small molecule drugs that can act on the same target or pathway as a biopharmaceutical are attractive to firms because they can take over biopharmaceutical markets, due to being easier to use.[21] Once a drug target is identified, there can be a race to find a small molecule drug with the same therapeutic effect as a biopharmaceutical. Since in-depth knowledge of the drug target improves the ability to find both biopharmaceuticals and small molecule drugs, firms that specialise in one of these two drug types have a strong incentive to build up capabilities in the other type.[22] For example, Genentech used its expertise with the HER family of receptors to develop Tarceva (erlotinib), a small molecule drug for lung and pancreatic cancer.

Of note, pharmaceutical firms will continue to develop both biopharmaceuticals and small molecule drugs, as they have different advantages. Biopharmaceuticals can act as agonists that stimulate function (such as Factor VIII or insulin), while small molecules are usually antagonists that inhibit biological function. Furthermore, firms continue to focus

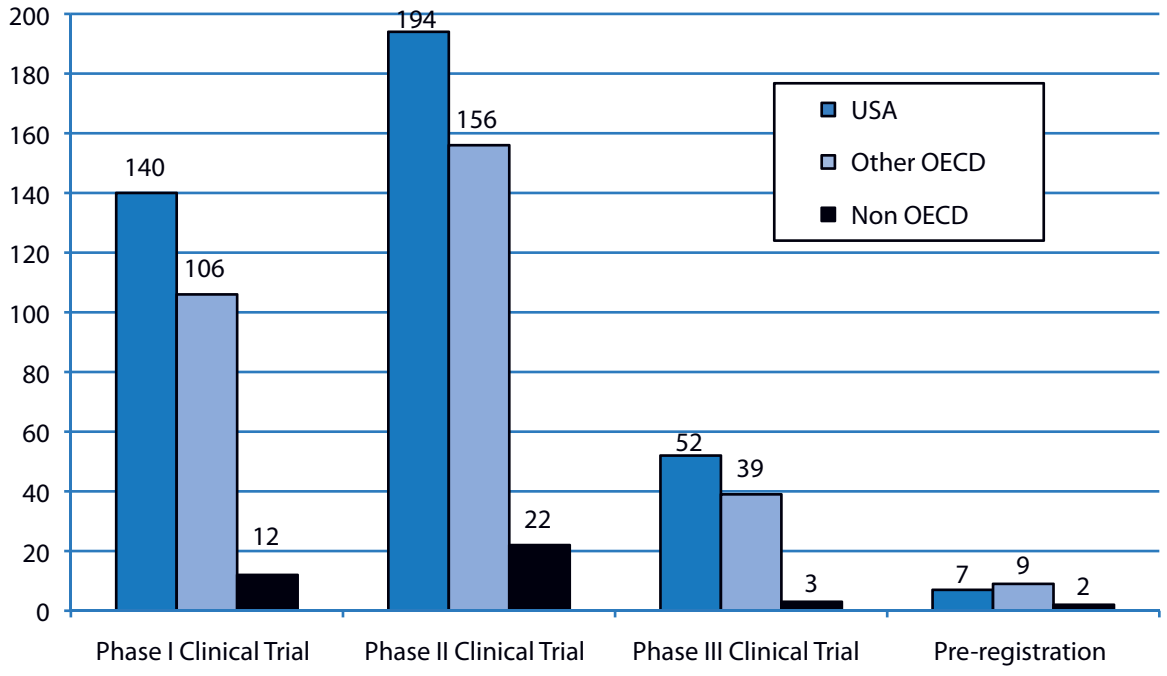
on small molecules because of the ease of dose administration and because small molecules can enter cells and pass the blood/brain barrier, reaching central nervous system targets (Cheng *et al.*, 2007).

Forecasting for health therapies

The proprietary databases Pharmaprojects and Pharmapredict include data on all pre-clinical studies, clinical trials, and pre-registrations of biotechnology compounds for most countries in the world. Additional information in these two databases on expected success rates from one phase to another, plus expected registration and launch times, permit forecasting of the number of biotechnology products that should reach the market by 2015. Information is available for 1173 preclinical studies, 724 clinical trials, and 18 products in the pre-registration process.

Figure 4 gives the number of pre-registrations and clinical trials by the location of the head office of the firm that owns the bio-NME.[23] Results are given for three regions: non OECD countries, the United States, and other OECD countries excluding the United States. In total, firms located in 25 identified countries have one or more bio-NMEs in clinical trials: seven non-OECD countries, the United States, and 17 other OECD countries. The lower number of Phase I than Phase II trials could be due to several Phase II trials for different indications for drug candidates that have passed Phase I and to cytotoxic drugs for cancer which can move directly from the pre-clinical stage to Phase II.

Figure 4. **Active clinical trials and pre-registrations by location of the originator firm for bio-NMEs as of December 2007**



Source: Authors, based on data from Informa (2007a).

Notes: 1. See Annex A, Table 28 for full data.

2. Location is defined by the head office of the originator firm.

As shown in Figure 2, American firms developed 57.8% of all biopharmaceuticals that reached the market after 2000. The American share of bio-NMEs in the pre-registration phase is 38.9%, suggesting a short-term dip in the next few years for the American share. However, the American share of products in clinical trials is approximately 55% for phases I to III.[24] This suggests that the American share of all bio-NMEs will only decline slightly over the next decade.

The major disease targets for the clinical trials consist of cancer (255 trials), infections (134 trials), cardiovascular diseases (54 trials), arthritis (28 trials), diabetes (18 trials) and asthma (11 trials).

The number of clinical trials in most countries is increasing from Phase III to Phase I, suggesting a continuing presence in biotechnology activity, whereas in other countries the pipeline is decreasing. Countries with a negative pipeline (more trials in Phase III than in Phase I) include Israel and Sweden. There are too few trials to estimate pipeline trends for Brazil, Finland, India and Malta.

Table 11 gives the type of bio-NME by phase. mAbs account for 25.1% of the total, followed by recombinant vaccines (18.6%) and recombinant therapeutics (15.6%). The remaining categories – experimental therapies and other – account for 40.7% of the total. A large majority of experimental therapies are in Phase II (54.6%) or Phase I (31.5%) trials. This indicates that there is a very strong biotechnology pipeline for these unproven or "experimental" therapies.

Research on experimental therapies is largely undertaken by small DBFs with only a few bio-NMEs in clinical trials. "Major" pharmaceutical firms (including the established biopharmaceutical firms of Amgen, Genentech and Genzyme) are defined here as firms with five or more bio-NMEs in clinical trials.[25] The majors only account for 18 of the 251 (7.2%) clinical trials or pre-registrations of experimental therapies. In comparison, the

Table 11. **Types of bio-NMEs in clinical trials or pre-registration as of June 2007**

Therapy Group	Phase I	Phase II	Phase III	Pre-registration	Total	Total share of all clinical trials
Antisense therapy	10	21	2	1	34	4.6%
Cellular therapy[1]	12	37	6	2	57	7.7%
Gene therapy	20	44	12	2	78	10.5%
Monoclonal antibody	79	78	25	4	186	25.1%
Recombinant therapeutics	24	63	22	7	116	15.6%
Recombinant vaccine	60	66	12	0	138	18.6%
RNA interference	2	3	1	0	6	0.8%
Stem cell therapy	12	7	4	0	23	3.1%
Other[2]	39	53	10	2	104	14.0%
TOTAL	258	372	94	18	742	100.0%

Source: Authors, based on data from Informa (2007a).

Notes: 1. Non-recombinant cultured mammalian therapeutic cells other than stem cells. Includes products such as dendritic cells, pancreatic islet implants, cultured wound healing products and cultured T-lymphocytes.
2. Includes gene delivery vectors, immunoconjugates, immunotoxins (toxins conjugated with mAbs), lyctic viruses and non-antisense, non-RNAi oligonucleotides.
3. Shaded rows are experimental therapies.

major pharmaceutical firms account for 89 (25.5%) of clinical trials for proven therapies using mAbs, recombinant vaccines and recombinant therapeutics.

The large number of small DBFs active in experimental therapies suggests that access to ample high-risk venture capital could be an essential factor. If true, the supply of venture capital in the life sciences (the leaders are Sweden, Denmark, Switzerland, Canada and the United States in that order) should be positively correlated with the national share of clinical trials in experimental therapies. However, there is no evidence to support a link between the supply of venture capital and the share of all clinical trials of biopharmaceuticals due to experimental therapies (see Table 12). There is no relationship with either the national share of GDP from venture capital investments in the life sciences or with the absolute level of venture capital for the life sciences in each country.[26] This could be because biotechnology firms draw on an international pool of venture capital, or because other factors, such as the number of years since establishment, determine the types of biopharmaceuticals developed by firms.

Table 12. **Share of all biotechnology clinical trials in experimental therapies, by country**

	All biotech clinical trials	Biotech clinical trials in experimental therapies	Experimental therapies share of all biotech clinical trials
Australia	14	5	35.7%
Austria	9	1	11.1%
Belgium	6	1	16.7%
Bermuda	4	0	0.0%
Brazil	2	1	50.0%
Canada	22	8	36.4%
China	11	1	9.1%
Denmark	25	5	20.0%
Finland	2	0	0.0%
France	24	8	33.3%
Germany	38	7	18.4%
India	2	0	0.0%
Ireland	3	0	0.0%
Israel	10	4	40.0%
Italy	14	4	28.6%
Japan	21	2	9.5%
Malta	1	1	100.0%
Netherlands	13	4	30.8%
Russian Federation	4	0	0.0%
South Korea	15	8	53.3%
Spain	1	1	100.0%
Sweden	6	1	16.7%
Switzerland	27	0	0.0%
United Kingdom	70	16	22.9%
United States	393	119	30.3%
Total	737	197	26.7%

Source: Authors, based on data from Informa (2007a).

Note: Includes drugs in clinical trial phases I, II, or III and pre-registration.

Forecasting for proven biopharmaceutical using Pharmapredict

Using the Pharmapredict database,[27] estimates were taken of the number of bio-NMEs expected to be registered between 2008 and 2018. The database gives information, by therapy group, on the number of drugs in different phases of development, success rates (the probability of reaching the market from Phase I, II and III clinical trials), and estimates (by quarter) for when they may reach the market.[28]

As shown in Table 13, Pharmapredict lists a total of 648 bio-NMEs in Phase I, Phase II, or Phase III clinical trials or pre-registration (Informa, 2007b). These 648 compounds were then categorized as therapeutics, vaccines, diagnostics or other. Given limitations in Pharmapredict methodologies and unavailable information, the following criteria were used to exclude some of the trials from the analysis:

- Phase I to market time was given as less than the minimum observed for Phase II to market & Phase III to market combined (2.25 years).
- Phase II to market time was given as less than minimum observed for Phase III to market (2 years).
- The estimated time to market was before 2008 or after 2018.
- Trials for experimental therapies where there was insufficient historical data to predict the registration date or the success rate.

For all biotechnology products, just over 61% had suitable data (see Table 13). This ranged from approximately 34.5% for "other" products to nearly 90% of bio-vaccines. The sizeable majority (186 products, or 75%) of the 249 products without suitable information were due to a lack of historical data for the particular biotechnology therapy (rather than an unrealistic timeline from Phase I or II to registration). Due to these exclusions, the final results underestimate the number of bio-NMEs that are likely to reach the market up to 2018.

Pharmapredict estimates that biopharmaceuticals spend an average of seven months, and all pharmaceuticals an average of ten months, between registration and market launch. Therefore, two quarters (six months) were subtracted from the estimated launch date to arrive at an estimated registration time for biopharmaceuticals. By year of estimated registration, each product was multiplied by the historical success rate for the class of bio-NME from the phase it was in (*e.g.* Phase I, II, or III).

These products were then summed to produce Figure 5, which shows the number of bio-NMEs (therapeutics, vaccines, and other) expected to reach registration between 2008 and 2018. As expected given the methodology, the number of products registered decreases to near zero for all types after 2015. There are two principal reasons for this. First, pre-clinical trials were not included in the analysis due to the focus to 2015. Some products in

Table 13. **Number and share of bio-NMEs with reliable data in Phase I-III or pre-registration**

	Therapeutics	Vaccines	Other	All biotech
Total compounds in trials	432	129	87	648
Compounds with reliable data	253	116	30	399
Percentage with usable data	58.6%	89.9%	34.5%	61.6%

Source: Authors, based on data from Informa (2007b).

Note: All results exclude formulations.

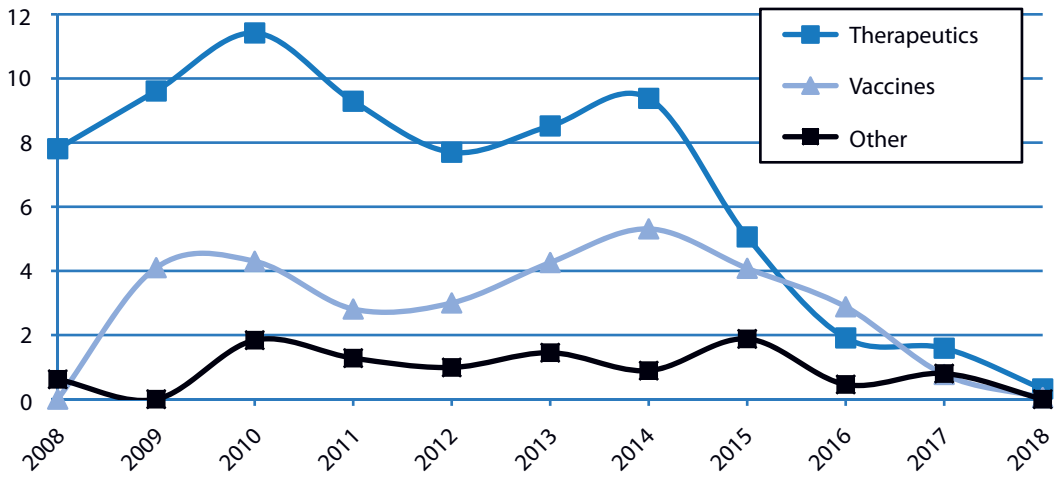
the later stages of preclinical trials, given the approximately 11.5 year average time from preclinical to registration for bio-NMEs, may be registered around 2018. Second, as noted, many experimental products omitted from the research, due to a lack of data, would not be expected to be registered until after 2015. It is important to note that, although these estimates are based on a robust historical data set, they are unable to take into account challenges (*e.g.* technical, safety, or regulatory) or unexpected successes arising during individual R&D projects. For instance, the predicted rate of 8.43 bio-NMEs reaching the market in 2008 was a small overestimate, as only 7 products reached the market.

The current estimate of the total number of bio-NMEs registrations (roughly 13 bio-NMEs per year from 2008-2015) is higher than the average of eight bio-NMEs per year between 2000 and 2007 inclusive (see Annex A, Table 27 for comparative data), but within the range of past approvals per year. There were 12 bio-NMEs registered in 1998, 2001, and 2006. If this increase in bio-NME approvals occurs, however, it does not necessarily translate into a significantly increased percentage of biopharmaceuticals as a share of all pharmaceuticals, as compared to historical trends (see the following section).

Forecasting the share of biopharmaceuticals out of all pharmaceuticals

Between 2000 and 2007, biopharmaceuticals accounted for slightly more than 12% of all pharmaceuticals (OECD, 2009b). To estimate the future share of bio-NMEs out of all NMEs, the Pharmapredict database was used. The same analysis was performed on all *non*-bio NMEs as for bio-NMEs, with one exception. The Pharmapredict data indicate that non-bio NMEs require three months longer to move from registration to market (as opposed to two quarters for bio-NMEs). Nine months were therefore subtracted from the estimated launch date to arrive at an estimated registration time.

Figure 5. **Number of bio-NMEs products expected to reach registration, by year**



Source: Authors, based on data from Informa (2007b).

Notes: 1. All results exclude formulations.

2. Other includes gene delivery vectors, immunoconjugates, immunotoxins (toxins conjugated with mAbs), lyctic viruses and non-antisense, non-RNAi oligonucleotides.

3. The steep drop off in products following 2015 is due to the methodology, and not an expected decline in biopharmaceuticals. See text for details.

