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BUILDING THE BIOECONOMY 2016 ANNEX

Enabling Factors and Economy Case Studies

This report was commissioned by the Biotechnology Industry Organization. The views represented here are those of the authors only.

CONTENTS

LIST OF ABBREVIATIONS

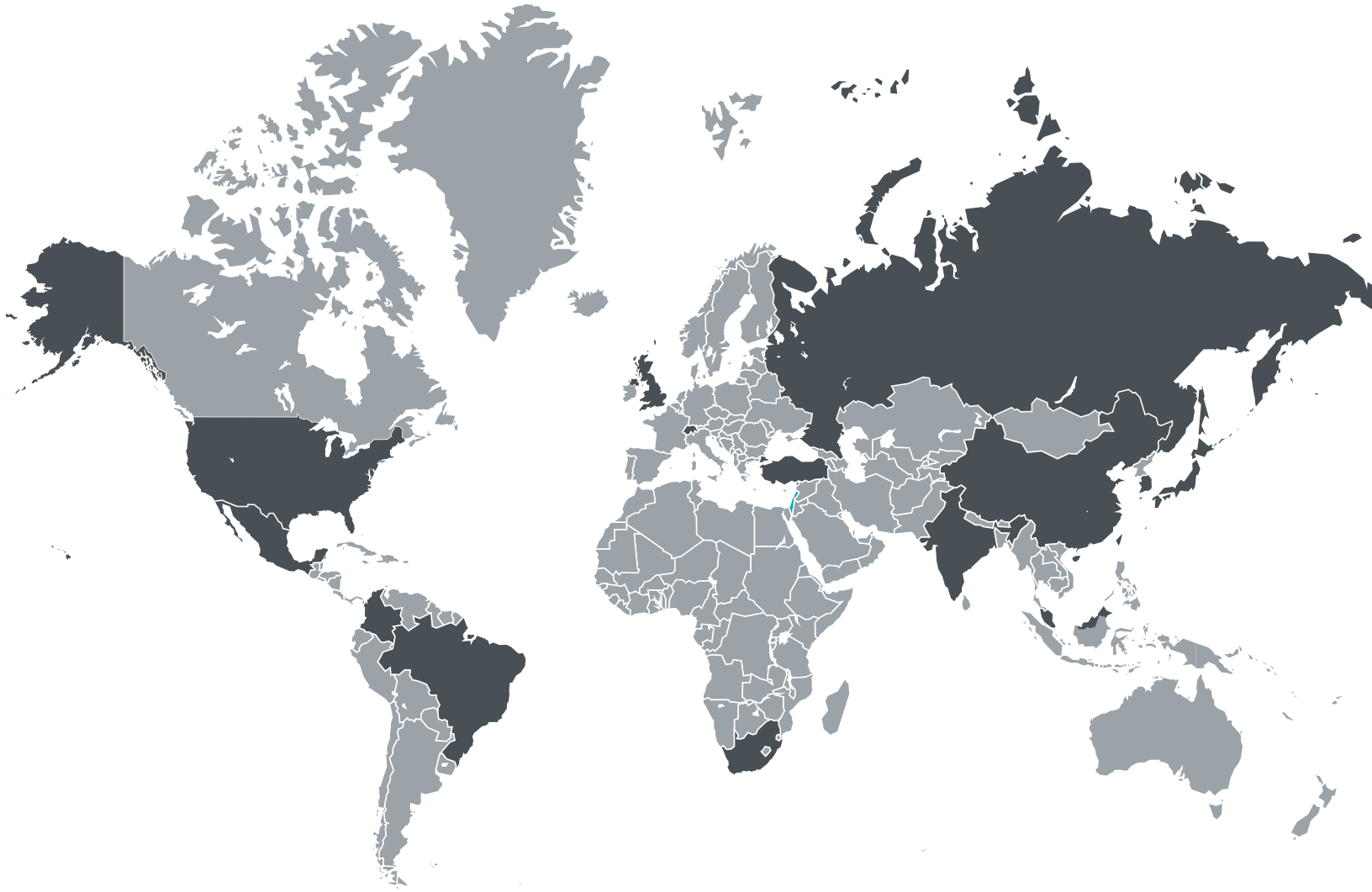
ANVISA	Brazilian National Health Surveillance Agency
API	Active Pharmaceutical Ingredient
A*STAR	Agency for Science, Technology and Research (Singapore)
BNDES	Brazilian Development Bank
BRICS	Brazil, Russia, India, China, South Africa
CDSC	Central Drugs Standard Control (India)
CLs	Compulsory Licenses
CONEP	Brazilian National Research Ethics Commission
CTI	Commission for Technology and Innovation (Switzerland)
CTNBio	Brazilian Biosafety Technical Commission
DTI	Department of Trade and Industry (South Africa)
EMA	European Medicine Agency
EMBRAPA	Brazilian Agricultural Research Corporation
EPA	US Environmental Protection Agency
FINEP	Funding Authority for Studies and Projects (Brazil)
FDA	US Food and Drug Administration
FDI	Foreign direct investment
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GM/GE	Genetically Modified/Genetically Engineered
GMO	Genetically Modified Organism
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICT	Information and Communications Technologies
INPI	Brazilian Patent Office
IP	Intellectual Property
IPRs	Intellectual Property Rights
IRP	International Reference Pricing
MOA	Ministry of Agriculture
MNC	Multi-National Company

LIST OF ABBREVIATIONS (continued)

NGO	Non-Governmental Organization
NIH	US National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
PE	Private Equity
P&R	Pricing & Reimbursement
PCT	Patent Cooperation Treaty
PPP	Purchasing Power Parity
PRO	Public Research Organization
RDP	Regulatory Data Protection
R&D	Research and Development
SFDA	State Food and Drug Administration (China)
SME	Small and Medium Enterprises
STI	Science, Technology and Innovation
S&E	Science and Engineering
TRIPS	Trade-Related Aspects of Intellectual Property Rights
TUBITAK	Scientific and Technological Research Council (Turkey)
USDA	US Department of Agriculture
USPTO	US Patent and Trademark Office
USTR	US Trade Representative
VC	Venture Capital
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

ENABLING FACTORS AND ECONOMY CASE STUDIES

Accompanying the *Building the Bioeconomy 2016* main report this Annex contains a full and detailed discussion of each of the seven enabling factors used to map each economy's biotechnology environment. The Annex provides the underlying data and information for each enabling factor used for the main report including the Biotech Policy Performance Measure. It is a reference tool to be used together with the main report.



Brazil

Brazil's total GDP was USD2.3 trillion in 2014, making it the world's seventh largest economy. On a per capita basis Brazil is a middle-income country, with a per capita GDP at PPP of USD16,155.[1] In 2015 the economy shrank by 3.8%.[2] This steep contraction, the worst for Brazil since 1990, was fuelled by political crisis, increased inflation and interest rates and decreased price of export commodities.[3]

In the World Economic Forum's Global Competitiveness Ranking 2015-2016, Brazil dropped dramatically from the 57th to the 75th position in just one year, the lowest among BRICS countries, because of deteriorating terms of trade and modest prospect of growth.[4] A high tax burden and labor costs coupled with poor infrastructure and low productivity continue to represent the main barriers to competitiveness.[5] In terms of cyclical factors, inflation has also depressed internal demand, although depreciation of the Brazilian real has supported exports.[6]

National Innovation Policy

In January 2016 Law 13.243/2016 (on the Regulatory Framework for Science, Technology and Innovation) came into effect. The law aims to enhance research and increase investments in the fields of science, technology and innovation by reducing red tape and facilitating public-private cooperation. Among various measures, the regulation introduces tax incentives and simplifies procurement for innovators, allows governmental entities to invest in research carried out by private companies and eases the procedure for businesses to hire foreign scientists and technologists.[7] It also releases BRL200million (USD 50million) in funding for research projects in all areas of science and technology.[8]

Less than two months before, on 17 November 2015, the new Law on Research relating to Biodiversity and Biotechnology entered into force.[9] The legislation (*Lei Ordinária* 13123/2015) is meant to simplify the registration procedure and reduce existing hurdles for researchers and the commercialization of new products and technologies. Requests to access genetics resources are to be managed by an electronic registry; yet to be created. Unfortunately the legislation and roll-out has been hampered by a number of challenges.

First, foreign companies will have to partner with national R&D institutions to be able to apply.[10]

Second, there is a high level of uncertainty surrounding the law as complementary regulation has yet to be released but already revoked the legal framework in place since 2001 (Provisional Measure 2186-16). The net effect is that researchers operate in a regulatory vacuum whereby requirements on issues such as consent, registration or handling of genetic materials are not defined.

Finally, an implementing Decree,[11] submitted for public consultation in April 2016, adds another hurdle for biotech investors by introducing a tax corresponding to 1% of the final price of products created from the country's biologic resources.

Following the 2014 new ordinance by the Ministry of Health on the "Productive Development Partnerships" (PDPs), interests in these public-private partnerships aimed to further R&D particularly in biopharmaceuticals reportedly grew for both local and international firms. Investments by the domestic pharmaceutical companies increased by 52% compared to the first five months of 2014, mainly directed to the production of biosimilars as part of PDPs.[12] In spite of stepping up their efforts to participate in PDPs (14 proposals submitted in 2015 against 32 in the period 2009-2014), international biopharmaceutical companies stress the need for continuous transparency and accuracy in choosing strategic technologies and controlling prices set within PDPs.[13]

Biopharmaceuticals

In 2015 the health and pharmaceutical sectors captured an estimated 35% of R&D public spending.[14] In February 2016, BNDES approved BRL401million (USD103 million) in funding for two biopharmaceutical production plants.[15] Working within a PDP agreement with the Brazilian

Government, in October 2015 Eurofarma became the first Latin American company to win regulatory approval for a biosimilar drug (Fiprima).[16] Also, in July 2015 a Brazilian biopharmaceutical company (Recepta Biopharma) granted use of its innovation to a US company, the first such intellectual property deal concluded by a Brazilian company.[17]

Although Brazil remains the biggest Latin American biopharmaceutical market, worth an estimate of USD20 billion in 2015[18], the biopharmaceutical sector continues to be hampered by regulatory hurdles, weak IP protection, significant government intervention through price controls and technology transfer requirements, and a high tax burden, which tend to indirectly support and/or provide negative incentives for investment in its local generic and biosimilar sectors. Brazil also has in place policies and laws encouraging local manufacturing in a number of industries including biopharmaceuticals. The 2010 law 12,349 established preferences for businesses producing goods in Brazil with a local preference margin of up to 25% over an equivalent bid from an importing company.[19] As part of the *Brasil Maior* initiative these preference margins were extended to the pharmaceutical industry in 2012 with decrees 7709 and 7713 with margins ranging from 8 or 20%.[20]

Looking at rates of product launches between 1983-2000, the percentage of products available in Brazil within five years of global launch was 32%.[21] This was squarely in the middle of the sampled economies.