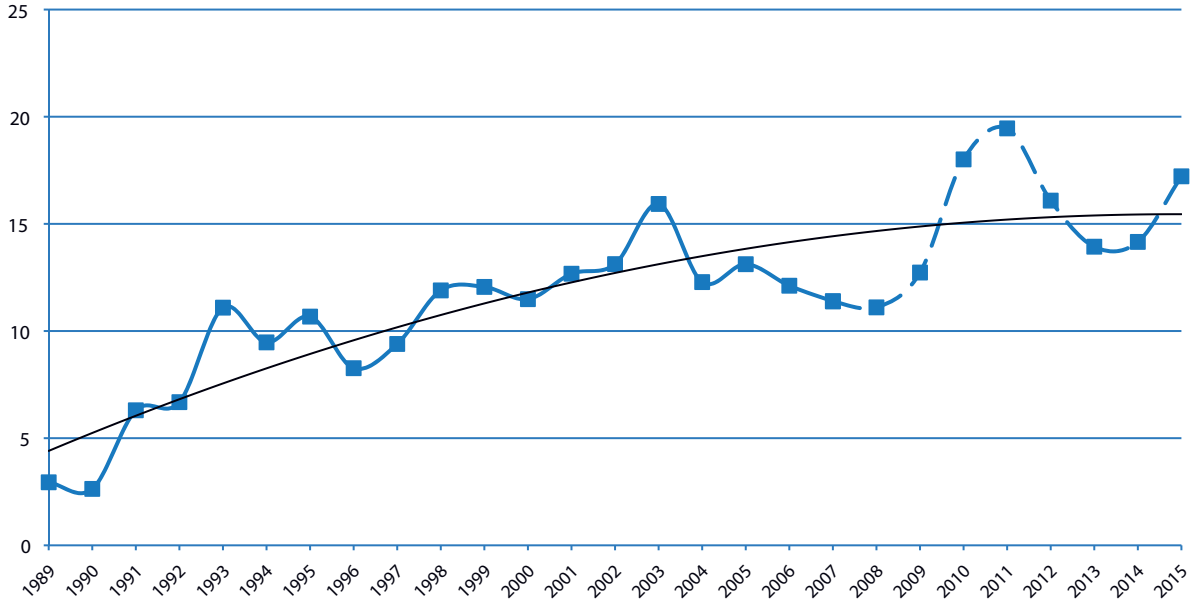
Table 14 summarizes the data used in the analysis. The same exclusion criteria were used as for bio-NMEs. A higher percentage of the data (85% as opposed to 62% for bio-NMEs) was usable in the analysis. The lower share of useable data for bio-NMEs could underestimate the bio-NME share in the future by up to 6 percentage points if the success rate for experimental biotherapies (the major cause of a lack of useable data) quickly approaches the average for other types of bio-NMEs (this is very unlikely).[29] As with the estimates for bio-NMEs, the reliable data were multiplied by the historical success rate for the relevant class of NME (*e.g.* anticancer, anti-infective, cardiovascular) by phase (*e.g.* Phase I, II, or III).

Table 14. **Number and share of Non-bio NMEs with reliable data in Phase I-III or Pre-registration**

	Phase I	Phase II	Phase III	Pre-registration	Total
Total compounds in trials	778	923	215	58	1974
Compounds with reliable data	715	766	164	37	1682
Percentage with usable data	91.9%	83.0%	76.3%	63.8%	85.2%

The results of the analysis are presented in Figure 6, which includes historical data up to 2007. While the share of biopharmaceuticals increases to 2010 – 2011, this should decrease to near historical levels afterwards. These results provide no evidence for a large surge in biotechnology drugs, or in the share of biotechnology drugs out of all drugs in the coming 5 to 10 years. Instead, the share of biotechnology drugs appears to be increasing gradually, as shown by the trendline in Figure 6.

Figure 6. **Observed (1989-2007) and Forecast (2008-2015) share of total biopharmaceuticals out of total pharmaceuticals (3 year running average), by year of first registration**



Source: Authors, based on Informa (2007a, 2007b).

Note: See Annex A, Table 27 for full information on the observed data and Annex A, Table 30 for projected data.

The only factors that could cause a significant change in biotech's share of all pharmaceuticals are either an increase in the success rate or a significant decrease in development time, as compared to non-bio-NMEs.

Although the biopharmaceutical share of all pharmaceuticals will probably remain relatively constant or only increase gradually in the foreseeable future, the real variable of interest is the effect of future biopharmaceuticals on public health. This is not possible to determine, but the HAS and *Prescrire* evaluations for therapeutic value (see Tables 4 and 5) show that biopharmaceuticals offer greater therapeutic value than other pharmaceuticals. The large number of experimental biopharmaceuticals, offering new modes of action, suggests that the future stream of biopharmaceuticals should provide substantial therapeutic advantages over existing therapies.

Forecasting for experimental therapies

It is impossible to generate an accurate historical success rate for experimental therapies because there are very few of these products on the market. Assuming, however, that development times and success rates in these areas will roughly mirror that of more established biotherapeutics, some products currently in Phase II and Phase III clinical trials could reach the market before 2015. The probability of this occurring would increase both as technical problems related to delivery and safety are overcome, and as more products come to market allowing regulatory agencies to gain more experience in the approval of such products.

Cell and tissue engineering forecasting

There are a number of cell and tissue engineering products in phase II (37) and III (6) clinical trials and two in pre-registration. Given the relatively large number of these products already on the market, several additional products should appear on the market by 2015. It is also possible that a number of non-invasive tissue engineering products, such as wound coverings, will be marketed by 2015.

Stem cell forecasting

Almost all of the stem cell trials in phase II or phase III (and therefore with a reasonable chance of reaching the market by 2015) use adult stem cells and are aimed at regenerating bodily tissue, similar to the one stem cell product already on the market. The other four are aimed at heart related diseases such as ischaemia and myocardial infarction.

Further research into the manipulation and use of embryonic stem cells could conceivably produce large therapeutic advances. However, even if rapid and successful development occurs, most of these products would arrive on the market after 2015 unless obvious efficacy and safety was apparent. In addition, recent advancements that can turn skin cells into cells behaving like embryonic stem cells may help skirt ethical concerns related to the destruction of embryonic stem cells and encourage further research in the area.

Gene therapy forecasting

Many experts believe that gene therapy will play a significant role in future medical treatment. A report by the Japanese National Institute of Science and Technology Policy (NISTEP, 2005) predicted that gene therapy for localized atherosclerotic lesions will be available in 2015 with gene therapies for familial hypercholesterolemia, diabetes mellitus, and cancer following in 2016 to 2018 (NISTEP, 2005). Given the strong research pipeline

for gene therapies (there are 44 gene therapies in Phase II, 12 in Phase III, and two in pre-registration) this may prove true, but historically, with the exception of China, these treatments have been totally unsuccessful in receiving regulatory approval.

Antisense therapy forecasting

In 2000, shortly after the release of the first and only antisense drug on the market, a report predicted that, "[t]he target year for antisense therapeutics achieving their remaining potential is 2010, although some among them may actually realise their potential earlier (Jain, 2000)." Presently, this forecast appears rather optimistic since no other anti-sense therapies have been approved, and none of the antisense therapies are beyond phase II clinical trials. This would indicate, given an average of 55 months from the start of phase III trials to market entry for biotech products,[30] that few, if any anti-sense drugs will reach the market prior to 2010.

RNA interference forecasting

Given the relative newness of RNAi technology, there has been a great deal of activity in the area. With one product in Phase III trials and three in Phase II trials, it is conceivable that some products may receive regulatory approval by 2015. If this is indeed the case, a significant increase in RNAi therapies in clinical trials would be likely.

Nanobiotechnology forecasting

Analysts anticipate that the nanomedicine market will experience strong growth to 2015; however estimates of the actual size vary greatly due to measurement and definitional challenges. One study predicts the nanomedicine market to grow to USD 53 billion in 2011 and continue increasing to USD 110 billion in 2016, of which pharmaceuticals, diagnostics, and medical supplies and devices will make up USD 82 billion, USD 12.3 billion, and USD 16.2 billion, respectively (Global Information, 2007). Another study estimates the market to be much smaller, estimating that the combined market for nanotechnology in the life sciences (including environmental sciences and agriculture) will reach only USD 3.4 billion by 2010, 60% of which will be in medical applications (BCC Research, 2005a). Neither of these estimates identifies the nanobiotech share, but it is likely that the segment will also experience strong growth over the same period.

Given the small number of products in clinical trials and the average timescale needed to reach the market from clinical trials (7.5 years from end-phase I and 4.5 years from end-phase II), it is very unlikely that there will be more than one, or possibly two, nanoformulations of biotechnology therapeutics arriving on the market by 2015. Even this is highly dependent on the success of the three products in clinical trials at present and with immature regulatory guidelines for nanobiotech products, this is doubtful. There may be some other non-formulated nanobiotherapuetics reaching the market, but, this is unlikely to be a large number, and it is impossible to give an accurate estimate due to lack of data.

Synthetic biology

Synthetic biology is a new area of research and, at present, no products have even reached clinical trials. It is therefore very unlikely that any synthetic biology therapeutic will reach the market by 2015. A more likely outcome is that a few drugs, in part based on synthetic biology principles, could be "pharmed" from synthetic cells and available as soon as 2009 or 2010 (Zimmer, 2006). An example is artemisinin.

Forecasting for small molecule therapeutics

There are no databases that provide data on the use of biotechnology in the manufacture, discovery, clinical trials, or prescribing patterns for small molecule drugs. Consequently, it would be very difficult to accurately predict the effect of biotechnology on the development of small molecule drugs up to 2015. The only available information is from interviews with pharmaceutical firm executives or from small surveys.

An unpublished German survey of biotechnology firms in 2006 found that 27% of firms active in the health sector were using biotechnology for target validation for NCEs in development and 33% were using biotechnology for target validation for diagnostics development. The results cover both diagnostic and pharmaceutical firms combined, so the actual percentage when limited to pharmaceutical firms alone is likely to be much higher.[31]

Interviews by Michael Hopkins with three large pharmaceutical firms found a range in approaches to the use of biotechnology in small molecule drug development. An executive from one firm commented that "Everything in the pipeline is touched by genomics one way or another", although some of the products could have still been developed without the use of genomics. One of the other firms is using biotechnology in small molecule development, but has so far invested less in its use.

Due to a lack of consistent information, it is impossible to forecast the percentage of small molecule drugs that will receive market approval, between 2007 and 2015, for which biotechnology was used in manufacturing, drug development, or clinical trials. Nevertheless, biotechnology is very likely to be increasingly used somewhere in the development process for almost all NMEs. At some point in the near future, the current division between biotechnology firms and biotechnology drugs, and other firms and other types of drugs, is likely to become meaningless, with biotechnology playing a significant role in the development of all drugs. At this point all value added in the pharmaceutical sector will be partially dependent on biotechnological knowledge.

Potential

Biopharmaceuticals will not account for 100% of pharmaceuticals by 2015 or even by 2030, due to the ongoing production of both generic and new small molecule drugs. Consequently, biopharmaceuticals will not account for 100% of employment or revenues in the pharmaceutical sector. However, the rapid increase in the use of biotechnological knowledge in small molecule drug development suggests that the "pharmaceutical" sector by 2030 will more accurately be described as the "biopharmaceutical" sector.

An alternative non-economic measure of the potential of biotechnology is to assess its impact on public health. One method is to estimate the target population of people with diseases that are treatable with current biopharmaceuticals or which could be treated with biopharmaceuticals that are expected to reach the market by 2015. This section provides some preliminary results for current treatments.

Table 15 gives the rate for specific diseases that are already treatable using biopharmaceuticals on the market plus an estimate of the potential population of patients in Australia, Canada, Japan, the United States, and the 25 member states of the European Union in 2003, with a total population of 960 million in 2003. The estimates are limited to these countries because of data availability and because these countries have the financial resources to pay for biopharmaceuticals. The estimates in bold are for chronic diseases and are based on prevalence rates, while the estimates in italics are for diseases that are treated over the short term and are based on incidence rates.

The largest market for biopharmaceuticals for chronic diseases is for Type II diabetes, with an estimated 56.5 million patients, followed by asthma with 54.8 million. The chronic diseases include a number of rare orphan diseases with less than 100 000 patients.

Biopharmaceuticals are frequently not the first line treatment for many of the chronic diseases listed in Table 15, such as Type II diabetes, asthma, psoriasis, and rheumatoid arthritis, nor for many acute diseases, including cancer. Consequently, the actual population of potential patients will be much lower than the total populations listed in the table. Nevertheless the results highlight the range of available treatments using biopharmaceuticals and their success in treating several severe orphan diseases.

Table 15. **Number of patients potentially treatable with biopharmaceuticals**

	Number of patients in selected developed countries	
Diseases	Number in thousands	Rate per 1000 population
Diabetes, Type II[1]	56 492.9	58.80
Asthma[1]	54 763.5	57.00
Age-related Macular degeneration[1]	35 548.2	37.00
Osteoporosis[1]	35 327.3	36.77
Infarction, myocardial[1]	26 690.0	27.78
Infertility[1]	21 809.3	22.70
Psoriasis[1,7]	14 613.2	15.21
Anaemia, general[1,8]	14 401.8	14.99
Arthritis, rheumatoid[1]	8 896.7	9.26
Virus, hepatitis-C[1]	7 061.6	7.35
Virus, hepatitis-B[1]	5 313.0	5.53
Foot Ulcer, diabetic[2]	4 784.6	4.98
Crohn`s disease[1]	1 767.8	1.84
Multiple sclerosis, relapsing-remitting[1]	1 373.9	1.43
Ankylosing spondylitis[1]	1 239.4	1.29
Hypoglycemia[1]	960.8	1.00
Thrombosis, deep vein[6]	*768.6*	*0.80*
Cancer, Breast[1]	*720.6*	*0.75*
Angina, unstable[2]	576.5	0.60
Virus, cytomegalovirus[2]	384.3	0.40
Lyme disease[1]	*355.5*	*0.37*
Arthritis, rheumatoid, juvenile[3]	240.2	0.25
Cancer, Lymphoma[1]	*211.4*	*0.22*
Cancer, Lymphoma, non-Hodgkin`s[1]	*192.2*	*0.20*
Cancer, Melanoma[1]	*192.2*	*0.20*
Diabetes, Type I[1]	124.9	0.13
Cancer, Kidney[1]	*115.3*	*0.12*
Cancer, Leukemia[1]	*105.7*	*0.11*
Prader-Willi Syndrome[1,3]	85.5	0.089
Cancer, Thyroid[1]	*73.0*	*0.076*
Hemophilia[1]	71.1	0.074
Cystic fibrosis[1,3]	69.2	0.072
Cervical dystonia[2]	54.8	0.057
Cancer, Myeloma[1]	*52.8*	*0.055*

Table 15. **Number of patients potentially treatable with biopharmaceuticals** *(continued)*

Thrombocytopenia, general[1]	*52.8*	*0.055*
Acromegaly[9]	48.0	0.050
Growth hormone deficiency[1]	44.2	0.046
Pompe`s disease[5]	*24.0*	*0.025*
Fabry`s disease[4]	17.3	0.018
Cancer, Kaposi`s sarcoma[3]	16.3	0.017
Gaucher`s disease type I[1]	12.5	0.013
Colitis, ulcerative[1]	*11.5*	*0.012*
Osteopetrosis, malignant[3]	7.2	0.0075
Mucopolysaccharidosis type I[1]	4.3	0.0045
Mucopolysaccharidosis type VI[3]	1.5	0.0016
Chronic granulomatous disease[1]	1.1	0.0011

Sources: 1. *www.wrongdiagnosis.com* 2. *www.clinicalevidence.com* 3. *www.orpha.net*
4. *www.ec.europa.eu* 5. *www.rarediseases.org* 6. *www.emedicine.com*
7. *www.fda.gov* 8. *www.who.int* 9. *www.pituitary.org.uk*

Note: Shaded rows are prevalence rates and non-shaded rows are incidence rates. See *www.wrongdiagnosis.com*.

Health therapy summary

Table 16 summarizes the main developments in health therapies that are expected by 2015.