With regards to the BCI Survey Brazil ranked last of the economies included in *Building the Bioeconomy* with an overall score of 53.52. [22]

Ag-bio

Brazil has a tradition of strength in the agricultural biotech sector, and is the second biggest grower of biotech crops after the US, with 44.2 million hectares in 2015.[23] This accounted for one fourth of all biotech crops globally. Brazilian production increased by 2 million hectares compared to 2014 with soybean experiencing a rapid increase.[24] Growing hectarage can also be ascribed to more important aid packages for 2015/16 compared to the previous crop season, although at higher interest rates. Indeed, availability of Government subsidized credit lines for farmers grew by 20%, reaching a record high of USD70 billion.[25]

EMBRAPA has also developed and registered an extensive portfolio of international patents. Over the years the Agency has accumulated over 200 IP and developed 350 cultivars.[26] It is also becoming more active in public-private partnerships, including with international industry. EMBRAPA has through a number of private-public partnerships developed and brought to market new ag-biotech products and technologies. For instance, in 2015 Brazil approved cultivation of a 20% higher yielding homegrown eucalyptus developed by FuturaGene in cooperation with the Agency.[27]

Industrial biotechnology

The domestic Brazilian sugar-cane ethanol industry is one of the biggest in the world, projected to increase further by 5% to 30.68 billion litres from 2015 to 2016.[28] Public subisides for the ethanol industry were cut as BNDES reduced its funding for sugar, ethanol and bioenergy industry from BRL6.8 billion in 2014 to 5 billion in 2015.[29] 2015 also saw the Inter-ministerial Sugar and Ethanol Council authorize the increase the ethanol blend in gasoline from 25% to 27%.[30] In addition to supporting sugar-based ethanol, the Brazilian Government has also backed soybean based biodiesel by instituting a national biodiesel mandate. The mandate went into force in 2008 requiring a 2% biodiesel blend nationally. Legislation adopted in March 2016 increases the current blend composition to 8% and to 9% in the next 2 years and to 10% by the next 3 years.[31] The bill authorizes blending of up to 15% biodiesel if automobile manufacturers approve its use.[32]

Performance in key enabling factors

Human capital

Brazilian universities are not widely recognized in international rankings. No Brazilian university is included in the top 100 of the 2015-16 *Times Higher Education* rankings.[33] The University of São Paulo, which in 2014-15 ranked at the 92nd place in the life sciences ranking, did not make it to the top 100 in 2015-16.[34] In terms of academic

and research publications, Brazil has compared to other *Building the Bioeconomy* countries relatively low numbers of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Brazil had 49.65 publications per million population.[35] Brazilian academic publications did not rank highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with only 6.72% of publications among the 10% most cited.[36]

Examining the number of graduates in higher education and number of researchers Brazil has seen a steady increase in the last decade. Looking at number of researchers in the population the latest (2010) data from the World Bank shows that Brazil had 698 researchers per million people.[37] This is almost a doubling of researchers since 2000 when the equivalent figure per million population was 423.[38] However, it still remains low when compared to other middle income counties such as China and Turkey.

Brazil in 2011 introduced an international student exchange program Science Without Borders (*Ciência sem Fronteiras)*, which has since then funded around 101,000 scholarships.[39] This program seeks to:

- place Brazilian science and technology students at international universities and research institutions;
- attract foreign science and technology students to study in Brazil;
- internationalize Brazilian higher education institutions by promoting partnerships and collaboration with institutions in other countries; and
- promote the return of Brazilian scientists and graduates to Brazil.[40]

However, against the background of the national financial and economic crisis, the budget for this program has been slashed from BRL4,8 billion in 2015 to less than 2 billion in 2016.[41]

Infrastructure for R&D

Brazil is a major investor in R&D in Latin America. In 2011, Brazilian gross domestic R&D spending totalled USD27.4 billion at PPP.[42] Brazil also has a relatively competitive level of R&D spending as a percentage of GDP in comparison to other BRICS and middle-income countries. Updated 2012 figures show R&D spending as a percentage of GDP at 1.15%.[43] This is lower than the OECD average of 2.40%.[44]

Looking at biotechnology triadic patenting, Brazil's share of global total average for the period 1999-2012 is 0.12%, the lowest among the BRIC countries.[45]

Overall the clinical trials environment is challenging and clinical research in Brazil is below levels expected. Although the total number of trials is relatively high (4,944 being out of a regional total of 7,170 in Latin America),[46] Brazil is still behind other markets on a per capita basis, with 22.89 trials per million population; ahead of Russia China and India but below levels of world-leaders such as Singapore, Korea and the US.[47]

Looking at recent clinical trials for biologics Brazil's levels was relatively low. Between 2010-2015 Brazil had on average 0.74 biologic trials per million population; ahead only of China and India.[48]

Brazil has 2% of the clinical centres in the world performing research and, according to local scientists and clinicians, is losing potential trials to other countries due to its burdensome regulatory requirements.[49]

Brazil is not viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Brazil is ranked last in The *Venture Capital & Private Equity Country Attractiveness Index* with a score of 61.3. [50]

Intellectual property protection

A number of developments took place in 2015 that negatively affect the environment for biotech patenting in Brazil.

ANVISA continues to have the right to provide prior consent to pharmaceutical patents that are being examined by the INPI. Consequently, decisions on whether to grant a pharmaceutical patent are based on examination not solely by patent specialists and officials at INPI, but also by ANVISA. This introduces a requirement of dual examination and is in violation of the TRIPS Agreement. The exact meaning and nature of ANVISA's right to prior consent has been questioned in a court of law. In fact, in a number of these cases ANVISA's authority has been questioned and injunctions granted. In June 2015 a potentially landmark decision was issued by a Federal District Court in Rio de Janeiro.[51] The decision held that ANVISA was in fact permitted to review pharmaceutical patents and the insertion of ANVISA into the review process was an essential element of safeguarding public health. The ruling also held that a denial by ANVISA of a patent application should result in a refusal by the INPI. Wide adoption of this ruling and its interpretation of the relevant laws and ANVISA's role would exacerbate what is already a challenging environment for biopharmaceutical innovators in Brazil.

Moreover, a pending patent reform initiative, Bill No. H.R 5402/2013, would broaden the statutory role of ANVISA in the patent examination process.[52] Under the amendments, ANVISA would be required to review pharmaceutical patent applications on the basis of the patentability criteria in the Brazilian patent law (including the new amendments) and deny patent applications for new uses and forms of existing compounds as well as more broadly pharmaceutical compounds that are considered by ANVISA to be of strategic importance to access to medicines in the country. The amendments also confirm and establish in law that ANVISA's decision overrides patent office examination. Specifically, the amendments would expand Article 229C considerably, stating:

Article 229C – The granting of patents for pharmaceutical products and processes shall depend on the prior consent from the National Sanitary Agency – ANVISA, ***that shall examine the object subject to the patent application in light of public health.***

§ 1 – A patent application shall be considered as contrary to public health, according to further regulation, where:

I – the product or pharmaceutical process in the patent application presents a health risk, or

II – the patent application for pharmaceutical product or pharmaceutical process ***is of interest to an access to medicines policy*** *or to a pharmaceutical care program under the National Health System – SUS,* ***provided that it does not meet the patentability requirements and the other criteria established by this law.***" [Emphasis added]

§ 2 – Following the prior consent examination and after the decision is published, ANVISA shall return the application to the Patent Office, that shall examine the approved application, and definitively archive the application that has not been approved."

The current procedure has already led to a great deal of uncertainty, delays and costs. Around 200 cases of undecided applications were documented in 2014 alone due to conflicting opinions between ANVISA and INPI. Moreover, the procedure adds one year on average to the already long patent approval process.[53]

Indeed, severe patent office delays represent a further barrier to patentability in Brazil. The patent office's backlog of patents is estimated at an average of ten years, further exacerbated by the involvement of ANVISA in the patent examination process.[54] This is particularly pronounced for sectors such as biopharmaceuticals, where a number of applications filed in the late 1990s are still awaiting a decision. Several initiatives have been introduced to attempt to address this backlog however they have yet to have a significant impact.[55] In some cases they have also been targeted only toward "strategic" pharmaceutical inventions that are in line with the Ministry of Health's priorities.[56] The last few years has seen suggestions by the patent office to repeal an existing 10-year minimum patent period guarantee (which is in place to safeguard innovators for the long delays and backlog) and reduce an innovator's exclusivity period to a

fraction of the internationally accepted 20-year period enshrined in the TRIPS agreement.[57]

The other major challenge in relation to patentability in Brazil centers around consideration of legislation that would introduce an additional criterion to patentability on top of the basic three requirements in the TRIPS Agreement. On top of confirming and expanding ANVISA's role in the patent examination process Bill No. H.R 5402/2013 also emulates many of the requirements of India's Section 3(d).[58] Among other things, the bill purports to narrow patentability criteria even further, disallowing patents on new uses or new forms of known substances unless a significant improvement to the known efficacy is present, in many ways matching India's Section 3(d) requirements. The bill also seeks to raise the inventive step standard so that an invention must show a significant technical advance with regard to the current state of art.[59] If adopted, the legislation could lead to a patenting environment even more out of sync with international norms, and introduce further uncertainty and subjectivity to the patenting process.

Finally, with regards to biotechnology patentability rules for biotech are narrow by international comparisons. For example, fundamental research areas in industrial and environmental biotech such as isolated microorganisms (including bacteria and yeast) are not patentable.[60] Existing patent law only allows patents for transgenic microorganisms even though the use of all microorganisms in biotech R&D is increasing and leading to new innovations.[61]

Unlike many OECD economies and a growing number of middle-income countries Brazil only provides regulatory data protection of submitted clinical test data for fertilizers, agrochemical products, and pharmaceuticals for veterinary use. Biopharmaceuticals for human use are not covered by existing regulations.

The regulatory environment

Since the 1970s Brazil has built an institutional framework supporting investment and innovation, including the National Development Bank (BNDES) and FINEP (Funding Authority for Studies and Projects).[62]

Biotechnology is regulated primarily by ANVISA and CTNBio. ANVISA is responsible for the regulation of biologics as well as biosimilars (a biosimilars pathway was introduced in 2010/11).[63] CTNBio is responsible for the regulation of all activities (including research and commercialization) of biotech and GM products or technologies.[64]

Approval for clinical research needs to go through two separate bodies (CONEP, the National Commission for Ethics in Research, and ANVISA) and can stretch to over one year compared to three months in the US and EU.[65] ANVISA's recent efforts to streamline the approval process (Resolution RDC No. 9 from March 2015) mainly reduce evaluation timelines for synthetic drug Phase III trials. If approval is not granted within 90 days, trials can be initiated after CONEP review. However, as concerns biologics, ANVISA established a 180-day approval target, but its response remains mandatory to commence the trial.[66]

As mentioned, with regards to the processing of patent applications the INPI continues to have a large backlog of patents (estimated at about 11 years) and processing times are quite long for all art groups. Problems are particularly pronounced for high tech sectors including biopharmaceuticals and telecommunications where delays can reach 13 years.[67] INPI tried to address it with adoption of Rule 151/2015 in November 2015. The rule allows prior examination for applicants that can show a third party is reproducing the subject matter of their patent application.[68] At the same time, it formally revokes the possibility for the Ministry of Health to fast-track applications of drugs regularly purchased by the public health system. Finally, it also implements a pilot program between USPTO and INPI that grants priority examination to patent applications when USPTO has issued a note of allowance for the same invention.[69] However, the program covers only oil and gas technologies.

Technology transfer

Brazil has a number of policies and regulations in place to promote the transfer of technology. For instance, a key tenet of the 2004 Innovation Law was to encourage the transfer and commercialization of technologies through

incubation services for public researchers and greater encouragement of start-up activities.[70] The law provides incentives including royalty guarantees to inventors. The new Regulatory Framework on Science, Technology and Innovation is expected to improve conditions for partnership between businesses and universities. It allows teacher of public universities to take up jobs in the private sectors and almost doubles the time that researchers from public bodies can spend working on research projects outside university without loosing career benefits.[71] Additionally, universities will be allowed to share their laboratories and teams with companies to carry out research.[72] There are regulatory and formal requirements in place that limit the attractiveness of licensing and widespread technology transfer. For example, to become effective and binding on third parties licensing agreements must be published in the INPI's *Official Gazette*.[73] Agreements must also be approved by INPI. There are also limitations on fees and payments between the contracting parties.[74] Exclusive licensing agreements are also subject to more onerous publication requirements than non-exclusive licenses making this process more time-consuming.[75]

And looking at concrete tech transfer outputs Brazil lags behind. As of 2015, no Brazilian university was ranked among the top 50 university PCT applicants.[76] Indeed, according to a 2015 industrial survey by the National Industrial Confederation, most executives consider the level of innovation in the country as low or very low, mainly because of insufficient links with universities, as well as lack of incentives and human resources.[77]

Market and commercial incentives

Brazil has R&D tax credits in place under Law N. 11.196. These include a potential 160% super-deduction on eligible R&D related expenses.[78] This deduction can also escalate rising to a maximum 180% when reaching certain conditions if there is a year-on-year cumulative increase in R&D spending. There is also an additional 20% deduction available once an invention has been patented. However, this is available only once a patent has been issued. The recent Regulatory framework on Science, Technology and Innovation reduces taxes for import of research materials and exempts from mandatory bid procedure to purchase R&D materials up to BRL75,000.[79]

With regards to the biopharmaceutical market relatively strict price controls are in place. Reference pricing is used extensively and is calculated on the lowest average ex-manufacturing price of the biopharmaceutical product in a basket of countries. Countries included in the basket are Australia, Canada, Spain, US, France, Greece, Italy, New Zealand, Portugal as well as the country of origin of the drug. In addition, there is a separate price calculation for "exceptional medicines" to which a "Coefficient Adequacy Price" (CAP) is applied.[80] The CAP is calculated comparing Brazil's GDP with the GDP of the selected reference country. CAP calculation can be applied when the product being priced is not on the market in at least 3 countries in the IRP basket.

In September 2015 the Brazilian High Chamber proposed to forbid court-ordered injunctions against the government that require it to pay for treatments not covered by the Brazilian Essential Drug List, such as innovative and orphan drugs including those imported. Healthcare-related lawsuits against the government, such as these, are reportedly rising and currently estimated to account for one third of the total.[81] Law 13,137/2015 adopted on 22 June 2015 increases the tax burden on various imported products, of which medicines are expected to be the most affected.[82] According to industry estimates, the proposed tax hike would result in a 6.2 increase in drug prices overall.[83]

Legal certainty (including the rule of law)

The Brazilian judiciary is independent although the courts are overburdened and the resolution of contract disputes can be a lengthy process.[84] These challenges are reflected in Brazil's ranking on international indices measuring the rule of law. For example, in the 2015 *Rule of Law Index* Brazil ranked 46nd out of 102 countries mapped.[85]

China

China is the world's second largest economy with a national GDP of USD10 trillion in 2014.[86] The World Bank defines China as an upper middle-income country, with GDP per capita at PPP of USD13,216 in 2014.[87] Though having slowed somewhat over the past few years due to global cyclical dynamics and internal structure factors, China's economic growth remains robust relative to the rest of the world.[88] China ranks 28th out of 140 in the World Economic Forum's 2015-16 Global Competitiveness Index, its position largely unchanged over the past several years.[89]

National Innovation Policy

Building on and reiterating some of the objectives of the 2006 Medium- and Long-term Plan for Science and Technology Development 2006-20", China's latest five-year plan strengthens the country's focus on innovation with an emphasis on "biological technology." According to the plan, approved on 16 March 2016, China will increase science and technology investment by 9.1% to CNY271 billion (USD 41 billion) in 2016.[90] As already included in the 2006 Plan, R&D funds are expected to reach 2.5% of GDP by 2020, up from 2.05 in 2014.[91] Science and technology innovation is to be achieved by strengthening basic research and building on existing technologies.[92] Accordingly, funding for basic research is also expected to rise from 5% to 10% of total R&D spending by 2020.[93] Furthermore, the new five-year plan promises to better protect of IP rights, create new innovation clusters, national laboratories and market-oriented research institutions, empower universities to decide more autonomously on their research and funding as well as organising international scientific programs.[94] Chapter VI of the plan outlines priority areas for indigenous innovation, including neuroscience and genetic research, clean use of coal and high-tech medical devices.[95] Prime Minister Li mentioned tax breaks for companies that invest in high-priority areas and a reduction of bureaucratic hurdles to promote R&D.[96]

In a further major national innovation development in February 2016, the Ministry of Science and Technology launched a new national R&D program to streamline and increase efficiency of existing redundant programs. The plan will merge over 100 programs, including biotechnology ones, into five plans.[97]

Biotech sector by sector policy overview

Biopharmaceuticals

Looking at biopharmaceuticals, R&D in China has been expanding rapidly with R&D expenditures in the pharmaceutical industry reaching USD3.249 billion in 2011 compared to just USD162 million in 2000.[98] However, a large proportion of this funding went towards biosimilar products and traditional Chinese herbal medicines. A similar pattern can be found in the distribution of public sector funding with USD26.65 million earmarked for biologics compared to USD105.7 million for chemical medicines and USD41.87million for herbal remedies.[99]

Like many emerging markets China has adopted a range of policies attempting to 'localize' innovation through erecting trade barriers and/or local manufacturing/R&D requirements. Opinion N.44 and the ensuing implementing measures adopted in November 2015 (Circular N.230) introduce various other measures aimed at improving the quality and transparency of the drug approval system, encourage R&D of new drugs and tackle the registration backlog of drug applications.[100] Among these, a revised, more restrictive definition of "new drugs" is set to favor the national industry to the detriment of innovators, as drugs that have been marketed outside China but not in China will be regarded as generics (see a more detailed discussion below under "Intellectual Property").[101]

With regards to the BCI Survey China ranked in the lower third of the economies included in *Building the Bioeconomy* with an overall score of 54.54. [102]

Ag-bio

While it has long been a priority for Chinese policymakers to build a strong biopharmaceutical capacity, with regards to the agricultural biotechnology sector the picture is more mixed.

On the one hand the central government is on track to spend USD4 billion dollars on GMO seed research by 2020 and has invested in related infrastructure (for example a massive warehouse to store genetically modified seeds).[103] But on the other hand, key decision-makers have expressed caution about full commercialization and use of ag-bio products. Similarly, public fears of GMO food have resulted in very few GMO seed varieties being commercialized. Indeed, the regulatory pathway to commercialization has not been easy to navigate either for international or Chinese innovators. The Ministry of Agriculture has only approved six GMO plants since 1997.[104] An ongoing revision of biotech regulations would raise the bar even further by adding "economic and social factors" to the GM approval process, raising uncertainty for applicants.[105] Currently, the Ministry allows the growing of GM cotton, peppers, tomatoes and papayas and the importation of GM soybeans and corn.[106] However, reports of illegal plants of GM crops have increased over 2015,[107] leading to an unprecedented wave of warning notices to farmers from local authorities ahead of the 2016 crop season.[108]

Still, there are indications that the government recognizes that public fears of genetically modified products must be quelled if the country is to successfully feed its population. In its 2016 "Number one Central Document", an annual report that focuses on the countries agricultural sector, China committed to gradually promote GM-related technology.[109] Other recent developments show that the Chinese Government might be shifting its focus from simply promoting basic research to developing commercially viable solutions. A major breakthrough for China's biotechnology industry is ChemChina's recent USD43 billion bid for agricultural company Syngenta,[110] a move set to bring technology and know-how to the Chinese fragmented seed industry, and to possibly ease public resistance to GM by building a national champion in the field. The deal can be read against the wider framework of the country's recent Five Year Plan, which calls for modernization of the domestic food production and maintains biotechnology as a strategic emerging industry for the Chinese economy to move up the value chain.[111] The revised Seed Law lists various supporting measures for the national seed industry, such as subsidies, building of infrastructure and support to insurers as well as financial and research institutes engaging in the field.[112] Moreover, two Chinese seed companies, Da Bei Nong and Origin, in 2015 announced that they were ready to get cultivation approval for their biotech corn varieties, a process expected to take three to four years.[113]

Industrial biotechnology

Looking at industrial biotechnology and the biofuels sector, China is not a large producer of biofuels. While significant investment has been made into renewable energies since the early 2000s (particularly in wind and hydropower) biofuels lag behind. China has a commitment to reach specific targets in biofuels production. For bioethanol (from non-food grain) and biodiesel (the two main forms of biofuels) 2020 targets are 12,7 billion litres (10 million tonnes) and 2,54 billion litres (2 million tonnes), respectively.[114] Yet, estimates show that production in 2015 was 3.08 billion litres of bioethanol and 1,14 billion litres of biodiesel.[115] In 2014 China produced 2.9% of global biofuels. This is far behind countries like the US and Brazil (at 42.5% and 23.5% respectively) and puts China behind countries like Indonesia (3.5%) and Argentina (3.6%).[116] Yet, recent policy developments are likely to increase demand for renewable energies, including biofuels, such as the nationwide Emission Trading Scheme announced in September 2015 and planned to begin in 2017. The 13th Five Year Plan attaches greater attention to green economy and investments, such as for instance new low-carbon energy vehicles, although no specific targets have been set yet.[117]

Performance in key enabling factors

Human capital

Chinese universities are becoming more competitive internationally. In the 2015-16 *Times Higher Education* rankings Peking University is ranked 42th overall and Tsinghua University is ranked 47th gaining respectively 5 and 12 places from the previous year.[118] Looking at the life sciences, the University of Science and Technology of China is included in the top 100 at 95th place.

In terms of academic and research publications, China has compared to other *Building the Bioeconomy* countries relatively low numbers of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 China had 35.66 publications per million population.[119] Chinese academic publications did not rank highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with only 6.72% of publications among the 10% most cited.[120]

The past decade China has seen tremendous growth in the number of university graduates particularly in science and engineering. China is the world's number-one producer of undergraduates with degrees in science and engineering. These fields account for 49% of all degrees obtained in the country.[121] Between 2000 and 2012, the number of S&E bachelor's degrees awarded in China rose more than 300%, from 300,000 to 1.3 million, significantly faster than in any other country.[122]

China also produces a very high number of doctoral degrees in science and engineering, surpassing the United States as the world's largest producer of natural sciences and engineering doctoral degrees in 2007.[123] In 2012 this was close to 32,000 degrees, up from 6,000 in 1998. China is estimated to have one of the highest numbers of life sciences graduates in the world and a large number of Western educated life sciences PhDs (80,000 by 2010) have returned back to China to work in industry and academic research.[124]

A growing share of China's workforce consists of researchers. Looking at the number of researchers in the population the latest (2013) data from the World Bank shows that China had 1,089 researchers per million people.[125] This is an increase of close to 100% since 2000 when the equivalent figure per million population was 547.[126]

Infrastructure for R&D

As a percentage of GDP R&D spending in China is quite high compared to other countries. 2014 figures show R&D spending as a percentage of GDP at 2.05%,[127] which is greater than many higher income countries such as the UK (1.70%) as well as the estimated EU28 average (1.94%).[128] Chinese R&D spending is largely made up of industry spending. The latest data from 2014 show industry expenditure on R&D at 75.2% of the national total.[129]

China's attractiveness for clinical trials is increasing, but the current performance remains mixed. The number of clinical trials per capita is low, at 5.03 per million population.[130] Particularly low is the number of biological trials per capita, 0.3 for the period 2010-2015, the lowest rate among the countries included in *Building the Bioeconomy* after India.[131] However, of these biological trials, a higher proportion than in other countries was on more complex Phase I and II.[132]

While China is a global leader in patenting (including for biotechnology) under the PCT and domestic route, looking at biotechnology triadic patenting it lags behind the top performers on an absolute basis and if adjusted for population. China's share of the global total average for the period 1999-2012 is 0.92%.[133]

China is viewed as mixed market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* China was ranked in the middle of *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 77.3. [134]