Table 16. **Main short-term trends in biopharmaceuticals to 2015**

	Forecast outcomes
Employment	Current pharmaceutical employment of 1.43 million in the OECD is likely to continue to decline slowly. Biotechnology will increasingly have a significant effect on pharmaceutical employment due to its use in the manufacture, development and prescribing practices for small molecule drugs.
New pharmaceuticals	Between 1998 and 2007, biopharmaceuticals accounted for approximately 12.6% of all NMEs receiving market approval. This could increase to an average of 14.8% between 2008 and 2015. In absolute terms, the number of NME biopharmaceuticals that obtain market approval should increase from an average of 8 per year between 2000 and 2007 to 13 per year between 2008 and 2015. There is a very strong pipeline for experimental biopharmaceuticals, with most of these compounds in Phase I (28%) or Phase II (57%) clinical trials, but these therapies are likely to have low success rates. The main disease targets for future biopharmaceuticals are cancer (34.8% of clinical trials) and infections (18.2% of clinical trials).
Biotechnology "advantage"	A higher share of biopharmaceuticals than small molecule therapeutics offers a significant therapeutic advance over existing therapies. Although the biopharmaceutical "advantage" has declined since 2000, new experimental therapies in clinical trials could improve future therapeutic performance.
American dominance	American pharmaceutical firms developed 59% of all biopharmaceuticals between 2000 and 2007. This share is expected to fall slightly to 54% between 2008 and 2015.
Small molecule drugs	By 2015 the majority of small molecule drugs in development are likely to depend, in part, on the use of biotechnology for discovery (particularly for target identification), to improve the efficiency of clinical trials (application of pharmacogenetics for safety), or to affect prescribing practices. The widespread use of pharmacogenetics to identify respondent and non respondent subgroups in clinical trials is unlikely to occur before 2015.
Experimental therapies	Experimental therapies include cell and tissue engineering, stem cells, gene therapies, antisense, RNAi, nanobiotechnology (drug delivery) and synthetic biology. Several new tissue engineering products are expected to reach the market by 2015, but most other experimental therapies are likely to produce only a few products that reach the market by this date (gene therapy, approved drugs manufactured using synthetic biology) or no products (antisense, RNAi, nanobiotechnology).

Diagnostics, bioinformatics, and pharmacogenetics

Current status of diagnostics

Biotechnology, in addition to being used to develop therapeutics, has made substantial contributions to diagnostics.[32] Biotechnology based diagnostics are used to identify both genetic 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.

In-vivo diagnostics

In-vivo diagnostics require the, "insertion of a substance (like a contrast medium) into the body through the skin or a body orifice (Universidad de Grenada, 2001)." Tests detect pathogenic agents or antibodies to diagnose infectious diseases. Other tests can distinguish cancer cells from normal cells.

Thirteen biotechnology *in-vivo* diagnostics have been registered or obtained market approval and eleven are in clinical trials (see Table 17). Of the thirteen approved or registered products, eleven were originated by American companies and three by a Cuban institute (Center of Molecular Immunology). Eight of the approved *in-vivo* products are for the diagnosis of cancer, two for coronary functions, and the others for diabetes, hypoglycaemia and infection.

Originators of diagnostic trials come from a wide geographic range. Four of the ten trials are being undertaken by American companies, three by British firms, one by Danish, one by Brazilian and one by a Japanese enterprise. Of those in clinical trials, seven are in preclinical phase, two are in phase I and one is in phase II. The vast majority of the *in-vivo* diagnostics in clinical trials aim at detecting cancer.

In-vitro *diagnostics*

In-vitro diagnostics (IVD) include any diagnostic procedure which is conducted outside of the body. 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.

Table 17. **List of biotechnology-based *in-vivo* diagnostics – as of March 2008**

Scientific name	Developer company	Country	Diagnosis
Diagnostics with market approval or registration			
arcitumomab	Immunomedics	USA	Diagnosis, cancer
capromab pendetide	Cytogen	USA	Diagnosis, cancer
glucagon, Lilly	Eli Lilly	USA	Diabetes, general
glucagon, ZymoGenetics	ZymoGenetics	USA	Hypoglycaemia
Tc 99m votumumab	Intracel	USA	Diagnosis, cancer
ibritumomab tiuxetan	Biogen Idec	USA	Cancer, lymphoma, non-Hodgkin`s
imciromab	Centocor	USA	Diagnosis, coronary
ior-cea1	Center of Molecular Immunology	Cuba	Diagnosis, cancer
ior-egf/r3	Center of Molecular Immunology	Cuba	Diagnosis, cancer
satumomab pendetide	Cytogen	USA	Diagnosis, cancer
sulesomab	Immunomedics	USA	Diagnosis, infection
thyrotropin alfa	Genzyme	USA	Diagnosis, cancer
nimotuzumab	Center of Molecular Immunology	Cuba	Diagnosis, cancer
Diagnostics in clinical trials	**Originator company**		
Preclinical phase			
AGT-100	ArmaGen Technologies	USA	Diagnosis, CNS
anti-TEM7 MAb, Kirin	Kirin Pharma	Japan	Unspecified
COU-1 antibody, NatImmune	NatImmune	Denmark	Diagnosis, cancer
HuHap-1/78, Wyeth	Wyeth	USA	Diagnosis, hepatic
MFECP1	Cancer Research Technology	UK	Cancer, general
MUC-1 aptamers	Cancer Research Technology	UK	Unspecified
TAPET vectors	Vion Pharmaceuticals	USA	Unspecified
Phase I			
hu3S193	Recepta biopharma	Brazil	Cancer, colorectal
SM3	Cancer Research Technology	UK	Diagnosis, cancer
Phase II			
depelestat	Dyax	USA	Cystic fibrosis

Source: Authors, based on Informa (2007a).

Note: Some of the diagnostics listed have therapeutics uses as well.

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* fertilization (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).

Table 18 lists some examples of genetic and immunological diagnostic technologies using modern biotechnology.

Unlike *in-vivo* diagnostics which are closely regulated, IVD regulation is considerably less demanding because they are not traditionally seen as damaging to health. Without such stringent registration guidelines, it is difficult to know the exact number of IVD products using biotechnology, but estimates do exist.

Table 18. **Examples of diagnostic techniques using modern biotechnology**

Type of Technology	Technique	Example(s) of diagnosis/ risk factor[1]
Genetic tests	Target: DNA/RNA	
Blotting methods[2,4]	Identifies similar macromolecules, e.g. sets of DNA or RNA fragments, that are separable by gel electrophoresis.	Anaemia Huntington's disease
DNA methylation[4]	Measures the amounts of 5-methylcytosine which arises from the methylation of cytosine bases. The methylation status of DNA corresponds to its functional status.	Cancer
DNA microarray[4]	A glass slide or bead containing microscopic DNA samples in an orderly pattern are treated with complimentary-DNA and used to detect the relative expression level of each gene.	Cancer
Fluorescent In Situ Hybridization[4]	A procedure involving the use of fluorescent DNA probes to locate in a tissue section specific regions of DNA in the chromosomes.	Williams-Beuren syndrome
Nuclear probes[4]	A procedure involving the use of radioisotope labelled oligo- or polynucleotide to detect complementary sequences.	Cancer Lymphoma of Burkitt
Polymerase Chain Reaction (PCR)[4]	A specific sequence of nucleotides within a double-stranded DNA is amplified to test for disease and detect rare mutations.	Anaemia Infectious diseases Huntington's disease AIDS/HIV
Immuno-diagnostics	Target: proteins (antibody, antigens…)	
Blotting methods[3,4]	Identifies similar macromolecules, *e.g.* mixtures of intact proteins, that are separable by gel electrophoresis.	Hepatitis Infectious diseases AIDS/HIV
Enzyme-Linked ImmunoSorbent Assay[4]	The measurement of specific biochemical substances that depends upon the specificity and high affinity shown by suitable antibodies for their complimentary antigens, which are labelled with an enzyme as an indicator.	Prostate cancer Infertility Infectious diseases AIDS/HIV
Imaging agents[5]	The production of an image of all or part of the body to examine gene expression or proteomic data.	Cancer
Indirect Immuno-Fluorescence Assay[4]	An antigen or antibody is made fluorescent by conjugation to a fluorescent dye and then allowed to react with its complimentary antibody or antigen in a sample.	Lyme disease
Monoclonal antibodies[6]	Detect particular antigens by analyzing the immunoglobulin secreted by a single clone of antibody producing cells which are only able to react with a single specified antigen.	Rheumatoid Arthritis Cancer Hepatitis Diabetes type I
Radioimmuno-precipitation[4]	Precipitates a protein out of a mixture by reaction with a specific radioisotope labelled antibody or antigen.	AIDS/HIV

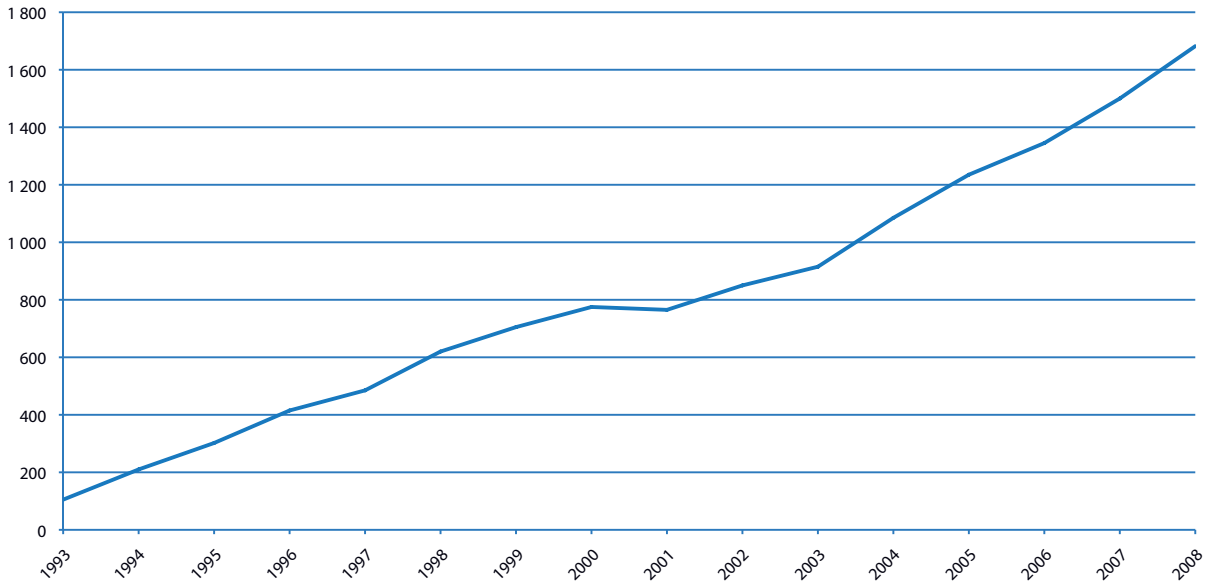
Source: Authors, with definitions adapted from the Oxford (2007).

Notes: 1. The list of "example(s) of diagnosis/risk factor" is not exhaustive.
2. Blotting methods in genetic testing are southern blot and northern blot.
3. Blotting methods in immunodiagnostics are western blot, south-western blot and far western blot.
4. *In-vitro* diagnostic technique.
5. *In-vivo* diagnostic technique.
6. Can be both an *in-vivo* and an i*n-vitro* diagnostic technique.

As shown in Figure 7, genetic tests are available for over 1 600 diseases according to GeneTests (2008). 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, 2007c).

Figure 7. **Number of diseases for which genetic testing is available as reported to GeneTests, by year**



Source: Authors, based on GENETests (2008).

The 2007 report "*Consequences, opportunities and challenges of modern biotechnology for Europe*" estimated revenues from biotechnology-based diagnostics and IVDs for 2004, by region of the world (see Table 19). The total IVD market was estimated at USD 27.6 billion of which:

- molecular diagnostics accounts for 5% (USD 1.4 billion),
- immunochemical diagnostics accounts for 24% (USD 6.6 billion),
- other (non-biotech) diagnostics account for 71% (USD 19.6 billion) (ETEPS NET, 2006).[33]

As shown in Table 19, biotech-based IVDs represent an important share of the entire IVD market, ranging from 37% in the United States, to 29% in the EU-5, and 21% in all other countries. The United States spent slightly more on biotechnology based IVDs than all other countries combined, representing 51% of all biotech IVD revenues, while the EU-5 accounted for 26% of global revenues and other countries for 23%.

Table 19. **Estimate of biotechnology-based diagnostics and *in-vitro* diagnostics revenues – 2004**

	A	B	B/A
	IVDs (USD billions[2])	Biotechnology-based IVDs (USD billions[2])	Share of biotech in IVDs
EU-5[1]	7.2	2.1	29%
USA	11.6	4.3	37%
Others	8.8	1.8	21%
Total	27.6	8.2	30%

Source: JRC (2007).

Notes: 1. Includes France, Germany, Italy, Spain, and the United Kingdom.
2. Converted from original using 1 Euro = 1.24333 USD in 2004, *www.industrie.gouv.fr*, accessed 13 August 2007.

Medical Product Outsourcing (2006) profiled the 15 leading IVD manufacturers for 2005. These 15 firms represent an estimated 77.8% (USD 24.6 billion) of sales of the USD 31.5 billion global IVD market in 2005 (see Table 20).[34] Unfortunately, the data do *not* differentiate between biotech diagnostics and other types of diagnostics. Although the leading firm, Roche Diagnostics, is Swiss, nine of the top 15 firms are based in the United-States. American firms account for 41.2% of global IVD sales. Of the other firms, three are based in Japan, one in Germany, and one in France.

Table 20. **Leading *in-vitro* diagnostic companies – 2005**

Company/Origin country	2005 IVD Sales (USD billions)	IVD Sales 2002-2005 (% change)	Total 2005 Company Sales (USD billions)	IVD as % of Total Business (2005)
Roche Diagnostics – Switzerland	6.3	21%	27	23%
Abbott Laboratories – USA	3.8	41%	22.3	17%
Bayer Diagnostics – Germany	2.5	19%	32	8%
Becton, Dickinson and Co. – USA	2.5	32%	5.4	46%
Beckman Coulter – USA	1.9	27%	2.4	79%
Dade-Behring – USA	1.7	31%	1.7	100%
Ortho-Clinical Diagnostics – USA	1.4	40%	1.4	100%
bioMérieux – France	1.2	29%	1.2	100%
Sysmex – Japan	0.7	102%	0.7	100%
Bio-Rad Labs – USA	0.6	36%	1.2	52%
Arkray – Japan	0.5	N/A1	0.5	100%
Diagnostic Products – USA	0.4	N/A1	0.4	100%
Olympus America – Japan	0.4	N/A1	8.3	5%
Cytyc – USA	0.4	N/A1	0.5	71%
Gen-Probe – USA	0.3	N/A1	0.3	100%
TOTAL	24.6	N/A1	105.3	23%

Source: Authors, based on Medical Product Outsourcing (2003, 2006).

Note: 2002 data not available.

Nearly half of the leading 15 IVD companies are specialized only in IVD. These dedicated firms tend to be small however, accounting for only 19.7% of global sales. In contrast, the top three firms account for 40% of global IVD sales. All of the top 10 firms remained in the top 10 from 2002 to 2005, and all of them increased their sales over the time period.

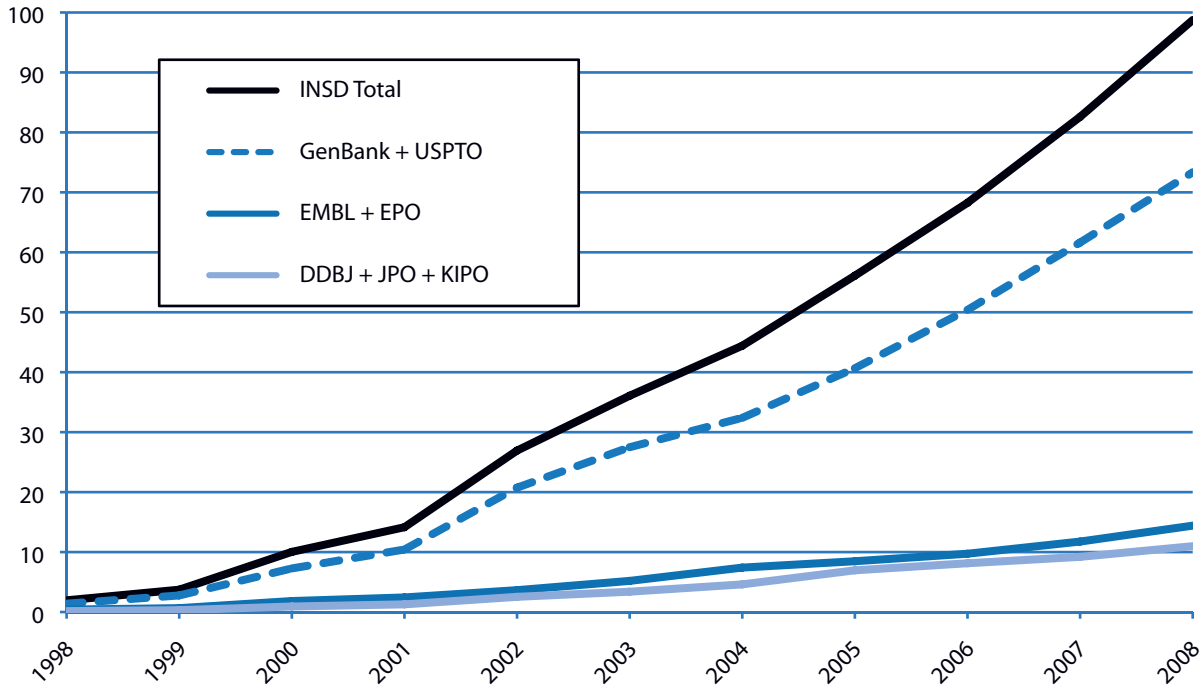
Current status of bioinformatics

Bioinformatics facilitates the practical use of information from complex biological data. According to the OECD, this involves the "creation of extensive electronic databases on genomes, protein sequences, etc. Secondarily, it involves techniques such as the three-dimensional modelling of biomolecules [including systems biology[35]] (OECD, 2005a)."

The worldwide bioinformatics market was estimated at USD 1.02 billion in 2002 (BBC Research, 2005b), though this may be highly influenced by definitional issues. In 2004, it was estimated that USD 775 million was spent on informatics for drug development and that figure would increase to over USD 1 billion in 2008 (Lawrence, 2005).

Bioinformatics are increasingly powerful, allowing researchers to garner more knowledge about more complex organisms and systems. From its foundations in the 1980s through the 1990s, bioinformatics involved the creation and management of databases containing experimental genomic and proteomic data, along with the full genome of some cellular

Figure 8. **Billions of DNA base pairs included in INSDC, 1998 to 2008**



Source: Authors, based on DDBJ (2009).

Notes: 1. USPTO = United States Patent and Trademark Office; EMBL = European Molecular Biology Laboratory; EPO = European Patent Office ;DDBJ = DNA Data Bank of Japan; JPO = Japan Patent Office ; KIPO = Korean Intellectual Property Office

2. KIPO entries only began in 2008.

organisms (today more than 100 are available). Researchers use these databases coupled with bioinformatics tools (*e.g.* ThermonucleotideBLAST) to compare their research results with known DNA, RNA, and protein sequences and to identify the function of some individual genes and proteins. Today, there are hundreds of databases available[36] many of which contain knowledge created from the analysis of earlier databases in areas such as protein function sites, protein interactions, and ortholog (ancestor) groups (Kanehisa and Bork, 2003).

In addition to numerous privately established databases in universities and the private sector, in the mid-1980s the International Nucleotide Sequence Database Collaboration (INSDC) was created, allowing free and unrestricted access to data (both human and non-human) from GenBank in the United States, the European Molecular Biology Laboratory (EMBL), and the DNA Data Bank of Japan (DDBJ). In August 2005, the INSDC reached 100 gigabases of RNA and DNA data (NCBI, 2007; USNLM, 2005). Since then, the number of DNA base pairs has grown from over 45 million entries to nearly 100 million by the end of 2008 (see Figure 8). Large scale biobanks[37] have also been established in a number of countries including, Australia, Canada, Estonia, Iceland, Japan, Latvia, Sweden, and the United Kingdom.[38] It is hoped that analyses of these datasets will improve the prevention, diagnosis, and treatment of a wide range of illnesses.

In addition, a number of public and private entities provide bioinformatics design tools. For example, companies provide design programs which facilitate the design of large and small DNA fragments, the optimization of expression in desired hosts, the construction of DNA from building blocks or the analysis of peptide sequences (DNA 2.0, 2007; Innovagen, 2007). A number of online bioinformatics tools are also available for designing PCR primers, which are required to identify the DNA sequence to be amplified during PCR.[39] While some of these tools are subject to fees, some are offered for free by companies that propose complementary, for-fee, services, and many are provided online free of charge by non-commercial entities.

Many of these tools underpin the rapidly growing genome synthesis industry. At present, there are commercial companies in over 18 countries that offer synthesised DNA sequences, and there are many more with universities and private and public laboratories that have the same capability.

The continued development of bioinformatics simultaneously helps advance and depends on two other technologies: genome sequencing and pharmacogenetics and genomics.

DNA sequencing

DNA sequencing "is the determination of the order of the nucleotides (the base sequence) in a DNA molecule (NCBI, 2004)." It is one of the key technologies necessary to populate bioinformatics databases with genetic information. Advances in technology have significantly reduced the cost and time of sequencing. The Human Genome Project, begun in 1990, was completed in 2003 two years ahead of schedule and USD 300 million dollars below budget. Many experts have attributed this success with the development of faster and cheaper sequencing machines and methods, such as shotgun sequencing.

Over the past decade these technologies have led to a 500-fold increase in productivity, measured in the number of base pairs sequenced per person per day, and a cost reduction over three orders of magnitude, from USD 1 to USD .001 per base pair. This corresponds to a doubling of productivity every 2 years (Carlson, 2007). Although full genome sequencing remains time-consuming and expensive, it is now possible to sequence all *known* human genes for around USD 1 000 (Herper and Langreth, 2007). The race is on however for full

genomes. The Archon X Prize for genomics is offering a USD 10 million prize to the first team to sequence 100 human genomes at a cost of less than USD 10 000 per genome in less than 10 days. The hope is that this will catalyze the development of sequencing technologies that reduce time and cost (Archon X-Prize, 2007).

Current status of pharmacogenetics

Pharmacogenetics is "the study of the effects of variations in DNA sequence (genetic differences) on drug response, in terms of both metabolism (pharmacokinetics) and action (pharmacodynamics) of the drug delivered (OECD, 2007d)."[40] Pharmacogenetics, which relies heavily on the identification of biomarkers, can affect every phase of drug research and development (target identification, selection of clinical trial subject, etc.) and prescription practices.

The OECD has identified three ways in which pharmacogenetics is 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, 2007d)."

The global pharmacogenetics market was estimated at USD 1.24 billion in 2004 (39.2% of which was for diagnostics) and expected to grow at 24.5% per year to 2009 (BBC Research, 2005c). However despite this activity, less than a dozen pharmacogenetic testing products were on the market in 2007 (OECD, 2007d) (see Table 21 for some examples).

The widespread use of pharmacogenomics and pharmacogenetics could lead to personalized medicines, where the chemical and biological composition, as well as the dosage of drugs, is tailored to an individual's genome. There are a number of potential benefits to the application of these technologies development and delivery:

- Decrease drug development time and cost
  - Encourage drug failure earlier in the development process
  - Smaller, targeted clinical trials
- Decreased drug approval times
- Personalized (*i.e.* more effective) dosages
- Fewer adverse drug reactions (ADRs)
- Potential to decrease overall healthcare expenditures

There are numerous challenges in several domains that are influencing the large-scale development of pharmacogenetics:

- ***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.

Table 21. **Examples of pharmacogenetic tests**

Disease	Test	Positive Result Recommendation
Breast cancer	High levels HER2 RNA or protein	If present, prescribe trastuzumab (Herceptin)
Chronic myeloid lukemia	Mutated bcr/abl gene	If present, prescribe imatinib (Glivec, Gleevec)
Maturity-onset diabetes of the young	Altered KATP gene	If present, prescribe sulphonylurea
Venous thrombosis	Mutated factor V Leiden gene	Avoid prescribing oral contraceptives, as they may trigger venous thrombosis
HIV	Variations in HLA-B*5701 & Hsp70-Hom genes	Avoid treatment with abacavir as it may cause fever, rashes, digestive difficulties & breathing problems

Source: The Royal Society (2005).

- ***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.[41] 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 the work of The International Conference on Harmonisation (ICH). The ICH, which comprises the 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.[42] 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, non-Caucasian ethnic groups and women are under-represented in clinical trials (Murthy *et al*., 2004; OECD, forthcoming).

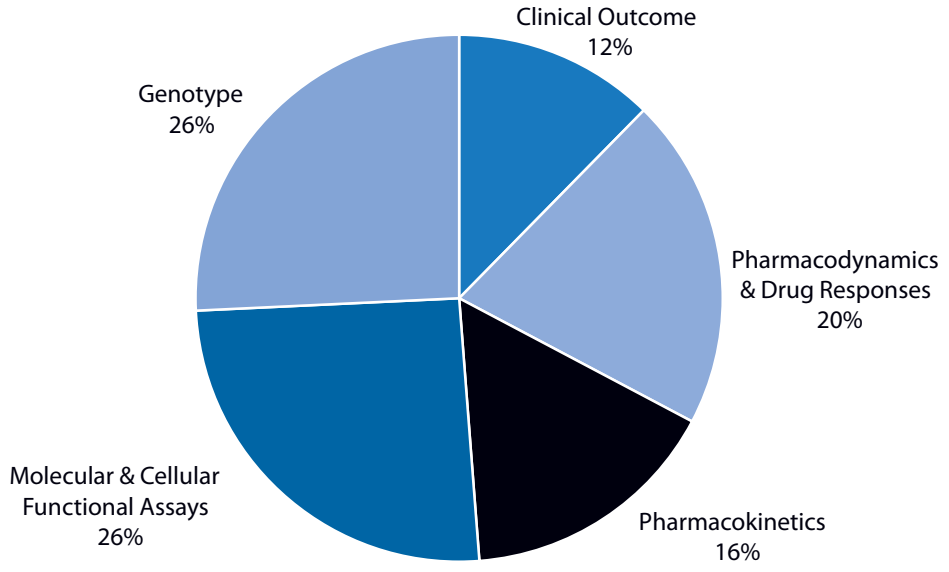
- ***Lifestyle choices*** – Not enough is known about the interaction between genetics and lifestyles (*e.g.* exercise, diet, alcohol consumption and smoking) as a factor in how individuals respond to medicines.

The PharmGKB database (*https://www.pharmgkb.org/*) aims to push forward pharmacogenomic research by collecting information that can be used to establish the link between drugs, diseases, and genes. As of December 19, 2007, the database had compiled information on 529 drugs whose effect was influenced by a specific gene variant. Of the numerous genes identified, 26 have been identified as "very important" or "of particular relevance to Pharmacogenetics and Pharmacogenomics" (PharmGKB, 2007). Some reviews have pointed out the difficulty in replicating evidence for gene association. A study of more than 600 positive associations between gene variants and diseases, of which 166 have been studied three or more times, showed that only six were consistently replicated (Hirschhorn *et al*., 2002).

A detailed analysis of the PharmGKB database, performed by the authors, identified 6 532 gene-drug links. As shown in figure 9, 12% were for clinical outcomes (*e.g.* efficacy and toxicity), 20% for pharmacodynamics and drug response (*e.g.* target, mechanism of drug reaction, and response), 16% for pharmacokinetics (*e.g.* absorption, distribution, metabolism, and excretion), 26% for molecular and cellular functional assays (*i.e.* altering molecular test results), and 26% for genotype (*i.e.* inherited genetic information).

The analysis also identifies the year of identification of each of the drug-gene links, by using the first relevant publication in the database. Despite several years in which the number of identifications declined,[43] since the early 1990s the number of identified gene-drug links has soared (see Figure 10).

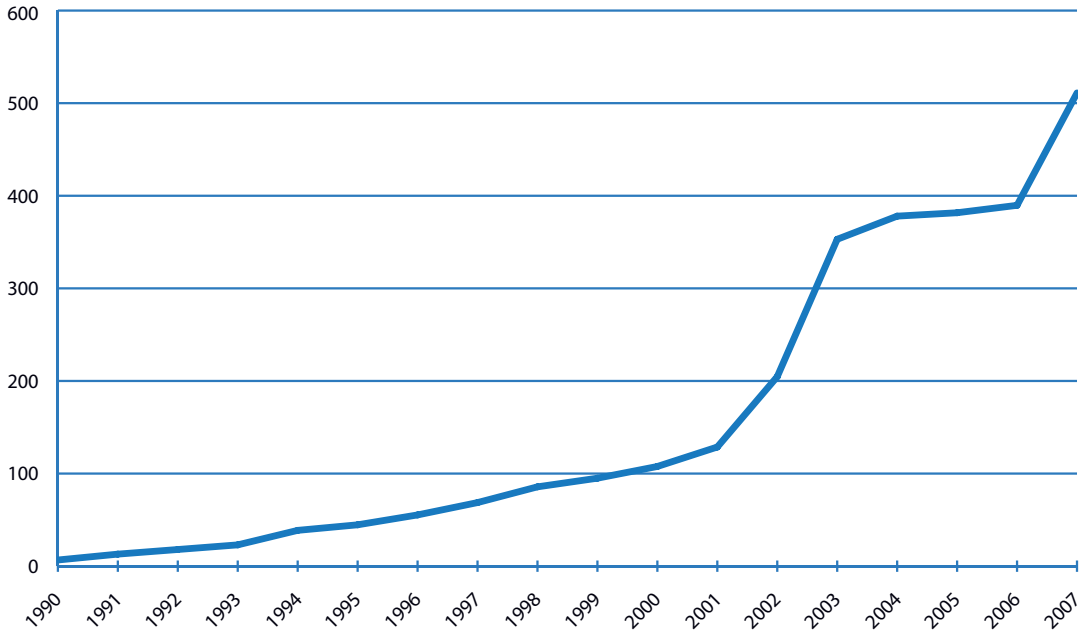
Figure 9. **Types of drug-gene relationships identified in the PharmGKB database**



Source: Authors, based on PharmGKB (2007).

Note: As of December 10, 2007.

Figure 10. **Number of identified drug-gene relationship, 3-year running average, by year of first publication**



Source: Authors, based on PharmGKB (2007).

Note: As of December 10, 2007.

This trend is similar to the trend for publication references to "pharmacogenetics" and "pharmacogenomics" (see Figure 11). An analysis of the archives of PubMed, which contains 16 million biomedical journal abstracts and articles from over 300 research journals, shows a rapid increase in the mention of "pharmacogenetics" and "pharmacogenomics" from 2000 to 2007. These results mirrored very closely the same analysis performed on the archives of the Journal of the American Medical Association (JAMA). JAMA is a broad medical journal that is widely read by general medical practitioners, indicating that interest in this research is a part of a general trend.

Biomarkers

The FDA defines a biomarker as valid 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)." As shown in Table 22, as of April 2008, the FDA had identified 27 valid biomarkers: four are required, nine are recommended, and 14 are identified as for "information only". This was a 50% increase in the number of validated biomarkers over October 2006 levels. In addition, the proportion of those biomarkers for "information only" decreased from 72% to 52%.

The share of FDA approved drugs containing pharmacogenetic information on their labels has increased significantly over the past 25 years. While only 10% of all FDA approved drugs contain such information, the percentage has increased more than 7 times from only 5% of drugs approved in 1990 to 37% of drugs approved in 2005 (see Figure 12).