Intellectual property protection

Although improving, the protection of IP and enforcement of IPRs in China has long been a challenge to innovators. Chapter XII of the 13th five–year plan reiterates the goal to set-up a modern property right system promoting the rule of law, including for intellectual property in support of innovation. However, the enforcement of IPRs has long been difficult with the counterfeiting of goods (including biopharmaceuticals) rife.[135]

As a WTO member China offers standard 20-year patent protection. However, while this protection has been available for biopharmaceuticals the patent examination practice and basis for

awarding patents has been out of line with international best practices. First, with regards to biologics the scope for patent protection is narrower in China than in other countries.[136] Patent examiners often require a significant amount of biological data yet deny patents for pharmaceutical products that have been granted in other jurisdictions.[137] This phenomenon is largely based on the patent office, SIPO's, interpretation of the sufficiency of disclosure requirement in Chinese patent law which limit the amount of data that can submitted after filing, require the submission of experimental data and emphasize the "sufficiency" requirement over other patentability criteria like inventive step.[138] This approach has led to a relatively high rate of patent rejections due to lack of sufficiency of disclosure compared to other major jurisdictions, particularly over the last several years. According to estimates by local legal experts, of a set of applications rejected by SIPO roughly only a quarter to a third of these were rejected by the USPTO, EPO and JPO.[139] Of these rejections, over 80% included experimental data aimed at demonstrating the use or effect of a given compound, but these were not considered adequate to support the claims. SIPO has attempted to soften these standards somewhat, but thus far with limited effect. In 2013 guidance,[140] SIPO clarified that novelty, inventive step and industrial application should be the focus in patent examination – and not whether or not an application contains experimental data – and that experimental evidence is only required to the extent it is necessary to establish a technical solution included in the claim (which is particularly the case for new uses of known compounds). Moreover, importantly, post-filing experimental data should be accepted during the examination process to confirm (but not establish) the technical solution or other aspects provided by the claim. Nevertheless, the guidelines do not clearly define what will be considered confirmatory in nature (and not ground-breaking). Therefore, in practice the amount of data that should be submitted at the time of filing remains unclear, as does whether data accumulated following the application filing and submitted as supplemental data would be accepted.[141] This continues to lead to patent rejections, and more broadly, to a great deal of uncertainty and delays in obtaining patent protection.[142]

One area within the realm of the inventive step criterion where China is following countries like India is rejections of patents for new uses of existing compounds. A recent precedent-setting case is that of a patent on Gilead's Hepatitis C treatment, Sovaldi, which was rejected in 2015 by SIPO despite being patented in many other countries.[143] Sovaldi is an inactive form of an existing compound, sofosbuvir, (which is patented in China) that is activated once in the human body.[144] This decision also came at the same time a number of Chinese pharmaceutical companies had submitted applications to SFDA for approval of clinical trials on generic versions of Sovaldi (although since the base compound is still under patent in China marketing of generic versions is limited for the time being).[145]

China also places limits on, and special interpretations concerning, what is considered novel and industrially applicable, compared to other countries with particular rules on patentability of biopharmaceuticals; some that are specific to China and others that are also visible elsewhere. For example, in terms of the novelty standard up until 2008 a patent would be considered novel as long as the claim had not been "used" within China. This loophole allowed for the filing of patents that were already granted in other jurisdictions, so-called "patent hijacking". Since 2008 amendments to the patent law, patents face an absolute standard of novelty, meaning that patent examination must consider public use outside China as prior use.[146] Nevertheless, a trend of a high number of lower quality domestic patents has continued, with use of utility patents (which involve fewer substantive requirements and review) increasing over the past several years.[147]

Finally, patent amendments currently under consideration would place further limits on patenting of biopharmaceuticals, potentially outside the scope of the TRIPS Agreement. One set of amendments from 2015 states that methods for the diagnosis and treatment of diseases are not patentable. In addition, the amendments to Article 14 of the Patent Act include ambiguous language on defining how a patent should be exercised in order for it to be approved including, for instance, not "harm[ing] the public interest".[148] It is unclear what this refers to and how it might

be applied by patent examiners when considering what is patentable or not. It could leave room for interpretations that go beyond the scope of the three basic patentability criteria provided for in the TRIPS Agreement.

Under its WTO commitments and article 35 of the regulations implementing the Drug Administration Law China offers regulatory data protection for submitted test and clinical data for pharmaceutical or agricultural chemical products that utilize new chemical entities. Yet generic manufacturers have in some cases been granted marketing approval prior to the six-year term.[149]

The *Work Plan for the Reform of Chemical Drug Registration Categories* of March 2016 introduces a definition for "new drugs" that is stricter than the current one and requires an extensive level of investment – first global launch in China – in order to benefit from a range of existing advantages. Under the new rules only drugs not yet marketed anywhere in the world will be considered as "new" in China, and thus qualified for certain benefits such as a five-year "monitoring period" (i.e. akin to RDP). [150] Out of around 350 drugs approved in 2014, only 2.9% were drugs that had not been marketed anywhere in the world and none were the more advanced biological drugs.[151] Moreover, under new biosimilar legislation, biologics reportedly must not only have the first worldwide launch in China but also be produced there in order to qualify for the 5 year marketing exclusivity.[152]

Finally, with regards to biopharmaceuticals the Chinese "Three-Year Action Plan for Treating Cancer (2015–2017)", issued in September 2015 by China's National Health and Family Planning Commission, poses a potential threat to patent holders. The Plan proposes to step-up the country's fight against cancer by issuing compulsory licenses for patent protected drugs or threatening to use them during price negotiation in order to lower the price of drugs and speed up commercialization.[153]

Looking at ag-bio products, protection of IP has long been problematic. Illegal production of seeds and brand infringement are pervasive despite government enforcement efforts.[154] The new Seed Law recognizes this and aims to strengthen IP protection and enforcement, for instance by increasing penalties for those violating the Regulation on Protection of New Plant Varieties. [155]

The regulatory environment

The Chinese drug regulatory authority, the CFDA, has by comparison to many middle income countries a relatively elaborate and detailed regulatory structure in place.[156] Still, a number of challenges remain for all biotech sectors. In the biopharmaceutical space current regulatory requirements and procedures for clinical trials are by international comparisons onerous and delay product registration. There are also challenges in existing pharmacovigilance programs with reporting requirements for manufacturers of ADRs being an area in need of reform and enforcement.[157] Measures have been presented in 2015 (CFDA Circular N. 117 and N. 140) to expedite procedures at the CFDA, where about 21,000 drug applications are awaiting review.[158] These include, for instance, centralized review of the same type of drug applications, submission of self-audited clinical trial data and blacklisting of applicants submitting false data.[159]

Looking biosimilars the "Technical Guideline for the Research, Development and Evaluation of Biosimilars" issued in 2015 were largely inspired on the scientific content of the EMA guidelines.[160] However, the Chinese guidelines lack the same level of detail and, more importantly, do not incorporate many recommendations by the ICH, notably with regard to quality, efficacy and safety requirements from scientific and technical aspects and elimination of unnecessary delay in the global development and availability of new medicines.[161]

With regards to agricultural biotechnology the MOA and the National Biosafety Committee are responsible for the regulation and approval of imported agricultural GM products and/or the domestic production of GM products in China.[162] Entry into force of the amended Seed Law on 1st January 2016 simplifies registration requirements for 23 crops in a bid to make it easier to introduce new plant varieties on the market.[163] Seed producers will also be exempted from additional approval to introduce registered varieties to similar ecological regions in other Chinese provinces.[164]

However, a number of regulatory related barriers to market entry persists. They include: the requirement that a product must be registered and approved in the country of export prior to an application for approval can be made in China; and a requirement that import applications include viable seeds.[165] The latter requirement has raised concerns among manufacturers about the protection of their IP.[166] In September 2015, China committed to speed up import process of genetically engineered crops within the framework US-China "Strategic Agriculture Innovation Dialogue".[167] As of 2015, seven US biotech traits were awaiting final import approval. [168]

Finally and more broadly, since the mid-2000s, China has introduced and implemented a range of policies making access to the Chinese market conditional on the sharing of technology and IP with domestic entities. These policies include the transfer of proprietary technologies in procurement, joint ventures, and standardization processes; local manufacturing requirements; and limitations on investment by foreign entities, without guarantee they will be protected from unauthorized disclosure, duplication, distribution, and use. Although some policies have been revoked at the central level at the provincial and local level these policies are still in place and continue to be introduced. For example, the Draft IP Abuse Antitrust Guidelines by the National Development and Reform Commission, issued for public comments in December 2015, continue to impose antimonopoly sanctions for refusals to license IP.[169]

Technology transfer

With regards to technology transfer and IP commercialization, Chinese universities have been encouraged since the mid-1980s to manage and commercialize inventions produced by their researchers, although formal ownership was retained by the state. This was changed through a number of reform initiatives culminating in the 2002 "Opinion on Exerting the Role of Universities in Science and Technological Innovation".[170] Combined with the overall growth and development of the Chinese economy, the results of this relative freedom for universities and researchers to pursue commercial ventures has been a sharp increase in university patenting, patent and technology transfers and number of spin-offs. Looking at university and PRO patenting rates these have increased dramatically and been a major contributor to China's rise as one of the world's top patenting nations. 2014 WIPO figures show how China's share of global university patenting applications under the PCT increased from 2.5% in 2008 to 7.5% in 2013.[171] For PROs the increase was even more pronounced growing from 3.1% in 2008 to 16.3% in 2013.[172] Data from WIPO ranks the Tsinghua University the 8th largest university PCT applicant, with 102 patents filed. Four additional Chinese universities figure in the top 50 ranking.

In February 2016, China announced new measures to speed up commercialization of research. State-sponsored research bodies and universities will be able to transfer the scientific outcomes of their work to enterprises without needing Government approval, and will be able to reinvest all revenues generated from their research, of which at least half should be used to reward scientists. Also, researchers will be allowed to temporarily leave their jobs to take up position in companies or set up their own business.[173]

Nevertheless there remain important challenges. First, many Chinese universities and research institutes have explicitly had a policy of promotion and evaluation based in part on number of patent applications. According to some studies patenting has become a substitute for peer-reviewed publications.[174] Second, there is still a lack of experience and tradition with regards to commercialization activities especially in the life sciences. According to industry sources Chinese universities and research institutions (with a few exceptions) do not have the institutional and professional experience to fully commercialise their research.[175]

As concerns business, licensing barriers have increasingly played a role. In particular, the 2015 Foreign Investment Law stipulates that investors must obtain pre-approval prior to investment, or alternatively submit detailed annual reports.[176] Similarly, new draft guidelines presented in September 2015 require a higher amount of global value chain profits from multinational companies

to be conducted and "booked" in China (including transfer and "enhancement" of IP) as well as greater tax presence in China (for instance, requiring a subsidiary in China in order to market in the country).[177]

Market and commercial incentives

China has a number of tax incentives in place to encourage R&D and high technology manufacturing, many of which the 13th Five Year Plan promises to expand. Measures include R&D super deductions, exemption from VAT, technology transfer special rates, as well as a host of sector specific incentives. There is a super deduction available equal to 150% of qualifying R&D spending.[178] Moreover, high-tech and innovative companies (this includes the biopharmaceutical and industrial biotechnology sectors) can receive a special reduced corporation tax rate of 15% although as mentioned there are localization requirements attached to a lower tax rate. Technology transfer activities up to RMB 5million (circa USD800,000) are exempt from corporation tax with activities over this amount exempt at a 50% rate.[179]

Targeted subsidies and support mechanisms for the biotechnology sectors are also in place. For example, there are direct subsidies for biofuels and industrial biotechnology. A direct subsidy between USD365-405 per hectare is offered to farmers using forest for biofuels production and/or biofuels crops.[180] The authorities also impose price controls on the cost of fuels with ethanol being priced at roughly 90% of the price of gasoline.[181] Subsidies in the form of a VAT rebate for bioethanol have been phased out in 2015 and replaced by a 5% consumption tax for grain ethanol aimed at limiting production.[182]

With regards to the biopharmaceutical market, this is hampered by a difficult pricing and reimbursement environment, as well as increasingly by tendering procedures. For example, the National Reimbursement Drug List does not include any monoclonal antibodies, used for example in cancer treatment.[183] The Chinese government has reinforced the centralized drug purchasing system in an effort to further push drug prices down. A centralized negotiation mechanism for patent-protected oncology, cardiovascular and pediatric drugs, is being transitioned in.[184] In 2015, the National Health and Family Planning Council issued new guidelines on public hospital procurement, introducing a spending cap for drugs (not more than 25% of their operating costs)[185] as well as a ban on mark-ups or profits.[186] The State Council Drug Reform Opinion of August 2015 also launched a review of the state pricing mechanism that is expected to further prioritize budgetary considerations at the detriment of innovative products.[187]

These negative moves follow the positive step taken in 2015[188] to remove restrictive price caps previously set by the central government on a large share of drugs (those listed in the National Basic Medical Insurance Catalogue on top of other patented medicines).[189]

Legal certainty (including the rule of law)

The Chinese legal environment can be challenging generally and for specific industries and sectors. Legal redress, enforcement of contracts and administrative justice can be difficult and inconsistently available or applied. In the 2015 *Rule of Law Index* China was ranked 71th out of 102 countries.[190]

Colombia

Colombia is the third largest economy in Latin America. As of 2014, Colombia's total GDP was USD377 billion in 2014. On a per capita basis Colombia is a middle-income country, with a per capita GDP of USD7,903.[191]

Colombia is the 61st most competitive economy in the world according to the World Economic Forum's 2015-16 Global Competitiveness rankings, a rise of 5 spots from the 2014-2015 rankings, and 8 spots from the 2013-2014 rankings.[192]

Since 2000 Colombia has changed rapidly. The economy has expanded and developed aided by relative political stability and a significant and sustained improvement to the security situation. GDP growth since 2000 has been

robust, averaging 4.4% per year in the period 2000-2014.[193] During this time period the structure and composition of the Colombian economy has shifted from basic manufacturing to commodity exports and minerals (primarily oil) which is responsible for circa 7% of economic output per the OECD.[194] Colombia has successfully participated in international trade negotiations, including most notably with the US, and increased its overall participation in world trade.

The sustained levels of economic growth and political stability have moved Colombian government policy to focus on modernizing the economy, shifting to an innovation, knowledge-based socio-economic development model. Since 2013 Colombia has been in accession talks to the OECD.

National Innovation Policy

Colombia has a number of institutions and layers of government working towards promoting greater innovation and building R&D and innovative capacity within the economy. These range from specific governmental departments (such as *Colciencias*, the Administrative Department of Science, Technology and Innovation), to sector specific initiatives (discussed below with regards to biotechnology) to two major general policy levers/mechanisms for innovation policy which includes:

- Successive National Development Plans (2010-2014; 2014-2018) which both provide a sustained and significant focus on strengthening science and technology in Colombia and the economy's innovation capacity; and

- the General Royalties System which in 2011 introduced a 10% diversion of royalties from mineral income to science and technology development.[195]

In addition to providing the strategic roadmap for Colombia's economic development together these two general levers also provide much of the major policy framework and direction for Colombia's biotechnology specific policies. Indeed, biotechnology development figures heavily and in detail in both national development plans.

Colombia has long recognized its biodiversity and the importance of biotechnology and the potential of this sector. A national biotechnology institute and specific national program was introduced as early as the 1980s and 1990s, respectively, and a national framework/strategic plan has been in place since the late 1990s.[196]

More recently, a number of policies and Government-led initiatives have been introduced with the view of stimulating research and the growth and development of the biotech sector. For example, early in his first term current President Santos emphasized the need for developing an economic model based on innovation, science and high-tech sectors including biotechnology.[197] In 2011 a framework for the commercialization and development of biotechnologies was introduced.[198] And biotechnology figures heavy in current Government plans and strategies including the 2014-2024 *Programa Nacional de Biocomercio Sostenible*.

Plan Nacional de Desarrollo 2010-2014 "Prosperidad para Todos

Colombia's first National Development Plan of 2010-2014 – *Plan Nacional de Desarrollo 2010-2014 "Prosperidad para Todos"* – placed a heavy emphasis on strengthening Colombia's science, technology and innovation capacity.[199] A major part of this plan was developing and building the biotechnology sector. More specifically, it included the "Policy for the commercial development of biotechnology from the sustainable use of biodiversity" (CONPES 3697), a framework for the commercialization and development of biotechnologies, released by the National Council for Economic and Social Policy and National Department of Planning.[200]

CONPES 3697 sought to improve the investment environment in the area of biotechnology in order to draw in greater private and public investment in commercial development within the sector, with a total public investment of 27 billion USD.[201] The framework targeted a wide range of biotech sectors including cosmetics, biopharmaceuticals, food and agriculture. It sought/seeks to strengthen support for biotech activities across public and private sectors. Specifically

the framework boosted support for various government agencies (including the Ministry of Commerce and *Colciencias*); scientific capacity building and applied research in universities and research institutions; as well as support for industry-academic collaboration, technology transfer and biotech start-ups. Another key feature of the framework was to enable greater access to genetic and biological resources, adjusting the regulation on the production and marketing of biological drugs, and establishing venture capital funds.[202] A major part of this plan was the potential creation of a national bioprospecting company.[203] As of the time of research the establishment of such an entity was still being debated.

CONPES 3697 built on previous strategic biotechnology initiatives: the Policy to Promote the Research and Innovation in Colombia from 2008, and the National Policy of Science, Technology and Innovation of 2009, both of which focused on biotechnology as a strategic sector. The framework was introduced as part of the Santos' administration's broader policy goals of improving the conditions for private sector investment as well as increasing public spending on science and technology.[204]

Plan Nacional de Desarrollo 2014-2018 Todos por un Nuevo País

The most recent national development plan covers the period 2014-2018. It focuses on three main pillars: peace, equity and education. These pillars are to be achieved with what is termed five "cross-cutting strategies.[205] These strategies cut across all segments of socio-economic development from general competitiveness and improvements to infrastructure (physical as well as technological); social mobility; security and reforms to the justice and legal system; and an emphasis on good governance. Improving the framework and culture of innovation, building human capital and improving scientific and technological capacities is a key part of the plan.

In addition to being a strategic vision and outline of Colombia's future development the 201-2018 National Development Plan also includes legislation directly affecting the incentives for biotechnology innovation and R&D.

For example, article 70 widens the basis for the issuing of compulsory licenses in a manner that goes beyond the TRIPS Agreement, Article 31 and the 2001 Doha Ministerial Declaration and subsequent General Council decision concerning Paragraph 6.[206] The provision allows Colombian authorities to define public health emergencies broadly and to actively seek out compulsory licenses, allowing for grounds outside extreme circumstances including industrial or commercial objectives, to play a role in the issuing of compulsory licenses.

In addition, both articles 70 and 72 link two distinct and independent processes with regulatory approval of biopharmaceuticals: patent examination and pricing decisions.[207] Article 70 allows the Ministry of Health and Social Services to participate in the patent review process by the Ministry of Industry. This potentially allows non-legal or factors outside of technical patent criteria to be factored into decisions on whether to grant a biopharmaceutical patent, rather than examination solely by patent specialists and officials based on established and accepted legal and technical criteria. Article 72 links approval of biopharmaceuticals with pricing decisions. Specifically pricing decisions must be made as part of the market approval process. This is outside international standards and the process used in developed markets. In most countries pricing and reimbursement decisions (whether they be by a public or private health payer) is a separate process from product registration and market approval. Decisions on registration and product approval are based solely on scientific and technical determinations examining the safety, quality and efficacy of a given product and technology.

Additional biotechnology policy frameworks

In addition to the national plans there are a number of biotech specific initiatives taking place at various levels of the Colombian Government. For instance, *El Programa Nacional de Biocomercio Sostenible de Colombia 2014 – 2024 (PNBS)* – is a 10-year program aimed at improving Colombia's position as a major competitor in the global trade of biotechnological products,

or 'bio-trade'.[208] The program presents a revised framework which is based on an ecosystem conception, adaptive management, and the development of sustainable value chains from a shared management of natural resources.[209] Specifically, the plan sets to harmonize the legal, regulatory, institutional and political frameworks across Colombia, prioritize the potential of different value chains in order to identify and address the technological needs of each value chain, achieve international accreditation for locally-produced biotechnological products, and encourage investments of the private sector in R&D and bioprospecting as a strategy for conservation and sustainable economic development.[210] The funding for this plan comes from a national support system comprised of several national funds, designated governmental budgets (such as from *Colciencias*) as well as from general taxation and BANCOLDEX, the Colombian Business Development Bank.[211]

Colciencias has also laid out an ambitious plan to develop the country's biotechnology capacity. The plan includes targets of increasing innovation in the private sector, the development of commercial biotechnology products, increased levels of patenting and significantly increasing the contribution to national GDP from biotechnology.[212] The plan has focused on 4 strategic areas of development:

1. Science – This includes investing in new research and mapping of new biological finds through increased exploration. There is also a target of increasing the number of doctoral students and scientific infrastructure.

2. Business/commercial development – This includes creating incentives, partnerships and the right conditions for the commercial development of biotechnologies and concrete products for market in Colombia and internationally. A target has been set to increase rates of innovation and partnership with Colombian companies with 2,000-8,000 companies to partner with *Colciencias*.[213]

3. Institutional capacity building – This area focuses on both developing new and using existing institutional and regulatory frameworks at the national and regional level to promote the biotechnology sector. An emphasis has been placed by *Colciencias* on improving existing regulatory capacity and capabilities.

4. Socio-cultural development – The plan also seeks to encourage national participation and ownership as it relates to biotechnology. In particular the plan aims to encourage greater awareness of Colombian biodiversity and the sustainable use of existing biological resources.

Biopharmaceuticals

Currently, the Colombian biopharmaceutical market is relatively small but growing at a fairly robust rate. Looking at the pharmaceutical market as a whole (without distinguishing biotech products), in 2009-11 the projected annual average growth rate was 6% and around 5% in 2012-15. Based on the most recent projections, the market is valued at around USD3.3 billion (COP9,101 billion) and is set to grow over 5% (in local currency terms) between 2015 and 2016 (though this represents a drop of 12% in US dollar terms).[214] Based on a 2013 survey from the national statistics agency DANE, while as a share of the total manufacturing industry in Colombia the pharmaceutical sector represents just under 5% of the total value added. Among the manufacturing sectors it is the 6th largest contributor to value added out of 64 sectors.[215]

Estimates vary but on average around 30% of the total biopharmaceutical market today is composed of biotech products (including biologics and biosimilars).[216] Just around 5% of biotech firms in Colombia are reportedly focused on biopharmaceuticals.[217]

Looking at rates of product launches between 1983-2000, the percentage of products available in Colombia within five years of global launch was 32%.[218] This was squarely in the middle of the sampled economies.