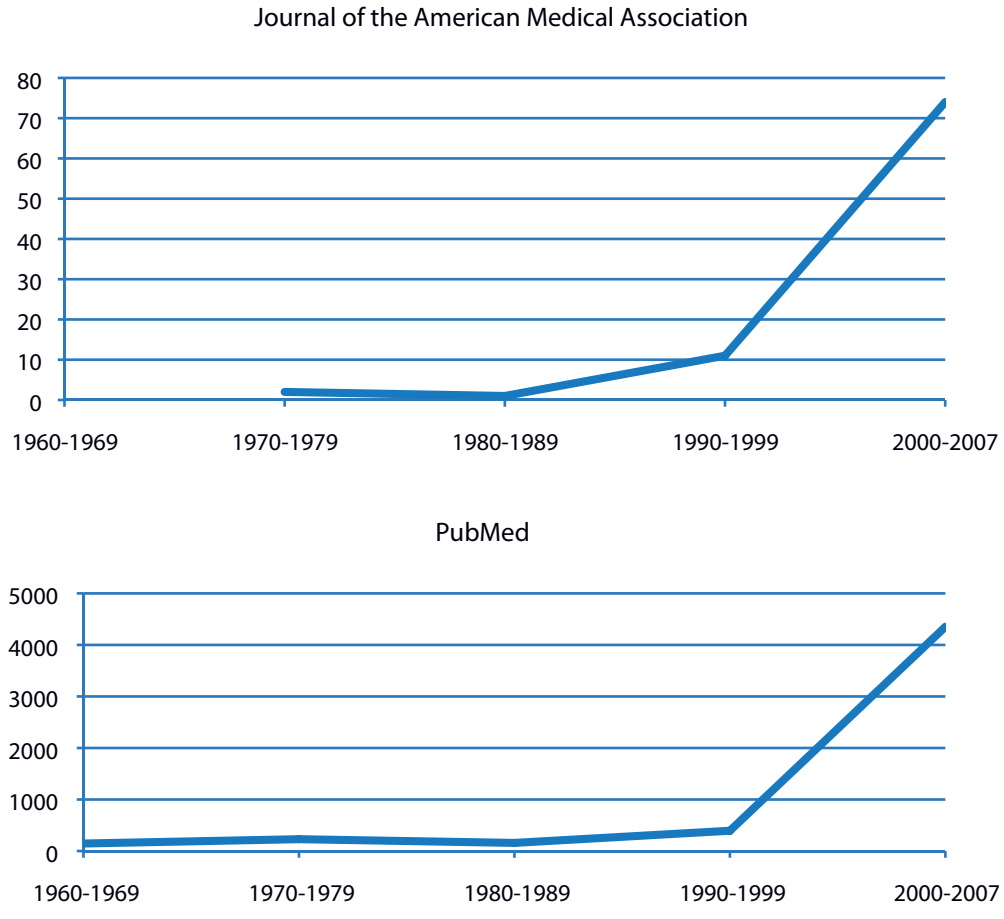
Table 22. **Valid FDA genomic biomarkers and genetic testing requirements – October 2006 and April 2008**

FDA Category	Number of Drugs as of October 2006	Number of Drugs as of April 2008
Test Required	2	4
Test recommended	3	9[2,3]
Information only	13	14
Total	18[1]	27[4]

Source: Authors, based on FDA (2008).

Notes: 1. One drug (Cetuximab) is counted twice because testing is required for colorectal cancer and recommended for head and neck cancer.
2. One drug (Warafin) has three associated genomic biomarkers for which testing is recommended.
3. Testing for one drug (Carbamazepine) is only recommended for at risk persons
4. In addition to those drugs cited in notes 2 & 3, one drug (Cetuximab) is counted twice because testing is required for colorectal cancer and recommended for head and neck cancer.

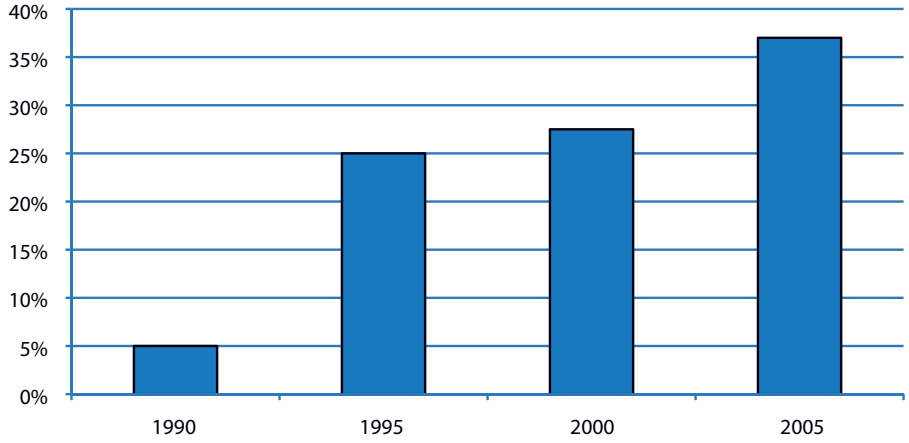
Figure 11. **Number of publications with "pharmacogenetics" and "pharmacogenomics" as keywords**



Source: Authors, based on PubMed (2007).

Notes: 1. Chart scales are different.
2. Searches performed December 6, 2007.

Figure 12. **Labels of FDA approved drugs with pharmacogenomic information**



Source: Frueh (2006).

Forecasting for diagnostics

The importance of diagnostic tests, and hence biotechnology based diagnostics, are likely to continue to increase to 2015. This will be particularly apparent if trends towards the increased use of pharmacogenetics (see the section on "forecasting for pharmacogenetics") and preventative medicine continue in unison.

In-vivo *diagnostics*

As shown in Table 17, the pipeline for biotechnology *in-vivo* diagnostics is relatively small. With only a few products in clinical trials, it is very difficult to ascertain with any certainty the number of products likely to enter the market by 2015. However some general conclusions can be drawn by examining the success rate from the Pharmapredict database for all diagnostics and imagining agents, which includes biotechnology *in-vivo* diagnostics. This category has a short average product development time (93 months from phase I to launch), the highest historical success rate from preclinical trials to market, and an above average success rate across all development phases. It is therefore likely that several of the products currently in development will reach the market before 2015. Also, since some products will go from the end of preclinical trials to launch in less than 93 months, there may also be some products that arrive on the market in 2015 which are not yet even in preclinical trials.

In-vitro *diagnostics*

In-vitro diagnostics are likely to see much stronger growth to 2015 than *in-vivo* diagnostics. Many experts see double digit annual growth in diagnostics sales through 2015, in part driven by the increased use of pharmacogenetics (see the section on "forecasting for pharmacogenetics").

As noted in the section on diagnostics, 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.

Forecasting for bioinformatics

The creation, population, and maintenance of databases will continue to be a very important function of bioinformatics to 2015. These databases are likely to become increasingly complex, integrating information from disciplines beyond biology and computer science, such as physics and chemistry (Kanehisa and Bork, 2003). This information is required in order to model cells as systems, a necessary step to predicting function (Tsoka and Ouzounis, 2000).

Databases will continue very rapid growth to 2015. Not only will more base pairs and sequences be available, but so will the full genome of an increasing number of organisms. The rapid rate of increase in data compilation shown in Figure 8, will continue, particularly if the cost of sequencing continues to fall as projected. Indeed the cost of genome sequencing will probably continue to decline rapidly. If the cost per base pair continues to decline at historical rates, "Thousand Dollar Genome" could become a reality around 2020 (Carlson, 2007). There are however indications that this could occur much sooner. The gene sequencing firm Complete Genomics, for instance, has announced that it will soon start offering sequencing of 8 or more full human genomes for USD 20 000 each and 1 000 or more full human genomes for USD 5000 each (Duncan, 2009).

BCC Research estimates that the worldwide bioinformatics market will reach USD 3.0 billion in 2010, corresponding to a 15.8% average annual growth rate over 2002 levels. The report concludes the use of bioinformatics will reduce the time for drug discovery and the annual cost of development by 30% and 33%, respectively by 2010 (BBC Research, 2005b).

Forecasting for pharmacogenetics

Similar claims regarding reducing drug discovery time and cost have been made about the closely related field of pharmacogenetics. PWC (2005) states that "using pharmacogenomics in clinical trial design is expected to reduce the clinical development time from 10 to 12 years in traditional commercialization to just 3 to 5 years." Jean-Pierre Garnier, CEO of GlaxoSmithKline, is less optimistic. He recently commented that "pharmacogenetics is not going to transform this market any time soon … it's going to take 20 years plus" (Hirschler, 2007).

Indeed, due to the highly varied nature of the challenges facing pharmacogenetics, it is very difficult to perform a quantitative analysis leading to projections of the number of pharmacogenetic products arriving on the market by 2015. In the end, a complicated convergence of regulatory policies, business plans, and scientific developments are going to determine the final trajectory of these technologies, but we can draw out a few general observations regarding likely near term developments.

An increasing number of drugs that are tailored for groups of people who share specific genetic characteristics are likely to reach the market by 2015. This is shown by the increase in the number of gene-drug links identified, publications examining "pharmacogenetics" and "pharmacogenomics", and drug labels containing pharmacogenomic information (see

the section on the "current status of pharmacogenetics"). Also, there are encouraging signs such as the work of ICH on guidelines for the validation of biomarkers (ICH, 2008) and FDA – EMEA collaboration on harmonizing rules for pharmacogenetic data submissions. There is also the possibility that pharmacogenomic data submissions for new drug applications will become mandatory (PWC, 2005). This sort of increased collection of standardized pharmacogenetic data could have a major impact on pharmacogenetic drug development.

The use of pharmacogenetics up to 2015 is likely to focus on improving safety and reducing ADRs. Concern over high-profile drug withdrawals (such as Vioxx) should also encourage firms to use pharmacogenetics during drug development to minimize severe adverse drug reactions. Another application is to use pharmacogenetics to identify sub-groups of responders. This could "rescue" drugs that fail in clinical testing by identifying sub-groups of patients for which the drug is safe and effective (DePalma, 2006). However, this is more difficult and expensive than identifying subgroups that develop ADRs. Astra Zeneca adopted this approach to rescue its lung cancer drug candidate Iressa, but failed.

BCC Research (2005c) estimates that the global market for pharmacogenomics is likely to grow by 24.5% per year, from USD 1.24 billion in 2004 to USD 3.7 billion by 2009. Diagnostics formed 39.2% of this market in 2004 and should account for 45.3% of the market in 2009.

Potential

The Human Genome Project and other related initiatives have led to the identification of several genes that increase the risk of an inherited disease. This allows the development of new kinds of molecular diagnostic tests that can diagnose diseases caused by more than one gene and determine a patient's genetic predisposition to a given disease. Yet it is very unlikely that biotechnology-based diagnostics will dominate the IVD market by 2015. Most molecular diagnostics do not replace existing tests, but add new market segments, such as for diagnostics to identify multi gene diseases or for use in personalized medicine in combination with pharmacogenetics.

Diagnostics, bioinformatics, and pharmacogenetics summary

Table 23 summarizes the main developments in biotechnology-based diagnostics, bioinformatics, and pharmacogenetics that are expected by 2015.

Table 23. **Main short-term trends in biotechnology-based diagnostics, bioinformatics and pharmacogenetics to 2015**

	Forecast outcomes
Diagnostics	The importance of biotechnology based diagnostic tests will continue to increase to 2015. This is particularly the case for *in-vitro* diagnostics which are likely to see much stronger product development to 2015 than *in-vivo* diagnostics. While the number of diagnostic tests produced could slow somewhat due to a saturation of gene targets, the increased use of pharmacogenetics and personalised medicine could spur development, particularly of multi-gene tests based on micro-arrays.
Bioinformatics	The continued creation, population, and maintenance of databases will continue to be a very important, perhaps even primary, function of bioinformatics to 2015, but this data will often be more complex. The amount of information stored in large genetic databases will continue to grow, in part due to a fall in the price of genome sequencing.
Pharmacogenetics	The number of drugs where prescribing practice depends on a genetic test should continue to grow to 2015. The primary purpose is likely to be to reduce ADRs (i.e. warfarin) but the number of responder linked drugs should also increase (i.e. HER2 test for Herceptin). The widespread use of pharmacogenetics to identify respondent and non respondent subgroups in clinical trials, however, is unlikely to occur before 2015.

Miscellaneous: functional foods, nutraceuticals and medical devices

This miscellaneous category includes areas where biotechnology has possible applications to health, but to date the effect of biotechnology has been fairly minor.

Functional foods and nutraceuticals

Health Canada defines functional foods and nutraceuticals as follows:

- "A **functional food** is similar in appearance to, or may be, 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 forms not usually associated with foods. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease (Health Canada, 1998)."

It is not possible to determine what percentage of the overall food products and beverage sector is involved in functional food and nutraceuticals (FFN). However, the FFN sector is estimated in Canada to account for approximately 5.3% of the total food and beverage sector (see Table 24). This roughly corresponds to the estimate of 5.4% provided by comparing total food and beverage sales in the United States (USD 592 billion) (EU KLEMS, 2007) with estimates of functional foods sales in the United States (USD 32 billion) for 2005 (Nutrition Business Journal as cited by US GAO, 2000).

Other research provides large variations in the estimated size of the FFN sector. For example, the Nutrition Business Journal as cited by Sloan (2005) indicates that the global functional food market was USD 47.6 billion in 2001, with the United States accounting for USD 18.25 billion. The US market was expected to grow at 7.5% through 2005 bringing the overall United States functional foods market to USD 24.4 billion in 2005. Another study estimated that the FFN sector in the United States was much smaller, only USD 1.26 billion in 2001 (Food & Drink Weekly, 2001). Although estimates of the overall market size tend to vary significantly, analyst seem to agree that the industry is growing at a rapid pace (double digit per annum) when compared to the conventional food sector which is growing by just 2% to 3% per year (Van Dusen, 2007).

Table 24. **Employment in the functional food and nutraceutical (FFN) sector in Canada**

Total Canadian FFN employment (2004)	Total Canadian food products and beverage employment (2003)	% of all Canadian food product and beverage employees working in FFN
12 872	241 000	5.3%

Source: Authors, based on FFN employment data from Palinic (2007) and Canadian employment data from OECD (2007a).

While most analysts do not appear to differentiate between functional foods and nutraceuticals, a rough estimate of the overall FFN share can be gleaned from the Canadian employment data cited in Table 24. Of the 12 872 Canadian employees active in FFN, 4 024 are involved in functional foods, 6 471 are active in nutraceuticals, and 2 377 are working in both fields (Palinic, 2007). This implies, as a very rough estimate, that functional foods and nutraceuticals account for roughly 40% and 60%, respectively, of the overall FFN market.

Of note, many functional foods (*e.g.* foods with added nutrients) and nutraceuticals, such as fish oils, have been available for decades and are not produced using modern biotechnology. Biotechnology can however be applied to plants and animals to engineer or select specimens with increased levels of certain nutrients or functional components that can then be consumed or extracted for use. There is no data available to determine the exact percentage of the overall FFN sector which currently uses biotechnology. The authors assume that the biotechnology share is relatively small, not exceeding 10% and probably far less.

Increased knowledge in the "omics" (*e.g.* genomics, proteomics, metabolomics, etc.) may lead to an era of nutragenomics, where dietary regimes are tailored to a person's specific genome to prevent disease or improve health. This form of personalized medicine would likely make use of both functional foods and nutraceuticals, but appears to be far in the future.

Current status of functional foods

Table 25 provides some examples of functional food components. While many of these benefits are unverified, some have received approval from the United States' FDA as "qualified health claims." These are general claims that indicate a specific substance *may be* effective in reducing a health risk such as heart disease, high blood pressure, osteoporosis, etc. Some of these functional components (zeaxanthin, beta-carotene, omega-3 fatty acids, stanol) are currently or have been the subject of genetically modified (GM) field trials.[44]

Some examples of functional foods using biotechnology which are available or currently under development are:

- In the United States, researchers are using biotechnology to increase the amount of ellagic acid, a cancer protective agent, in strawberries (Smith, 2007).
- Soybeans have been developed through conventional breeding (*e.g.* Vistive 1 from Monsanto) which produce no trans fats when cooked due to their low levels of linolenic acids. Soybeans with both low levels of linolenic acids and increased levels of oleic acid and low saturated fats are under development using biotechnology (Powell, 2007).
- An English-German-Japanese consortium has developed a GM tomato containing 3.5 times the level of b-carotene of a normal tomato (BBC News, 2000).

In addition, some biotechnology functional foods have been or are being developed to address the needs of the developing world:

- Golden rice and iron-enriched rice are genetically engineered to provide enhanced levels of iron and b-carotene. This could have an impact on common health problems caused by nutrient deficiencies such as blindness and anaemia (Hasler, 2002).

Table 25. **Examples of functional food components**[1]

Functional components[2]	Current Source[1]	Potential benefits
Carotenoids		
Beta-carotene[4]	carrots, pumpkin, sweet potato, cantaloupe	neutralizes free radicals, which may damage cells; bolsters cellular antioxidant defences; can be made into vitamin A in the body
Lutein, Zeaxanthin[4]	kale, collards, spinach, corn, eggs, citrus	may contribute to maintenance of healthy vision
Lycopene	tomatoes and processed tomato products, watermelon, red/pink grapefruit	may contribute to maintenance of prostate health
Fatty Acids		
Monounsaturated fatty acids (MUFAs)[3]	tree nuts, olive oil, canola oil	may reduce risk of coronary heart disease (CHD)
Polyunsaturated fatty acids (PUFAs) – Omega-3 fatty acids – Alpha-linolenic acid (ALA)[4]	walnuts, flax	may contribute to maintenance of heart health; may contribute to maintenance of mental – Omega-3 fatty acids – ALA and visual function
PUFAs – Omega-3 fatty acids – Docosahexaenoic acid (DHA)/ Eicosapentaenoic acid (EPA)[3, 4]	salmon, tuna, marine, and other fish oils	may reduce risk of CHD; may contribute to maintenance of mental and visual function
Conjugated linoleic acid (CLA)	beef and lamb; some cheese	may contribute to maintenance of desirable body composition and healthy immune function
Phenolic Acids		
Caffeic acid, Ferulic acid	apples, pears, citrus fruits, some vegetables, coffee	may bolster cellular antioxidant defences; may contribute to maintenance of healthy vision and heart health
Plant Stanols/Sterols		
Free Stanols/Sterols[3, 4]	corn, soy, wheat, wood oils, fortified foods and beverages	may reduce risk of CHD
Stanol/Sterol esters[3]	fortified table spreads, stanol ester dietary supplements	may reduce risk of CHD
Prebiotics/Probiotics		
Inulin, Fructo-oligosaccharides (FOS), Polydextrose	whole grains, onions, some fruits, garlic, honey, leeks, fortified foods and beverages	may improve gastrointestinal health; may improve calcium absorption
Yeast, Lactobacilli, Bifidobacteria, and other specific strains of beneficial bacteria	certain yogurts and other cultured dairy and non-dairy applications	may improve gastrointestinal health and systemic immunity; benefits are strain-specific
Phytoestrogens		
Isoflavones – Daidzein, Genistein	soybeans and soy-based foods	may contribute to maintenance of bone health, healthy brain and immune function; and for women, menopausal health
Lignans	flax, rye, some vegetables	may contribute to maintenance of heart health and healthy immune function

Source: Authors, adapted from IFIC (2007)

Notes: 1. Examples are not an all inclusive list.
2. Functional food components also exist in dietary fiber, flavonoids, isothiocyanates, minerals, soy protein, sulfides/thiols, & vitamins.
3. US FDA approved health claim.
4. GM field trials undertaken or underway on this functional component.

- The BioCassava Plus programme aims to improve the nutrition of the more that 250 million sub-Saharan Africans who rely on cassava as a staple. The goal is to create cassava which deliver "enhanced bioavailable levels of zinc, iron, protein, vitamin A, vitamin E, and reduced quantities of toxic cyanogenic glycosides, improved post-harvest durability, and improved resistance against viral diseases (BioCassava PLUS, 2007)."

Current status of nutraceuticals

At present, almost all nutraceuticals are dietary supplements from basic plants. None appear to use biotechnology, but biotechnology (*e.g.* marker assisted selection or GM) could be used to change plant composition, thereby increasing extraction yield. Many vitamins are produced through fermentation and Vitamin B12 is produced exclusively through synthesis by micro-organisms. However, these are not "isolated or purified from foods" and are therefore not considered to be nutraceuticals.

Other biotech health benefits

Biotechnology can also be used to modify the composition of foods. While these are neither functional foods, due to the lack of bioactive compounds, nor nutraceuticals because they are consumed as normal foods (*i.e.* not in medicinal form), they can have an impact on human health. For example:

- Animal scientists are using biotechnology to create meat products, such as beef with lower fat content and pigs with a higher meat-to-fat ratio (BIO, 2007).
- Potatoes, produced through biotechnology, with altered starch content leads to less oil absorption during frying and therefore the consumption of fewer fat calories (Curtis, McClusky, and Wahl, 2002).

Forecasting for functional foods and nutraceuticals

As previously stated, estimates of the current FFN market are highly variable indicating that any projections will be unreliable. In 2000, one source predicts the United States' FFN market to reach USD 49 billion by 2010 (Nutrition Business Journal as cited by US GAO, 2000). Two years later, the estimate was revised downwards to USD 34.3 billion (see Table 26). Another source estimated the European FFN market in 2012 at USD 300 billion. This would amount to, "nearly two orders of magnitude larger than that of the United

Table 26. **United States functional food sales**

	Estimated 2001 (USD billions)	Projected 2010 (USD billions)
Beverages	8.9	13.4
Breads & grains	4.9	7.2
Packaged/prepared	1.6	4.8
Dairy	1.1	4.0
Snack foods	1.6	4.8
Condiments	0.15	0.1
TOTAL	18.25	34.3

Source: Nutrition Business Journal (2002) as cited by Sloan (2005).

States (Hodgson, 2002)." The report points out however that this large discrepancy is highly dependent upon the definition of FFN.

Definitional issues aside, most analysts see strong growth for the FFN sector in the near to medium term. The United States GAO has identified three factors contributing to this growth: "*(1)* the aging of the baby-boom generation, *(2)* an increased interest in self-sufficiency and prevention in health care, and *(3)* advances in science that are identifying new relationships between diet and disease (US GAO, 2000)."

Even by 2015, biotechnology is unlikely to play a large role in the FFN sector, but there are indications that active research applying biotechnology to FFN is occurring and that biotechnology's share of the FFN market may increase. Arundel and Sawaya (2009) provide estimates of the types of agricultural biotechnologies likely on the market by 2012-2015. The article demonstrates that GM trials for the product quality traits oils and fatty acids, and proteins and amino acids have increased since 2003, and that some of these product quality traits are likely to enter the market between 2010 and 2012 with a large increase in the number of product quality traits by 2015.

Medical devices

Medical devices include a wide range of technologies including surgical instruments and equipment (bandages, surgical gloves, bedpans etc), diagnostics, tissue engineering, medical imaging equipment, and products that effect the structure of a person but which do not achieve their effects through being metabolized *in vivo* (implants, prostheses, pacemakers, infusion pumps, dialysis machines etc). The regulation of medical devices depends on their potential for harm. Non-invasive devices such as imaging equipment can have mandatory performance standards but they are not regulated as stringently as invasive devices such as implants or heart valves.

Current status of medical devices

The medical device industry (or biomedical device industry) is commonly linked to biotechnology, particularly in the United States, but the link is due more to the structure of the sector, with a large number of venture-capital funded start-ups, than with shared technologies. An exception is diagnostics, including medical imaging, and tissue engineering (discussed above).

The medical device sector in the US had sales of 123 billion USD in 2006, but very little of this is in areas where biotechnology has possible applications (Lewin Group, 2007).

Many of the applications of biotechnology to medical devices are still in the lab. An example is biosensors that use changes in protein folding to determine activity of a substrate. Exposure triggers a movement in the protein which triggers an electrical device. Protein based sensors do not depend on a chemical reaction and consequently have a long lifetime, with a range of potential applications, such as in glucose monitoring for diabetics. Another example is regenerative medicine, in which stem cells are combined with mechanical devices or substrates.

Medical devices also include several new forms of drug delivery. Medgenics is developing a biopump, in which autologous cells from a patient are modified to produce biopharmaceuticals. The cells are reimplanted into the patient. This is essentially a drug delivery technology that avoids the need for injections (In Pharma Technologist, 2007). Other potential drug delivery devices include a nanodevice that releases drugs in response

to overexpression of undesirable proteins. According to experts, such a device would not be available by 2015, but could reach the market by 2030.[45] An alternative drug delivery device for insulin is to deliver it in tiny plastic particles of less than 2 microns.

Forecasting for medical devices

Due to a lack of data, it is not possible to forecast developments in medical devices, based on biotechnology, to 2015. A few new developments in drug delivery are likely to reach the market by 2015, but other devices such as biosensors are unlikely to reach the market until after 2015.

Conclusions

Based on an analysis of past success rates and the number of clinical trials for bio-NMEs in each phase of development, this article estimates that approximately 13 bio-NMEs will receive market approval each year to 2015, compared to an annual average of eight bio-NME market approvals between 2000 and 2007 inclusive. The increase is due to a large number of drug candidates in late stage clinical trials in biotherapeutic drug classes with high past success rates.

Biotechnological knowledge will also be used at some point in the development or use of almost *all* new small and large molecule pharmaceuticals by 2015. For example, biotechnology could be used to identify new drug targets, assess safety, or guide prescribing practices. Industrial biotechnology will be increasingly used to reduce the cost of manufacturing pharmaceutical precursors. Consequently, soon it will no longer be useful to separate the pharmaceutical sector from the health biotechnology sector.

New biopharmaceuticals will continue to improve health outcomes and some will reach "blockbuster" status. However, theses advances are unlikely to have a major impact on the way in which healthcare is delivered and received, and they will almost certainly – without substantial changes to regulatory and market frameworks – increase healthcare costs (OECD, 2009b).

However, the promise of biotechnology in health is much greater than simply adding new drugs to a doctor's existing arsenal. Experimental therapies of the kind described in this article have the potential to cure rather than treat numerous debilitating illnesses. While it is difficult to predict the short-term future of these therapies, a few successful treatments highlight the potential. For example, in 2008, a woman had her damaged trachea replaced by using donated scaffold cartilage covered with new tissue produced from her own bone marrow stem cells.

Substantial improvements to healthcare delivery could also come through the development of predictive and preventive medicine, which aim to predict the development of disease before symptoms are visible and to prevent or delay the onset of disease through treatment. This would partly involve the use of diagnostics, bioinformatics, and pharmacogenetics to identify and prescribe personalised treatments that account for interactions between the patient's genotype and response to drugs.

The key technology components for a personalised medicine system have been developing rapidly. 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, while at the same time sequencing efficiencies – measured in the number of base pairs a machine can sequence per day – are increasing at a nearly ultra-exponential pace. Both trends are expected to continue in the future. There has also been a rapid increase in the number of identified

gene-drug relationships, genetic tests available, publications on pharmacogenetics and pharmacogenomics, and drug labels containing pharmacogenetic information.

A transition from current healthcare models to a predictive and preventive health system has already begun. Healthcare reforms under consideration around the world are likely to continue this trend. In addition to solving a number of technological challenges, the success of predictive and preventive healthcare will require changes to how health products are developed, regulated, marketed, and delivered. These issues are extensively discussed in the OECD (2009b) book *The Bioeconomy to 2030: Designing a Policy Agenda.*

The contribution of biotechnology to health research will continue to grow, but it is too early to tell if it results in a radical improvement in health outcomes or it if the future lies in incremental improvements. The former is the preferable option, but achieving it will not only rely on solving technological and scientific problems. It will also depend upon changes in the private and public spheres to implement appropriate policies and business plans.

Notes

1. Humulin received FDA approval in 1982. Developed by Genentech and Eli Lilly, it is a human insulin produced by genetically modified bacteria.

2. The FDA categorizes all new drugs by their therapeutic potential. The highest to lowest categories are as follows: Priority NME, Standard NME, Priority non-NME, Standard non-NME. Of note, the classification is made before the completion of all clinical trials that are required for the drug approval process. This means that some drugs assigned to the highest priority could offer only minimal therapeutic advances over drugs that are already on the market.

3. Bioinformatics and diagnostics are often separated into two distinct fields. In this article diagnostics are viewed as a sub-category of bioinformatics because many biotechnological diagnostics depend on bioinformatics. For example, diagnostic genetic tests require extensive bioinformatics research to identify the genes that are responsible for a specific disease or the risk of developing a chronic condition such as heart disease.

4. For examples of the benefits of using large public databases, see Hall and Lucke (2007) and` Graham *et al*. (2005).

5. A small share of the economic effects from medical devices will be assigned to the medical and surgical instruments sector (NACE 33.1).

6. R&D intensive biotechnology firms that have no sales of manufactured products are assigned to International Standard Industrial Classification (ISIC) or NACE (revision 1) sector 73.1 (Research and experimental development on natural sciences and engineering). Many firms can remain in this sector for a decade or longer. Once they produce manufactured products, they are reassigned to manufacturing if their manufacturing sales force exceeds that of their services force. In most European countries, the R&D expenditures of these firms are assigned to the sector of the potential product (for instance pharmaceuticals), but in the United States the R&D is assigned to the service sector. This acts to depress estimates of R&D expenditures in pharmaceuticals in the United States and to reduce comparability between US and European R&D data.

7. In both countries, the value added output of the pharmaceutical sector has grown in absolute terms – it is only the pharmaceutical share of total value-added (similar to GDP) that has declined in the United States, due to faster growth rates in other economic sectors.

8. Gross value-added is approximately equal to GDP. Value added equals the sales revenues at current prices minus all material and capital input costs. Of note total value added can differ substantially from total sales. Global sales of pharmaceutical products are over twice as large as total value added in the pharmaceutical sector.

9. This list refers to newly registered medicines or those who obtained an extension of indication.

10. In medicine, indication refers to the condition that is treated by a specific drug or treatment.

11. The therapeutic advance of all other drugs is also falling, from 16.0% before 2001 to 10.6% afterwards, but the decline was not as steep.

12. This contrasts with the results given by Pisano (2006, pp 125 – 126) which show that the mid to large size firms are more active in developing novel drugs than small firms. The difference in results is largely due to the types of data used. First, Pisano uses market capitalisation rather than employment as a measure of size, which means that some highly capitalised biotechnology firms would be included with much larger firms in terms of employment. Second, Pisano's measure of novelty is for drugs in clinical trials, whereas the HAS and Prescrire results are for drugs that have received marketing approval. Third, the analyses in this report are based on the firm that developed the drug, instead of the firm that applied for market approval.

13. HAS gave ratings of between an "important improvement" and a "minor improvement" for seven of the biopharmaceuticals considered by Prescrire to be "not acceptable" (6 drugs) or "judgement reserved" (1 drug).

14. Twenty years after establishment allows sufficient time for the firm to develop a revenue stream from the sale of biopharmaceuticals. Development work on biopharmaceuticals that were marketed 20 years after establishment would have begun approximately a decade earlier.

15. Autologous cells are taken from an individual, cultured (or stored), and, possibly, genetically manipulated before being infused back into the original donor (FAO, 1999).

16. In October 2003, a gene therapy (p53, trademarked as Gendicine) developed by Shenzhen SiBiono GeneTech Co., Ltd. (*www.sibiono.com/*), obtained the marketing approval from the China State Food & Drug Administration (SFDA). In 2005, SFDA approved H101, developed by Shanghai Sunway Biotech.

17. Of these 66 projects, there are 4 on the market, 2 in pre-registration, 4 in phase III clinical trials, 12 in phase II clinical trials, 4 in phase I clinical trials, and 40 in preclinical trials. In contrast to other clinical trial analyses undertaken in this report, this data does include formulations as this is one of the primary areas of nanobiotechnology research.

18. See Cockburn (2006) and Hopkins, *et al*. (2007).

19. Cockburn (2006) provides data estimating that approximately 30% of drug candidates are withdrawn by pharmaceutical firms because of "prohibitively high manufacturing costs" or other unspecified reasons, and that this has increased from 5% in 1991. This suggests that there could be a substantial market for producing small molecule drugs in plants, animals or micro-organisms using rDNA technology.

20. An example is Carbamazepine, used to treat epilepsy. Patients with the allele HLA-B* 1502 can suffer serious adverse skin reactions.

21. Large protein molecule drugs need to be injected, frequently in a hospital or clinic setting, whereas most small molecules can be taken orally at home. Patients have a strong preference for the latter.

22. Before it was bought out by UCB, Celltech's strategy was to develop a mAb, then follow up with a small molecule drug (Personal communication, Michael Hopkins, December 2007).