With regards to the BCI Survey Colombia ranked second to last of the economies included in *Building the Bioeconomy* with an overall score of 53.64. [219]

Ag-bio

Agricultural biotechnology is currently the largest biotech sector in Colombia. Among biotech firms in the country the large majority are focused on agriculture and food (along with cosmetics). By some estimates, firms in the ag-bio sector represents around 40% of the total biotech sector in Colombia (with a related sector, food and alcoholic beverages, just under at around 30%).[220]

Within its wider development plan for the biotechnology sector, the Colombian government has made growth of the ag-bio sector a priority over the past 15+ years, among other factors in order to reduce reliance on food imports. Colombia has traditionally been a net importer of grains, particularly of corn (estimated at around 70% in 2010[221]). In this context, cultivation of biotech crops has taken place in Colombia since the early 2000s. As of 2015 the sector has grown exponentially (although a large portion is not yet dedicated to commercial cultivation), with genetically modified corn and cotton among the top crops produced. According to the Colombian Agriculture Institute the production of genetically modified corn has grown from around 7,000 hectares to close to 90,000 between 2007 and 2015.[222] Colombia has also approved GM seeds for certain plants, mainly limited to corn, cotton and flowers.

Nevertheless, within its national Cultivation Plan the government has set its sights on increasing GM crop cultivation by several times this current level – with targets for GM corn set at 790,000 hectares by the end of the decade in order to reduce imports by 50% within the period.[223]

By global comparison Colombia is notably an active country in terms of production of GM crops but still has substantial room for growth, including in the area of ag-bio innovation. In terms of R&D, available data on ag-bio R&D spending from the Inter-American Development Bank and the Food and Agriculture Association, though somewhat dated, suggests that Colombian R&D expenditure on ag-bio is very low. As a share of the total spending in Latin America in 2006, Colombia spent just 3.3% with Brazil responsible for over 50% if total investments.[224]

Industrial biotechnology

Since 2005 the Colombian government has targeted biofuels as a strategic sector, particularly in order to capitalize on rising global demand for renewable energy and to meet targets for reduced CO2 emissions in Colombia.[225]

As a result, the biofuels sector in Colombia has grown markedly over the past decade. The two largest segments within the sector are sugar cane-based ethanol and palm oil-based biodiesel. Colombia is one of the leading sugar cane producers globally, and a substantial portion of the sector is now devoted to ethanol production.[226] In addition, Colombia is considered to be the top producer of palm oil in Latin America and fifth largest in the world, producing more than 945,000 tons of palm oil and over 500,000 tons of palm oil-based biodiesel in 2014. Capacity for biodiesel production is reportedly already in excess of domestic demand, at around 800,000 tons per year (with demand in Colombia identified as around 520,000 tons per year).[227] In contrast, the ethanol segment in Colombia still has substantial room for growth to meet clean energy targets. For example, current estimates put daily ethanol production at about 1.65 million liters, representing about 8% of gasoline consumption in Colombia.[228] Yet production in Colombia still falls behind the regional leader, Brazil.[229] Moreover, today just about 8% of biotech firms in Colombia are focused on biofuels.[230]

Still, the Colombian biofuels sector is small compared to world leaders in the sector. Though reliable international data is difficult to find, energy giant BP provides an annual statistical breakdown of energy production globally, including renewables such as biofuels. The latest available data from BP suggest that Colombia is one of the top three producers of biofuels in Latin America, along with Brazil and Argentina.[231]

Performance in key enabling factors

Human capital

Colombian universities are not widely recognized in international rankings. No Colombian university is included in the top 100 of the 2015-16 *Times Higher Education* rankings.[232]

In terms of academic and research publications, Colombia has compared to other *Building the Bioeconomy* countries the lowest numbers of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Colombia had 9.81 publications per million population.[233]

Looking at number of researchers in the population the latest (2010) data from the World Bank shows that Colombia had 164 researchers per million people.[234] This is the lowest rate, bar India, of all the economies included in *Building the Bioeconomy* and less than a tenth of what Malaysia has and far behind the top performers.

Infrastructure for R&D

Colombia is not a major investor in R&D in Latin America. 2012 World Bank figures show R&D spending as a percentage of GDP at 0.226%.[235] This is the lowest of all the economies included in *Building the Bioeconomy.*[236]

Looking at biotechnology triadic patenting, Colombia's share of the global total average for the period 1999-2012 was very low, 0.001%, the lowest among all countries.[237]

Overall the clinical trials environment is limited although there are some reasons for optimism. Colombia is still behind other markets on a per capita basis, with 18.56 trials per million population; ahead of China and India but below levels of world-leaders such as Singapore, Korea and the US.[238]

Looking at recent clinical trials for biologics Colombia's levels was higher and relatively stronger than other economies. Between 2010-2015 Colombia had on average 1.69 biologic trials per million population; more than double the amount in Brazil.[239] However, compared to other economies a relatively low proportion of these trials – 27% – were early phase trials.

Colombia is not viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Colombia is ranked in the bottom third in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 64.1. [240]

Intellectual property protection

Colombia has in place a number of important mechanisms for the protection and enforcement of biotechnology specific IP rights. For example, a TRIPS standard 20 year term of patent protection is available, with some important exceptions discussed below, for most biotechnology and biopharmaceutical innovations. Unlike many countries in the region (including Brazil) Colombia has since 2002 through decree 2085 provided a five-year period of regulatory data protection for both pharmaceuticals and agrochemicals. Furthermore, Colombia has through the 2006 US FTA (in effect since 2012) committed to providing an effective patent enforcement mechanism linking and conditioning market registration for follow-on products with existing exclusivity periods for innovative products. And up until 2015 Colombia did not have a history of invoking compulsory licensing or the threat of issuing such licenses outside of public emergencies. Unfortunately, many of these critical IP rights and mechanisms are limited in their effective availability. And the IP environment in general for biopharmaceutical IPRs has worsened.

First, there are significant restrictions on the patentability of new biotechnologies and biopharmaceutical innovation. Generally speaking inventions will be granted patent protection in Colombia provided they are new, involve an inventive step, and have industrial application. Yet the Andean Court of Justice (whose decisions Colombia must adhere to as a member of the Andean Community customs union) has issued several legal opinions denying patents on new pharmaceutical indications and biologics that are capable of being isolated.[241] Patents are also not typically granted for therapeutic methods.

Second, the availability of RDP for submitted biopharmaceutical test data in Colombia is questionable. As mentioned while in a positive step Colombia has in place a clear regulatory mechanism providing this exclusivity and a term of protection of five years for new chemical entities, it is not clear that RDP is available for biologic products. Decree 1782, signed in September 2014, which modifies the registration process for biological medicines, does not discuss regulatory

data protection for biologics. As a result, in regard to RDP the legislation introduces ambiguity as to whether five years of protection are in fact afforded to biologics under the new regime.

Finally, up until recently the imposition, or threat, of compulsory licensing for biopharmaceuticals had not been a recurring issue in Colombia. However, as discussed above, article 70 of the latest National Development Plan widens the basis for the issuing of compulsory licenses in a manner that goes beyond the TRIPS Agreement.[242] The provision allows Colombian authorities to define public health emergencies broadly and to actively seek out compulsory licenses, allowing for grounds outside extreme circumstances including industrial or commercial objectives, to play a role in the issuing of compulsory licenses.

Echoing this legislative development the Ministry of Health and Colombian Government has recently been actively considering (on the basis of a recommendation of an internal committee) the issuing of a compulsory license on the oncology drug Glivec on grounds of high prices.[243] In a number of interviews the Minister of Health made clear that the driving reason for the potential over-riding of the existing patent for Glivec was the issue of cost. In May 2016 the Minister was quoted in the *Wall Street Journal* as saying that: "Technological pressure and high drug prices have brought the health-care system to a financial crisis…Colombia is a paradigmatic case of a middle-income country, with a growing health system and with rising expectations from its middle class, which cannot pay high prices for new drugs."[244]

At the time of research the Colombian Government had issued a "public interest declaration" which would allow the authorities the right to unilaterally reduce the price of Glivec.[245]

The regulatory environment

Colombia's regulatory environment is generally seen as by regional comparisons quite strong although there are significant concerns over long processing times, delays and, in the biopharmaceutical space the introduction of a biosimilars pathway which is outside international standards.

Looking at clinical research the government of Colombia and INVIMA have dedicated efforts in improving the clinical research environment to international standards and enhancing its relative attractiveness. In 2008, Resolution 2378 established the roles and responsibilities of actors involved in clinical research (sponsors, investigators, regulators and medical facilities), covering site accreditation, GCP inspection in accordance to ICH standards, trial protocol evaluation, and approval of the trial's agreement by the IRB.[246] The regulatory framework was further expanded with additional definitions and responsibilities, revised timelines and more.[247]

Today there are 63 GCP-certified institutional ethics committees (IRB) and over 120 medical facilities approved by INVIMA for clinical research. A clinical trial application must be reviewed by both bodies, except for phase 4 trials which only require an IRB approval. Colombia's medical facilities rank highly in regional comparison, and a pool of nearly 50 million people with adequate health coverage is accessible.[248] In addition, a number of global and local CROs operate in Colombia and maintain an open communication with INVIMA,[249] and a US-based clinical development company entered into an agreement with the Government of Colombia to position Colombia as a preferred destination for conducting clinical trials by US-based sponsors.[250] However, despite the efforts taken to enhance Colombia's attractiveness in the global clinical research arena, some challenges still exist in several aspects.

First, evidence suggest that approval times for clinical research are marred by significant delays. Trial approval times-frames in Colombia are currently very long. According to recent research conducted by the local biopharmaceutical trade association AFIDRO (*Asociación de Laboratorios Farmacéuticos de Investigación y Desarrollo*) the regulatory approval of a clinical trial in Colombia takes no less than 225 days: some 50-60 days for an approval by the Ethics Committee, and an additional 165 days for the approval by the regulatory agency.[251]

Second, the framework of collaboration between sponsors and local investigators, including

start-up companies and university hospitals, is lacking.[252]

Furthermore, while the number of medical facilities approved for clinical research by INVIMA has grown substantially in the past few years, only a fraction have adequate infrastructure and skilled staff for clinical research requirements.[253] Indeed, while hospitals within main cities (and particularly those with universities affiliations) have an electronic medical records system in place, some of the rural hospitals and clinics do not have a constant, reliable internet connection.[254]

In April 2016 Colombia's DRA INVIMA announced significant changes to the regulatory approval process of clinical trials.[255] First, the timeframe for approval would be reduced to only 2 calendar months, or 60 days. This would be achieved by two significant administrative changes:

- enabling parallel submissions of clinical trials applications; and
- transferring the trial protocol evaluation of clinical trials on biologic drugs, which require particular expertise, to a designated group within INVIMA (*Sala Especializada de Medicamentos y Productos Biológicos al Grupo de Investigación Clínica de la Dirección de Medicamentos y Productos Biológicos*).[256]

A reduction from the current 225 days for approving a clinical trial to 60 days would significantly improve Colombia's attractiveness in the global clinical research arena.

In 2014, Colombia issued its own biosimilars pathway through Decree 1782, which establishes the marketing approval evaluation requirements for all biologic medicines. This decree Colombia has established what, in many respects, was an unprecedented abbreviated pathway for registration of non-comparable products. The decree is inconsistent with WHO, FDA and EMA standards and could result in the approval of medicines that are not safe and/or effective. In contrast to the Full Dossier Route (for originators) and the Comparability pathway (pathway for Biosimilars found in WHO guidelines), the "Abbreviated Comparability Pathway" as described in the decree allows for summary approval of non-comparable products and does not provide adequate controls or any clarity regarding how the safety or efficacy of a product approved via this pathway will be evaluated and ensured. Furthermore, per the decree, a product approved via the "Abbreviated Comparability Pathway" will use the same non-proprietary name as the innovator, despite the fact that the proposed similar biologic product is not the same as the innovative product. Assigning identical non-proprietary names to products that are not the same could result in inadvertent substitution of the products and would make it difficult to quickly trace and attribute adverse events to the correct product.

Looking at the ag-bio sector Colombian regulations are generally science-driven.[257] Regulations and the policy framework are derived and guided by the "Technical Annex" (the main guiding document) and a number of agency specific resolutions and/or guidelines including the Ministry of Health's resolution 4254. Commercial cultivation has taken off dramatically since 2007 although remains, by international comparison, relatively low. The approval process has been criticized for being lengthy as it involves a number of ministries and government agencies and product approvals are handled on a case by case basis resulting in varying approval times. No new ag-bio products have been developed in Colombia.

Technology transfer

Looking at the existence of technology transfer frameworks, infrastructure and outputs Colombia lags behind other markets in both encouraging the commercialization of publicly funded research (whether through a PRO or university) and seeing real-world outputs. To begin with Colombian public sector researchers and university faculty are not allowed a second salaried income which essentially means that the incentivise to set up new businesses through spin-offs or start-ups is limited.[258] This was also a critical problem noted by the Colombian Government in 2013 in its comprehensive review of the biotechnology sector in Colombia.[259]

Looking at outputs relatively few universities derive significant forms of income from

commercialization and commercial research services. Data is relatively limited but analysis by the OECD suggests that the University of the Andes (a private institution) has been the most successful of the major institutions in generating research income. Over the decade 2001-2011 this income totalled just under COP175,000, circa USD60,000 at 2016 exchange rates.

Furthermore, no Colombian university was included among the top-50 patenting institutions for 2014 PCT applications.

Market and commercial incentives

Colombia has a number of R&D tax incentives in place. The most generous is a capital allowance of up to 175% for qualifying expenditure.[260] Qualifying entities must be pre-approved by COLCIENCIAS and there is a hard cap on the available funds in a given year for this incentive. Furthermore, VAT exemptions are available for qualifying imports and reduced rates of exemptions for development of software. However, local content requirements are in place for the latter with production in Colombia a prerequisite for qualification.

The pricing and reimbursement environment for biopharmaceuticals in Colombia is relatively challenging. Maximum sales prices for all medicines is since the signing into law of the 2015 health reform package (*Ley Estatutaria de Salud, 1751*) vested within the Ministry of Health and not with the now defunct *Comisión Nacional de Precios de Medicamentos.*[261] Drug prices set by the Ministry of Health are applicable to both private and public markets based on a system of international reference pricing. Prices are set according to wholesale levels with margins monitored by the Ministry of Health.[262] With regards to the reimbursement environment this remains uncertain with question marks as to the effect on access to innovative medicines with the difficult budgetary environment. Significant price cuts and reimbursement limits have been introduced and the Colombian Government has introduced more extreme price control measures including the threat of using compulsory licensing.[263]

Legal certainty (including the rule of law)

In the 2015 *Rule of Law Index* Colombia ranked 62nd out of 102 countries mapped with the Index highlighting challenges in regulatory enforcement and levels of perceived corruption.[264]

India

India is the third largest economy globally, with a GDP of USD2.06 trillion in 2014. The World Bank classifies India as a lower middle-income economy with per capita at PPP of USD5,833.[265]

In the 2015-2016 World Economic Forum Global Competitiveness Ranking, India jumped up 16 places from the 71st to the 55th place, after six years of sliding down the ranking.[266] The improvement is mainly due to more favorable sentiment of investor towards the current Government and its policy of improving the business climate.

National Innovation Policy

After years of discussing a draft document India unveiled at the end of 2015 a National Biotechnology Development Strategy 2015-2020[267] aiming at becoming a bio-manufacturing global hub and making biotech the new success story of its economy after the IT sector.[268] The Strategy aims at making the Indian biotech sector worth USD100 billion by 2025, up from the current USD7 billion.[269] It focuses on increasing technology transfer capacities and research facilities, build skilled workforce and improve the regulatory environment. In an effort to encourage greater rates of technology transfer and commercialization, the Biotechnology Strategy 2015-2020 pledges to create a Technology Development and Translation network across the country with a global partnership, including 40 new bio-incubators, five new bio-clusters, 150 technology transfer offices and 20 bio-connect offices in research institutes and universities.[270]

A few weeks after the launch of the Biotechnology Strategy, Prime Minister Modi announced another major initiative expected to support entrepreneurship and innovation in a bid to

further start-up businesses. The "Start-Up India" Action Plan puts forward financial means and entrepreneurship support measures for start-ups.[271] Specific measures for the bioeconomy include the creation of a Biotech Equity Fund, five Biotechnology Industry Research Assistance Councils, regional centres and the Bengaluru-Boston Biotech Gateway to India that will focus on genomics, computational biology, drug discovery and new vaccines. These efforts are hoped to create 2,000 biotech start-up by 2020.[272]

Biotech Sector by Sector Policy Overview

Biopharmaceuticals

The biopharmaceutical sector is by far the most developed and biggest of India's biotechnology sectors, accounting for 64% of total biotech revenues in 2013 (estimated at USD 4.3 Billion).[273]

Mostly a generic producer, in 2012 India spent USD2 billion in biomedical R&D, four times less than China and 60 times less than the US.[274] Yet, investment in R&D and advanced biopharmaceutical manufacturing has become a growing priority for the Indian government. For example, the Department of Pharmaceuticals has set the goal of making India a global drug discovery and pharmaceuticals innovation hub, attracting 15-20% of the world's R&D in 2020.[275] In 2015, it also signed a Memorandum of Understanding with the US Department of Health and Human Services for conducting cancer research.[276]

The Department of Biotechnology runs a "Medical Biotechnology Program" from which support and funding is offered for infectious diseases, chronic diseases, vaccine development, and stem cell research.[277] Tangible outputs from these programs include the development of products (e.g. a rapid test for the diagnosis of celiac disease and a method to detect Neisseria Gonorrhea and Chlamydia Trachomatis as well as the ROTAVAC virus[278]) as well as academic research: the chronic disease biology program has funded over 800 projects that have generated 400 papers with an average impact factor of 4.5.[279] The Department has also established 17 Centers of Excellence with research funding being provided for 69 projects.[280] To promote private sector growth, the government has created four Biotech Park and Incubation Centres located around the country and is in the process of building four more.[281]

Yet there remain significant challenges. India maintains relatively low levels of public health investment, in spite of the declared priority attached to the sector.[282] In 2014 total expenditure on health as a percentage of GDP stood at 4.7%; this figure has remained steady between 4-4.5% over the last decade.[283] Roughly 25-30% of this total expenditure is public spending on health.[284] This compares to an OECD average total health expenditure of 8.9% of GDP and other emerging markets such as Brazil and South Africa spending 9.1% and 8.9% respectively.[285]

There are also other sector-specific challenges, including for the protection of intellectual property, discussed below.

Looking at rates of product launches between 1983-2000, the percentage of products available in India within five years of global launch was 8%.[286] This was last of all sampled economies.

With regards to the BCI Survey India ranked in the lower half of the economies included in *Building the Bioeconomy* with an overall score of 58.72. [287]

Ag-bio

India is a major producer of biotech crops.[288] In 2015 the country had 11.6 million hectares of biotech cotton and became the biggest cotton producer worldwide.[289] Agricultural biotechnology is the third largest component of Indian biotech industry after biopharmaceuticals and bioservices, covering 14% of its revenue.[290]

Traditionally government support for ag-bio comes from the Agriculture Biotechnology Program within the Department of Biotechnology and from the New Millennium Indian Technology Leadership Initiative. The latter was originally launched in 2000 as a public/private research initiative aimed at promoting science and technology innovation.[291] In 2009, the Indian Government reaffirmed its support for the program by allocating INR7billion to the program in the eleventh Five Year Plan.[292] The revamped

program also included new funding mechanism including the ability to co-finance projects with venture capital funds.[293] Successes include the release of four GM plant varieties to farmers. These include two new varieties of Mentha Piperite (mint) known as CIM-Indus and Cim-Madhuras and low ligin varieties of Ochlandra Travancorica and Leucaena Leucocephala for use in paper products.[294] The Department of Biotechnology also houses an "Agriculture Biotechnology Program". This initiative has undertaken in-house projects such as wheat genome sequencing and the creation of a National Plant Gene Repository in New Delhi for research use.[295] In addition, over the past five years the program has provided funding to over 300 R&D projects[296] with several notable successes including the creation of heat tolerant wheat hybrids and 25 versions of the banana plant resistant to Banana Bunchy Top Virus.[297]

Yet the ag-bio sector in India has been hampered by significant levels of regulatory uncertainty. Since it came into power, the Modi Government has taken a softer stance on biotechnology derived crops. Eight state authorities have removed the veto on GM field trials since 2014. The Genetic Engineering Appraisal Committee resumed its meetings after the 2012-2014 interruption, granting approval to various field trials. The Committee has also recently begun examining final biosafety data related to GM mustard, the first proposal to be submitted since the 2010 moratorium on commercial cultivation of Bt Brinjal (eggplant).[298] Two transgenic events for resistance against gram pod borer in chickpea and pigeon-pea are also in the pipeline and should be submitted in the near future.[299]

Industrial biotechnology

In the industrial biotechnology space India also has a well-established framework and a number of policies in place, particularly for biofuels. In 1999 the Indian government charted the National Bio-resource Development Board with the mission of developing a countrywide framework for the development of bio-resources. Through the Department of Biotechnology the Bank has assisted in the creation of a biofuel research network comprised of universities, research institutions and private sector companies.[300] The network has invested in bioethanol, biodiesel, bio-butanol and bio-hydrogen research.[301] The Bank has also facilitated the creation of three Bioenergy Centers to assist in the commercialization of biofuels.[302]

Under the 2009 National Policy on Biofuels India has targeted a 20% biofuel blend by 2017.[303] Like China, and in an effort to ensure food security, India is focused on non-agricultural biofuels such as waste products and algae.[304] The Department of Biotechnology has reported that the country is successfully working towards the target deadline.[305] However, reports in 2015 present a bleaker picture, saying only 3.5% blending could be achieved by November 2015, against 5% mandated by the Government.[306] While the Government had identified *Jatrapha curcas*, a small tree poisonous to humans, as the most suitable oilseed for biodiesel production, a previous 20% blending target by 2012 was not achieved mainly because of insufficient *Jatrapha* feedstock and lack of R&D for high-yielding drought resistant seeds.[307]

The Government aims to have biofuels account for 15% of energy consumption over the next decade. In 2014-15, after the diesel market was deregulated and subsidies to production came to an end in 2014, the decision to allow direct delivery of biodiesel to bulk customers in 2015 opened new opportunities for the Indian biodiesel industry.[308] In August 2015, the Ministry of New and Renewable Energy proposed to extend the measures to all biofuels, so as to ensure they become available on the market, as well as to limit exports.[309]

Despite these measures looking at actual outputs India lags behind worldwide in terms of biofuels production and was responsible for 0.5% of global biofuels production in 2014.[310] Nevertheless, this is a 29% increase over 2013 levels and an even more impressive three-fold increase since 2010.[311]

Performance in key enabling factors

Human capital

In the 2015-16 *Times Higher Education* rankings no Indian university is ranked in the top 250

universities generally or in the top 100 universities for life sciences.[312]

In terms of academic and research publications, India has compared to other *Building the Bioeconomy* countries low numbers of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 India had 12.25 publications per million population; ahead of only Colombia.[313] Indian academic publications did not rank highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with only 6.77% of publications among the 10% most cited.[314]

Similarly, looking at number of researchers per million India is not a top performer.[315] There is a paucity of data but the most recent figures from the World Bank (2010) show that India had 157 researchers per million population.[316] This is the lowest rate among all economies included in *Building the Bioeconomy* and significantly behind other developed OECD economies.