23. These are defined by Pharmapredicts as "originator firms". They differ from the "developer" firms used in Figures 1 and 2 and Tables 6 and 7, which are defined as the firms that developed the NME. For most Phase I and II clinical trials, the developer firm is likely to be the same as the originator firm.

24. The US share is 55.1% of phase I trials, 52.3% of phase II trials, and 55.3% of phase III trials.

25. Majors are defined here as companies with 5 or more bio-NMEs or compounds in any clinical trial phase or pre-registration. They include Amgen, Astra Zeneca, AVI BioPharma, Bayer, Biogen Idec, Cancer Research Technolgy, Crucell, Cytos Biotechnology, Dynavax Technologies, Eli Lilly, Emergent BioSolutions, Genentech, Genmab, GSK, Green Cross, ImClone Systems, Immunomedics, Introgen Therapeutics, Isis Pharmaceuticals, Johnson &

Johnson, Medarex, Merck KGaA, Northwest Biotherapeutics, Novartis, Oxford BioMedica, PDL BioPharma, Pfizer, Sanofi-Aventis, Shanghai CP Guojian, Targeted Genetics, Transgene, Vical and Wyeth.

26. The analyses use OECD data on venture capital investments in the life sciences for 2001 to 2003 inclusive (van Beuzekom and Arundel, 2006) and for 2007 (van Beuzekom and Arundel, 2009). All R2 coefficients were under 0.04.

27. Pharmapredict (Informa, 2007b) is a quarterly publication. The version used for this analysis (Qtr4 2007) is based on data extracted in March 2008 from Pharmaprojects (Informa, 2007a), and on financial data supplied annually by EvaluatePharma.

28. Success rates and estimated launch dates are calculated with average time spent, for similar drugs, in each of the phases of development. Pharmapredict has been collating this data since 1989 and over 5500 development phase timings are included.

29. Without success rate data for the experimental bio-NMEs, it is very difficult to estimate the expected market approval date, as this requires an estimate of the probability of each biopharmaceutical moving from Phase I to Phase II, from Phase II to Phase III, and from Phase III to market approval. However, if we assume that 1) all products reach the market or fail between 2010 and 2015, 2) that the success rate for the 38% of bio-NMEs with no data equals that of the bio-NMEs with data, and 3) that the success rate for the 15% of nonbio-NMEs equals that of the nonbio-NMEs with data, then the average biopharmaceutical share of all approved pharmaceuticals between 2010 and 2015 increases from approximately 15% to approximately 21%.

30. Pharmapredict shows that biotechnology drugs spend a mean average of 36 months in phase 2, 30 months in phase 3, 17 months in pre-registration, and 8 months prior to market entry following registration.

31. Unpublished results from Boris Mannhardt, *biotechnologie.de.*

32. Diagnostics are classified as medical devices, but they are covered here because of their importance and link with bioinformatics.

33. Other diagnostics include, *inter alia*, assays for urea, glucose, cholesterol, sodium, potassium, hepatic and cardiac enzymes or faecal occult blood.

34. Though Medical Product Outsourcing does not provide a figure for the global IVD market in 2005, TriMark Publications (2007) gave the value of the global IVD market in as USD 31.5 billion in 2005.

35. Systems biology is a, "field that seeks to study the relationships and interactions between various parts of a biological system (metabolic pathways, organs, cells, and organisms) and to integrate this information to understand how biological systems function (National Institute of General Medical Sciences, 2006)."

36. For examples see *http://au.expasy.org/links.html* (ExPASy, 2007).

37. The OECD defines a biobank as a, "collection of biological material and the associated data and information stored in an organised system, for a population or a large subset of a population (OECD, 2005b)."

38. For detailed information on these, and other biobanks, see OECD (2006c) or, "The Victorian Cancer Biobank," *www.viccancerbiobank.org.au* (Australia); "CARTaGENE,", *www.cartagene.qc.ca/en* (Canada); "The Estonian Genome Project," *www.geenivaramu.ee/index.php* (Estonia); "DeCode," *www.decode.com/* (Iceland); "The Biobank Japan Project," *http://biobankjp.org* (Japan); "Latvian Genome Project," *http://bmc.biomed.lu.lv/gene/* (Latvia); "The Swedish National Biobank Program," *www.biobanks.se* (Sweden); and "The UK biobank," *www.ukbiobank.ac.uk* (United Kingdom).

39. For examples see, Abd-Elsalam (2003).

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

41. 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).

42. 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).

43. The number of identifications decreased from 72 in 1994 to 36 and 58 in 1995 and 1996 respectively before returning to 112 in 1997. Likewise, after 595 identifications in 2003, there were only 225 and 325 in 2004 and 2005 respectively. The number increased to to 619 in 2006.

44. The UNU-MERIT GM Field Trial database indicates that there has been one trial for the increase of zeaxanthin (potato), three trials for increased beta-carotene (Potato & Tomato), seven trials involving omega-3 fatty acids (soybean), and six trials for increased stanol content (soybean).

45. The examples in this section are from an interview on October 8, 2007 with Steve Dahms, Thomas Lobl, and Joseph Schulman.

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Annex A

Supporting tables on biopharmaceuticals and clinical trials

Table 27. **List of 155 biopharmaceuticals that received market approval between January 1989 and January 2009**

Scientific name	Registration year	Developer company	Head office country
131I-tositumomab	2003	Corixa	US
abatacept	2006	BMS	US
abciximab	1995	Centocor	US
adalimumab	2002	Cambridge Antibody Technology	UK
agalsidase alfa	2001	Transkaryotic Therapies	US
agalsidase beta	2001	Genzyme	US
aldesleukin	1989	Cetus	US
alefacept	2003	Biogen Idec	US
alemtuzumab	2001	Millenium	US
alfa-1 antritrypsin	2003	Mitsubishi Pharma	Japan
alglucosidase alfa	2006	Genzyme	US
alteplase	1996	Genentech	US
anakinra	2001	Amgen	US
antithrombin alfa	2006	Aventis	France
arctiumomab	1996	Immunomedics	US
ART-123 (thrombomodulin)	2008	Asahi Kasei Pharma	Japan
asparaginase (L-)	1994	Enzon	US
basiliximab	1998	Novartis	Switzerland
becaplermin	1998	Chiron	US
bevacizumab	2004	Genentech	US
capromab pendetide	1997	Cytogen	US
carperitide	1995	Suntory	Japan
Celmoleukin	1992	Ajinomoto	Japan
certolizumab pegol	2008	Celltech	UK
cetuximab	2003	ImClone	US
choriogonadotropin alfa	2000	Serono	Switzerland
Clotinab	2006	ISU ABXIS	South Korea
Coagulation factor VIIa	1996	Novo Nordisk	Denmark
Coagulation factor VIII	1993	Genentech	US
Coagulation factor VIII	1993	Genetics institute	US
Coagulation factor VIII	2008	Wyeth	US

Table 27. **List of 155 biopharmaceuticals that received market approval between January 1989 and January 2009** *(continued)*

Scientific name	Registration year	Developer company	Head office country
Coagulation factor VIII-2	1999	Bayer	Germany
daclizumab	1998	Protein Design Labs	US
darbepoetin alfa	2001	Amgen	US
denileukin diftitox	1999	Seragen	US
desirudin	1997	Novartis	Switzerland
dibotermin alfa	2002	Genetics institute	US
dornase alfa	1993	Genentech	US
drotrecogin alfa	2001	Eli Lilly	US
duteplase (tPA)	1993	Genetics institute	US
DWP-401	2001	Daewoong	South Korea
eculizumab	2007	Alexion	US
edrecolomab	1995	Centocor	US
efalizumab	2003	Genentech	US
endostatin	2005	Yantai Medgenn	China
Epoetin alfa (erythropoietin)	1990	Genetics institute	US
Epoetin beta	1989	Amgen	US
epoetin beta (pegylated)	2007	Roche	Switzerland
epoetin delta	2002	Transkaryotic Therapies	US
eptotermin alfa	2001	Stryker-Curis	US
etanercept	1998	Immunex	US
FGF (fibroblast growth factor)	2007	Sinobiomed	China
filgrastim	1991	Amgen	US
Filgrastim (pegylated)	2002	Amgen	US
follitropin alfa	1995	Serono	Switzerland
follitropin beta	1996	Organon	Netherlands
fomivirsen sodium	1998	Isis Pharmaceuticals	US
FSH (follicle stimulating hormone)	2006	LG Life Sciences	South Korea
galsulfase	2005	Biomarin	US
GEM-21S	2005	Biomimetic	US
gemtuzumab ozogamicin	2000	Wyeth	US
glucagon	1999	Eli Lilly	US
H-101	2005	Shanghai Sunway Biotech	China
hep-B vaccine	2000	Bio-Technology General	Israel
hep-B vaccine	2000	Evans Vaccines	UK
hep-B vaccine	1991	Biogen	US
hep-B vaccine	1991	Genentech	US
hep-B vaccine	2003	Rhein Biotech	Germany
hep-B vaccine	2005	Corixa	US
HPV vaccine	2006	CSL	Australia
HPV vaccine	2007	Medimmune	US
hyaluronidase	2005	Halozyme Therapeutics	US
ibritumomab tiuxetan	2002	IDEC	US

Table 27. **List of 155 biopharmaceuticals that received market approval between January 1989 and January 2009** *(continued)*

Scientific name	Registration year	Developer company	Head office country
idursulfase	2006	Transkaryotic Therapies	US
imciromab	1991	Centocor	US
Imiglucerase	1994	Genzyme	US
infliximab (TNF)	1998	Centocor	US
influenza vaccine	2003	Medimmune	US
influenza vaccine	2007	Medimmune	US
insulin aspart	1999	Novo Nordisk	Denmark
insulin detemir	2004	Novo Nordisk	Denmark
Insulin glargine	2000	Aventis	France
insulin glulisine	2004	Aventis	France
insulin lispro	1995	Eli Lilly	US
insulin recombinant human	1991	Novo Nordisk	Denmark
interferon alfa	1997	Amgen	US
interferon alfa 2a (peg)	2002	Roche	Switzerland
interferon alfa 2b	2002	Biogen	US
interferon alfacon1	2002	Amgen	US
interferon beta1a	1996	Biogen	US
Interferon beta1a	1998	Serono	Switzerland
Interferon beta1b	1993	Chiron	US
Interferon gamma1b	1991	Genentech	US
ior-cea1	1995	Center of Molecular Immunology	Cuba
ior-egf/r3	1995	Center of Molecular Immunology	Cuba
laronidase	2003	Biomarin	US
lenograstim	1992	Chugai	Japan
lepirudin	1997	Hoechst	Germany
Lutropin alfa (FSH)	2000	Serono	Switzerland
Lyme vaccine	1998	GSK	UK
mecasermin	1994	Fujisawa	Japan
mecasermin rinfabate	2005	Celtrix pharmaceuticals	US
monteplase (tPA)	1998	Eisai	Japan
moroctocog alfa	1999	Genetics institute	US
muromonab OKT3	1992	Ortho Biotech	US
nartograstim	1994	Kyowa Hakko	Japan
natalizumab	2004	Elan	Ireland
nateplase (tPA)	1996	Mitsui	Japan
nesiritide citrate	2001	Scios	US
nimotuzumab	2005	Center of Molecular Immunology	Cuba
nonacog alfa	1997	Genetics institute	US
octocog alfa	2003	Baxter	US
omalizumab	2002	Genentech	US
oprelvekin	1998	Genetics institute	US
OspA lyme disease vaccine	1998	GSK	UK

Table 27. **List of 155 biopharmaceuticals that received market approval between January 1989 and January 2009** *(continued)*

Scientific name	Registration year	Developer company	Head office country
palifermin	2004	Amgen	US
palivizumab	1998	Medimmune	US
panitumumab	2006	Amgen	US
Parathyroid hormone (human)	2006	Allelix	Canada
pediatric vaccine	2006	Chiron	US
pegaptanib octasodium	2004	Gilead Sciences	US
pegaspargase	1994	Enzon	US
pegvisomant	2002	Sensus	US
Pertussis vaccine	1993	Chiron	US
ranibizumab	2006	Genentech	US
rasburicase	2001	Sanofi-Aventis	France
reteplase (tPA)	1996	Roche	Switzerland
Rexin-G	2006	Epeius Biotechnologies	US
rhCG	2000	Serono	Switzerland
rhLH	2000	Serono	Switzerland
rilonacept	2008	Regeneron	US
rituximab	1997	IDEC	US
romiplostim	2008	Amgen	US
Sargramostim	1991	Berlex labs	US
Satumomab pendetide	1993	Cytogen	US
Sinteplase	1991	Integrated Genetics	US
somatomedin-1	1994	Biogen	US
somatomedin-1	2005	Tercica	US
somatropin	1994	Genentech	US
somatropin	2008	Cangene	Canada
sulesomab	1997	Immunomedics	US
tasonerim (TNF)	1999	Genentech	US
Tc 99m nofetumomab merpentan	1997	NeoRX	US
Tc 99m votumumab (HumaSPECT)	1998	Intracel	US
technetium Tc 99m fanolesomab	2004	Palatin	US
tenecteplase (tPA)	2000	Genentech	US
teriparatide	2002	Eli Lilly	US
thrombin alfa	2008	ZymoGenetics	US
thyrotropin alfa	1998	Genzyme	US
tocilizumab	2005	Chugai	Japan
tositumomab	2003	Corixa	US
trafermin	2001	Scios	US
trastuzumab	1998	Genentech	US
Tumour Necrosis Therapy	2003	Peregrine	US
ustekinumab	2009	Centocor	US

Source: Authors, based on Informa (2007a), FDA, EMEA.

Table 28. **Number of biotechnology clinical trials and pre-registrations by country**

	Phase I	Phase II	Phase III	Pre-registration	Total
Australia	7	7	0	0	14
Austria	4	4	1	0	9
Belgium	4	1	0	1	6
Bermuda	0	3	1	0	4
Brazil	1	1	0	0	2
Canada	6	13	2	1	22
China	3	8	0	0	11
Denmark	10	12	3	0	25
Finland	1	1	0	0	2
France	11	11	2	0	24
Germany	9	21	6	2	38
India	2	0	0	0	2
Ireland	0	3	0	0	3
Israel	1	7	2	0	10
Italy	4	8	2	0	14
Japan	5	12	3	1	21
Malta	1	0	0	0	1
Netherlands	7	5	0	1	13
Russian Federation	0	2	0	2	4
South Korea	6	5	3	1	15
Spain	0	1	0	0	1
Sweden	1	3	2	0	6
Switzerland	12	12	3	0	27
United Kingdom	19	37	12	2	70
United States	140	194	52	7	393
Total	258[1]	372[2]	94	18	742[3]

Source: Authors, based on data from Informa (2007a).

Notes: 1. The originator country was not specified for 4 biotechnology drugs clinical trials in phase I.
2. The originator country was not specified for 1 biotechnology drugs clinical trials in phase II.
3. The column does not sum do to the 5 biotechnology drugs clinical trials for which the originator country was not specified (see notes 1 and 2).

Table 29. **Number of experimental biotechnology therapies in clinical trials and pre-registrations by country**

	Phase I (experimental therapies)										
Therapy Type	Australia	Canada	Denmark	France	Israel	Japan	Malta	Netherlands	South Korea	United Kingdom	United States
Antisense	1	1	1	0	0	0	0	1	0	1	5
Cell & tissue, non-stem cell	0	0	1	1	0	1	0	0	1	1	6
Stem cell	1	0	0	0	1	0	0	0	1	0	9
Gene therapy	0	1	0	1	0	0	1	0	1	0	16
RNA-interference	0	0	0	0	0	0	0	0	0	1	1
TOTAL	2	2	2	2	1	1	1	1	3	3	37

Source: Authors, based on data from Informa (2007a).

	Phase II (experimental therapies)															
Therapy Type	Australia	Austria	Brazil	Canada	China	Denmark	France	Germany	Israel	Italy	Netherlands	South Korea	Spain	Sweden	United Kingdom	United States
Antisense	1	0	0	5	0	1	0	1	0	0	0	0	0	1	1	11
Cell & tissue, non-stem cell	2	0	1	1	0	1	2	1	0	1	2	0	1	0	4	21
Stem cell	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0	4
Gene therapy	0	1	0	0	1	1	3	0	2	2	1	3	0	0	3	27
RNA-interference	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
TOTAL	3	1	1	6	1	3	5	4	2	3	3	4	1	1	9	65

Source: Authors, based on data from Informa (2007a).

	Phase III (experimental therapies)								Pre-registration (experimental therapies)		
Therapy Type	France	Germany	Israel	Italy	Japan	South Korea	United Kingdom	United States	Belgium	Germany	United States
Antisense	0	0	0	0	0	0	0	2	0	0	1
Cell & tissue, non-stem cell	0	1	0	0	0	0	1	4	1	0	1
Stem cell	0	1	1	0	0	0	0	2	0	0	0
Gene therapy	1	0	0	1	1	1	3	5	0	1	1
RNA-interference	0	0	0	0	0	0	0	1	0	0	0
TOTAL	1	2	1	1	1	1	4	14	1	1	3

Source: Authors, based on data from Informa (2007a).

Note: Experimental therapies include cell and tissue engineering (including stem cells) and gene related therapies (including gene therapy, antisense and RNA-interference).

Table 30. **Number of NMEs and bio-NMEs expected to reach registration, by year**

Year	Non-bio NMEs expected to reach registration	Bio-NMEs expected to reach registration	Bio share of registrations
2008	71.3	8.4	11.8%
2009	66.1	13.7	20.7%
2010	81.8	17.6	21.5%
2011	82.8	13.4	16.2%
2012	110.1	11.7	10.6%
2013	94.7	14.2	15.0%
2014	92.6	15.6	16.8%
2015	55.7	11.0	19.8%
2016	36.3	5.3	14.5%
2017	24.1	3.2	13.1%
2018	13.7	0.4	2.7%
Total	729.1	114.4	15.7%

Source: Authors, based on Informa (2007b).

Note: Results exclude formulations. See the text for details and methodology.

Annex B

Therapeutic value tables

Table 31. **Highest HAS evaluation and indication for selected biopharmaceuticals**

	Generic name	Indication with highest evaluation	Highest Evaluation
1	Abatacept	Rheumatoid polyarthritis	2
2	Adalimumab	Rheumatoid polyarthritis	2
3	Agalsidase alfa	Fabry's syndrome	2
4	Agalsidase beta	Fabry's syndrome	2
5	Alemtuzumab	Leukemia	2
6	Alglucosidase alfa	Pompe disease	2
7	Anakinra	Rheumatoid polyarthritis	3
8	Basiliximab	Kidney rejection	4
9	Bevacizumab	Colorectal cancer	2
10	Cetuximab	Head and neck cancer	3
11	Choriogonadotropine alfa	Infertility	4
12	Daclizumab	Kidney transplant rejection	5
13	Darbepoetin alfa	Anaemia	1
14	Desirudin	Venous thrombosis	5
15	Dibotermin alfa	Bone regeneration	3
16	Dornase alfa	Cystic fibrosis	3
17	Drotrecogin alfa	Severe sepsis	6
18	Eculizumab	Anaemia	2
19	Efalizumab	Psoriasis	4
20	Epoetin beta	Anaemia after chemotherapy	1
21	Epoetin delta	Anaemia	5
22	Etanercept	Rheumatoid arthritis juvenile	2
23	Filgrastim	Neutropenia	3
24	Follitropin alfa	Infertility	4
25	Fomivirsen sodium	Cytomegalovirus	6
26	Galsulfase	Mucopolysaccharidosis, type VI	3
27	Idursulfase	Mucopolysaccharidosis, type II	2
28	Imiglucerase	Gaucher's syndrome	1
29	Infliximab	Crohn's disease	2
30	Insulin Aspart	Diabetes	5
31	Insulin glargine	Diabetes	3
32	Insulin lispro	Diabetes	5

Table 31. **Highest HAS evaluation and indication for selected biopharmaceuticals**
(continued)

	Generic name	Indication with highest evaluation	Highest Evaluation
33	Interferon beta 1a	Multiple sclerosis	1
34	Interferon beta 1b	Multiple sclerosis	5
35	Interferon gamma1b	Chronic granulomatous disease	4
36	Laronidase	Mucopolysaccharidosis, type I	2
37	Lutropin alfa	Stimulating ovulation	4
38	Moroctocog alfa	Haemophilia A	6
39	Natalizumab	Multiple sclerosis	3
40	Nonacog alfa	Haemophilia B	5
41	Octocog alfa	Haemophilia A	5
42	Omalizumab	Severe asthma	4
43	Palifermin	Severe oral mucositis	3
44	Palivizumab	Respiratory tract syncytial virus	3
45	Parathyroid hormone	Osteoporosis	5
46	Pegaptanib octasodium	Macular degeneration	3
47	Ranibizumab	Macular degeneration	2
48	Rasburicase	Lymphoma	5
49	Somatropin	Growth hormone	5
50	Tasonermin	Sarcoma cancer	6
51	Tenecteplase	Myocard infarction	4
52	Teriparatide	Osteoporosis	3
53	Trastuzumab	Breast cancer	1

Source: Authors, based on HAS (2008).

Note: Evaluation categories: **1** = Major therapeutic progress; **2** = Important improvement; **3** = Moderate improvement; **4** = Minor improvement; **5** = No improvement ("me too"); **6** = Judgement reserved.

Table 32. **Highest Prescrire evaluation and indication for selected biopharmaceuticals**

	Generic name	Indication with highest evaluation	Highest Evaluation
1	Abciximab	Coronary	3
2	Adalimumab	Rheumatoid polyarthritis	4
3	Agalsidase alfa	Fabry's syndrome	2
4	Agalsidase beta	Fabry's syndrome	5
5	Aldesleukin	Kidney cancer	6
6	Alemtuzumab	Leukemia	4
7	Alfa-1 antitrypsin human	Alpha-1 antitrypsin deficit	5
8	Alglucosidase alfa	Pompe disease	3
9	Alteplase rDNA	Myocardial infarction	4
10	Anakinra	Rheumatoid polyarthritis	5
11	Basiliximab	Kidney rejection	4
12	Becaplermin (gel)	Diabetic ulcers	4
13	Bevacizumab	Colorectal cancer	6
14	Blood Factor VIII hemophilia	Haemophiliacs factor VIII	2
15	Cetuximab	Head and neck cancer	4
16	Choriogonadotropin alfa	Infertility	4
17	Daclizumab	Kidney transplant rejection	5
18	Darbepoetin alfa	Anaemia	5
19	Dornase, alfa recombinant	Cystic fibrosis	4
20	Drotrecogin alfa	Severe sepsis	5
21	Efalizumab	Psoriasis	6
22	Epoetin alfa	Anaemia after chemotherapy	3
23	Epoetin beta	Anaemia after chemotherapy	4
24	Epoetine delta	Anaemia	5
25	Etanercept	Rheumatoid arthritis juvenile	3
26	Filgrastim	Neutropenia	4
27	Follitropin alfa	Infertility	5
28	Follitropin beta	Male sterility	3
29	Fomivirsen sodium	Cytomegalovirus	7
30	Galsufase	Mucopolysaccharidosis, type VI	7
31	Glucagon (rDNA origin)	Diabetes	5
32	Human parathyroid hormone	Osteoporosis	5
33	Ibritumomab tiuxetan	Lymphoma	6
34	Idursulfase	Mucopolysaccharidosis, type II	6
35	Imiglucerase	Gaucher's syndrome	2
36	Infliximab	Crohn's disease	3
37	Insulin asparte	Diabetes	5
38	Insulin determir recombinant	Diabetes	5
39	Insulin glargine	Diabetes	4
40	insulin glulisine recombiant	Diabetes	5

Table 32. **Highest Prescrire evaluation and indication for selected biopharmaceuticals** *(continued)*

	Generic name	Indication with highest evaluation	Highest Evaluation
41	Insulin lispro recombinant	Diabetes	4
42	Insulin recombinant human	Diabetes	2
43	Interferon alfa 2a (peg)	Chronic hepatitis C	4
44	Interferon alfacon 1	Chronic hepatitis C	5
45	Interferon alpha 2b	Karposi's sarcoma	2
46	Interferon beta 1alpha	Multiple sclerosis	3
47	Interferon beta 1b	Multiple sclerosis	3
48	Interferon gamma 1b	Chronic granulomatous disease	3
49	Laronidase	Mucopolysaccharidosis, type I	3
50	Lepirudin (rDNA) for injection	Anticoagulant	4
51	Lutropine alfa recombinant	Stimulating ovulation	5
52	Methoxy Polyethylene Glycol-Epoetin Beta	Anaemia associated with chronic renal failure	5
53	Muromonab-CD3	Kidney transplant rejection	3
54	Natalizumab	Multiple sclerosis	6
55	Omalizumab	Severe asthma	6
56	Palifermin	Severe oral mucositis	6
57	Palivizumab	Respiratory tract syncytial virus	4
58	Pegfilgrastim	Neutropenia after chemotherapy	4
59	Pegvisomant	Acromegaly	4
60	Ranibizumab	Macular Degeneration	3
61	Rasburicase	Lymphoma	5
62	Reteplase plasminogen activator	Myocardial infarction	5
63	Rituximab	Lymphoma	3
64	Somatropin rDNA	Growth hormone	4
65	Tenecteplase	Myocardial infarction	4
66	Teriparatide	Osteoporosis	5
67	Thyrotropin alfa	Thyroid cancer	4
68	Trastuzumab	Breast cancer	3

Source: Authors, based on *Prescrire* (various).

Annex C

Prescrire evaluations category definitions

Based on the results of its expert drug evaluations, *Prescrire* assigns each drug to one out of six categories, ranging from a "major" advance to "not acceptable" (the drug offers no benefits over existing alternatives but has potential or real disadvantages). In addition, a seventh category is used when the available data are insufficient for assessing the therapeutic value of the drug. A full definition of each evaluation category is given in Table 33.

Table 33. ***Prescrire* definitions**

	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 the 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 potential or real disadvantages.
7	Judgment reserved	*Ne peut se prononcer*	The editors postpone their judgment until better data and a more thorough evaluation of the drug are available.

Source: English definitions are from *Prescrire International*.

Annex D

Pharmaprojects biotechnology classifications

T2A1 RECOMBINANT INTERFERON – Interferons which have been produced using recombinant DNA technology (genetic engineering).

T2A2 RECOMBINANT INTERLEUKIN – Interleukins which have been produced using recombinant DNA technology (genetic engineering).

T2A3 RECOMBINANT GROWTH FACTOR – Growth factors which have been produced using recombinant DNA technology (genetic engineering) including colony stimulating factors, transforming growth factor, epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, nerve growth factor and ciliary neurotrophic factor.

T2B RECOMBINANT VACCINE – Vaccines, including cancer vaccines and contraceptive vaccines, which have been produced using recombinant DNA technology (genetic engineering). This includes prophylactic nucleic acid vaccines ("naked DNA" vaccines).

T2C RECOMBINANT HORMONE – Animal hormones which have been produced using recombinant DNA technology (genetic engineering) including calcitonin and somatomedin.

T2D LYTIC VIRUS – Replication-competent viruses, which lyse pathogenic cells directly, particularly oncolytic viruses which specifically attack cancer cells. These are normally GM to render them harmless to normal tissues.

T2Z RECOMBINANT, OTHER – Proteins and their derivatives which have been produced using recombinant DNA technology (genetic engineering), except interferons, interleukins, growth factors, vaccines and hormones, which have there own sections as shown above. Recombinant molecules in development include clotting factors, cell adhesion molecules, cytokine antagonists, enzyme replacement therapies and chimaeric molecules.

T3A1 MONOCLONAL ANTIBODY, MURINE – Monoclonal antibodies which are not conjugated to another agent and which are derived from immunization of mice and rats.

T3A2 MONOCLONAL ANTIBODY, HUMAN – Monoclonal antibodies which are not conjugated to another agent and which are completely derived from humans, or have fully-human sequences.

T3A4 MONOCLONAL ANTIBODY, CHIMAERIC – Monoclonal antibodies which are not conjugated to another agent and which are engineered to contain portions derived from both human and animal sources, but are less than 70% human. This section does not include humanized antibodies (see T3A5).

T3A5 MONOCLONAL ANTIBODY, HUMANIZED – Monoclonal antibodies which are not conjugated to another agent and which are engineered to contain 90-95% human sequences, with the remainder usually consisting of rodent sequences. Fully-human monoclonal antibodies are classified separately in T3A2.

T3A9 MONOCLONAL ANTIBODY, OTHER – Monoclonal antibodies which are not conjugated to another agent and which are derived from an unknown source, or cannot be classified in other T3A categories.

T3B1 IMMUNOTOXIN – Immunotoxins are conjugates or fusion proteins of immunoglobulins (usually monoclonal antibodies) and toxins. The immunoglobulin will deliver the toxin to cells exhibiting the appropriate antigen, without the toxin coming into contact with normal cells.

T3B9 IMMUNOCONJUGATE, OTHER – Conjugates of immunoglobulins with other agents, excluding toxins, which are listed in Immunotoxin (T3B1). With all of these agents the antibody part of the molecule is used to direct it to its target, where the effector part of the molecule will perform its action.

T4A GENE THERAPY – Gene therapy is a term used to describe vector-mediated introduction of a therapeutic genetic sequence into target cells in vivo or ex vivo. Vectors may be viral or non-viral (*e.g.* plasmids). Strategies include replacement of defective or missing genes (*e.g.* for cystic fibrosis), or introduction of more broadly-acting (*e.g.* immunostimulant) sequences for the treatment of multifactorial diseases (*e.g.* cancer). Gene therapy vectors may also be used to deliver antisense and RNA interference sequences (see T4B and T4F). Lytic viruses which do not deliver therapeutic DNA are covered in T2D and non-recombinant mammalian cells are covered in T5A (stem cells) and T5Z (other types). Direct administration of oligonucleotides without using vectors is covered separately in T4B (for antisense), T4F (for RNA interference) or T4E (for other oligonucleotide types). Platform technologies for gene delivery are covered separately in T4D.

T4B ANTISENSE THERAPY – Includes all entries for antisense compounds under development as potential therapeutics. Antisense compounds may be synthetic oligonucleotides, or antisense RNA may be expressed from a vector as a form of gene therapy (see T4A). They may prevent the expression of a specific protein in vivo by binding to and inhibiting the action of mRNA, since they have a specific oligonucleotide sequence which is complementary to the DNA or RNA sequence which codes for the protein.

T4D GENE DELIVERY VECTOR – Platform technologies for the delivery of therapeutic genes or nucleic acid vaccines. Viral and non-viral vectors (*e.g.* liposome systems) are included. Actual therapies and vaccines using these technologies are covered separately in T4A (for gene therapy) and T2B (for nucleic acid vaccines).

T4E OLIGONUCLEOTIDE, NON-ANTISENSE, NON-RNAI – Synthetic therapeutic oligonucleotides which operate by a mechanism other than antisense or RNA interference (RNAi). This includes ribozymes, aptamers, decoys, CpGs and mismatched and immunostimulant oligonucleotides. Sequences delivered using vectors (gene therapy) are covered separately in T4A. Antisense and RNAi oligonucleotides are covered separately in T4B and T4F, respectively.

T4F RNA INTERFERENCE – Includes all entries for products which act therapeutically via an RNA interference (RNAi) mechanism, including small interfering RNAs (siRNAs). These may be synthetic oligonucleotides, or RNAi sequences may be expressed from a vector as a form of gene therapy (see T4A). In vivo, these sequences block the expression of a specific protein by forming an RNA-induced silencing complex, which then specifically binds to and degrades a complementary mRNA encoding the target protein. The use of RNAi purely as a drug discovery tool (*e.g.* in transgenic animal model production or in target validation) is not covered in this section.

T5A STEM CELL THERAPY – Non-recombinant cultured mammalian stem cells used as therapeutics. Recombinant stem cells are classified separately as ex vivo gene therapy (in T4A).

T5Z CELLULAR THERAPY, OTHER – Non-recombinant cultured mammalian therapeutic cells other than stem cells. Includes products such as dendritic cells, pancreatic islet implants, cultured wound healing products and cultured T-lymphocytes.

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