Infrastructure for R&D

India is not a prolific spender on R&D. 2011 figures show total R&D expenditure at 0.81% of GDP.[317] This is significantly behind the other BRIC economies and mature OECD economies. Traditionally, the majority of this R&D is Government funded at 66%, which is the inverse to spending patterns in other countries.[318]

India is not an attractive destination for clinical research. The number of clinical trials per capita is low, at 2.1 per million population; less than half of China and significantly behind world leaders such as Switzerland, Israel and the US.[319] Particularly low is the number of biological trials per capita, 0.10 for the period 2010-2015, the lowest rate among the countries included in *Building the Bioeconomy*.[320] However, of these biological trials, a relatively high proportion was on more complex Phase I and II trials.[321]

Looking at biotechnology triadic patenting India is ahead of a number of countries but lags behind the top performers on an absolute basis and if adjusted for population. India's share of the global total average for the period 1999-2012 is 0.57% less than half of Israel's share of 1.15%.[322]

India is viewed as a mixed market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* India is ranked in the lower half of The *Venture Capital & Private Equity Country Attractiveness Index* with a score of 68. [323]

Intellectual property protection

The protection of IP and enforcement of IPRs in India has long been a challenge to innovators. And while 2015 did not see a material change in the environment for innovators, a number of positive steps were taken by the new Indian Government in particular by Prime Minister Modi himself. These include hiring more examiners to reduce the application backlog, improved anti-piracy efforts and passing the Bill on Commercial Courts, Commercial Division and Commercial Appellate Division of High Courts. In what is somewhat of a missed opportunity a *National Intellectual Property Rights (IPR) Policy* was finally unveiled by the Department of Industrial Policy and Promotion in May 2016.[324] The IP policy contains seven objectives each with proposed policy measures: IPR awareness, generation of IPRs, legal and legislative framework, administration and management, commercialization of IPR enforcement and adjudication, and human development. The document emphasizes the need for a balanced approach between IP and the need to protect public interest. It also aims to spread awareness among public about IP rights to promote innovation and calls for renewed enforcement efforts.[325] Positive aspects include centralizing the patent regime under DIPP and improving co-ordination between the federal and state level on compliance.[326] However, the text fails to address the main concerns over IP protection. The Government retains the prerogative of issuing compulsory licenses, as "*India will continue to utilise the legislative space and flexibilities available in international treaties and the TRIPS Agreement.*"[327] The policy does not open debate over data exclusivity, patent linkage and patent-term extension, nor on Section 3(d) of Indian Patent Act.[328] It also fails to introduce specialized

IP courts, as included in a previous draft of the text.[329]

With regards to ag-biotech India's current legal framework on the protection of plant varieties differs from international best practices as found with the International Union for the Protection of New Varieties of Plants. Specifically, requirements relating to the submission process, compulsory deposit of parental lines to a public gene bank, and potential claims of benefit sharing and compensation if crop performance is less than expected, make this framework less attractive than in other countries.[330]

The regulatory environment

India's regulatory environment faces a number of critical challenges. Looking at biopharmaceuticals there exists no equivalent to the Chinese CFDA, the US FDA or the EU's EMA. Instead, authority over medicines and pharmaceutical drugs is spread out over various layers of the Indian central government and state governments. On many critical issues of quality and safety regulations, there is divided authority between Central Government and the governments of individual Indian States.[331] The availability of counterfeit and substandard medicines remains high with lapses in manufacturing biopharmaceutical practices uncovered in the last few years. Serious quality-related concerns have been raised about some of India's largest biopharmaceutical firms, most notably with regards to manufacturing and quality control procedures at Ranbaxy.[332]

In March 2016, India's Central Drugs Standard Control Organization submitted new draft guidelines with the aim to clarify the regulatory pathway of similar biologics.[333] The draft guidelines build on an existing framework in place since 2012 and the WHO's "Guidelines on the Evaluation of Similar Biotherapeutic Products". At the time of research important components of the guidelines relating to patient health and safety were still being discussed. This includes guidance on the naming of a biosimilar; packaging and safety information updates; the type of products covered by the guideline; reference products (including foreign products) to be used and definitions of similarity; and evaluation of the manufacturing process of a reference product used.[334]

Technology transfer

Technology transfer and commercialization of public funded research remains relatively limited. 2015 statistics from WIPO suggest that patenting by Indian PROs and universities is still quite limited. In 2013 a total of 55 PCT patent applications were made by Indian universities and 104 by PROs. This compares with 3,920 applications by US universities (which were the largest source of patenting applications by all universities globally) and 829 PCT applications from PROs in France, which filed the most applications globally in 2013.[335] However, the trend is on the rise. The Council of Scientific and Industrial Research, the only Indian PRO among the 30 top applicants globally, increased its applications from 91 in 2013 to 117 in 2014.[336] And India had no university among the top 50 PCT applicants for universities.[337]

Very few Indian universities have functioning TTOs. The institutions with the most advanced and developed technology transfer capabilities are the Indian Institutes for Technology. The institutes in Madras and Mumbai have technology and start-up incubators in place and have incubated a growing number of start-ups in the past few years.[338] As mentioned, the Biotechnology Strategy 2015-2020 pledges to drastically increase technology transfer infrastructure.

Market and commercial incentives

India has long-standing R&D tax incentives. There are general R&D deductions (up to 100%) as well as super deductions for contracted out research to Indian entities.[339] And there are also targeted incentives for the biotech sector. After the 2015-16 budget fell short of introducing major R&D incentives expected by the "Make in India" initiative, the proposed 2016-17 budget was a mixture of incentives and cuts. On the one hand the proposed budget reduced the biotech specific R&D super deduction from 200% to 150% from April 2017 until financial year 2019-2020, and to 100% from 2020 onwards.[340] Counterbalancing this cut, was a proposed reduced 10% income

tax rate for royalties stemming from exploitation of patents developed and registered in the country.[341] Furthermore, in a bid to encourage start-up biotech research and innovation the budget puts forward a tax waiver on services provided by biotechnology incubators approved by Biotechnology Industry Research Assistance Council.[342] The 2016 budget also seeks to introduce a 3-year 100% tax exemption for start-ups created after April 2016.[343]

On the other hand, negative fiscal measures were introduced to promote local manufacturing, such as increasing duties on innovative drugs and the removal of duty exemption for pharmaceuticals. [344]

Looking at the biopharmaceutical market relatively strict price controls are in place for drugs and pharmaceuticals available through the National List of Essential Medicines. Over the last few years price restrictions have been extended to over 509 drugs, including anti-diabetic, cardiovascular and oncology treatments.[345]

In 2015 an inter-ministerial committee chaired by the Department of Pharmaceuticals proposed making market approval for biopharmaceuticals conditional on pre-negotiation of prices for patented drugs (excluding those under DPCO point 32 (iii)).[346] If implemented, this would move India's biopharmaceutical market and standards further from international standards in which scientific considerations such as ensuring the safety, quality and efficacy of a given product are what underpins market authorization. The practical effect would also be that there would be further delays getting innovative treatments to patients and added uncertainty to the market authorization process.

Legal certainty (including the rule of law)

The Indian legal environment presents a number of challenges. Legal redress, enforcement of contracts and administrative justice is not always available or consistently applied. In the 2015 *Rule of Law Index* India was ranked 59th out of 102 countries.[347]

Israel

Israel is a high-income OECD country with an estimated 2014 total national output of USD305.7 billion GDP at market prices (current USD).[348] Measured on a GDP per head basis Israel has a per capita income of USD37,206 for 2014 at current USD.[349] Israel is the 27th most open and competitive economy according to the World Economic Forum 2015-16 Global Competitiveness ranking.[350]

National Innovation Strategy

A vibrant high-tech hub for many years, Israel is committed to fostering domestic high-tech, innovative industries, including in biotechnology.[351] In this light Israel prioritizes the creation of a supportive policy environment, capacity building and providing adequate resources as well as specific incentives targeting innovation and investment, while also continuing to foster established industries, such as its world-leading generic biopharmaceutical industry. One of its flagship platforms is the Office of Chief Scientist operating under the aegis of the Ministry of Economy, which promotes industrial R&D through a number of programs. It allocates an annual budget of USD400 million to leverage the country's scientific and innovation potential and attract foreign capital and know-how.[352] These programs include a major R&D Fund which provides grants of up to 50% for approved R&D expenditure as well as a Technological Incubators Program that provides full financial support to various high-tech industries.[353] Biotech incubators enjoy the highest financial contribution from the Office, which invests 85% of their cost up to a value of USD2 million for three years. Israel is also seeking to build capacity for innovation through special "innovation visas" for foreign scientists and entrepreneurs as well as tax benefits for companies that develop intangible products and technologies in Israel.[354]

Moreover, since January 2016 the government formally launched a new entity, the National Authority for Technological Innovation, which will operate as an independent public corporation in charge of, among other elements, defining

technology transfer policies, entering into joint investments together with venture capital funds and commercial companies, and also issuing bonds.[355] The new body is expected to further improve funding for R&D and high-tech companies as well as strengthen regulations governing technology transfer, including relaxing rules regarding foreign ownership of publicly funded know-how.[356]

Though the biotechnology sector is still relatively young, a surge in enabling policies and incentives in the last 15 years has led to record growth of the sector in Israel over the past half-decade.[357] For many years, Israel's biotech sector consisted mainly of research organizations and early stage companies focused on licensing out technologies, with little development and commercialization of biotechnologies in Israel. A dedicated effort to improve enabling policies and incentives has taken place since 2000, when the Office of the Chief Scientist issued a "Bio-Plan" for Israel for the decade to 2010.[358] Among its key recommendations, the plan called for greater funding for early and later phase biotech companies, increased collaboration between industry and universities and PROs, and a strengthening of the regulatory framework and capacity. Since then the Israeli Government has taken a wide number of key measures aimed at achieving these targets, including within its wider innovation policy and annual R&D budget.

In the context of these and other policy improvements, the biotechnology sector in Israel has expanded significantly. Today, around 80% of the sector is focused on biomedical R&D, with emphasis on biopharmaceuticals and diagnostics, including tissue engineering, cell therapy, immunotherapy and vaccines.[359] Bioinformatics also represents a growing field in Israel, due in part to a historically strong emphasis and success in the field of information and communication technologies, with a significant number of partnerships between local bioinformatics companies and multinational biopharmaceutical companies.[360]

Biotech sector by sector policy overview

Biopharmaceuticals

As the most advanced biotech sector in Israel, a dynamic innovative biopharmaceutical and biomedical sector has sprouted up alongside its traditionally generic biopharmaceutical sector (while not detracting from the latter's global competitiveness). According to the Office of the Chief Scientist 2015 Innovation Report, the number of life sciences companies in Israel has increased by more than five times in the past 15 years (from 200 in the late 1990s to around 1,100 in 2015) and the sector represents around 18% of total exports.[361] Today at least 40% of the total biopharmaceutical sector includes companies involved in biopharmaceutical discovery, development and delivery (with 22% engaged in drug discovery).[362] Despite the market's relatively small size Israel hosts 17 local subsidiaries of research-based multinational biopharmaceutical companies.[363] Besides being traditionally involved in importing and marketing of their products, multinational research-based companies are active in R&D activities and play a critical role in cooperating with local firms and creating a vibrant innovation start-up platform.[364] Moreover, today the biomedical sector not only continues to play a role in many cutting edge treatments (with contribution from Israeli-developed technologies to a number of recent "blockbuster" biopharmaceuticals estimated at around 25%), but is also leading the development and marketing of cutting edge treatments, such as the Israeli company Protalix BioTherapeutics' plant cell-based enzyme replacement therapy for Gaucher disease.[365]

Looking at rates of product launches between 1983-2000, the percentage of products available in Israel within five years of global launch was 24%.[366] This was in lower third of the sampled economies.

With regards to the BCI Survey Israel ranked in the middle of the economies included in *Building the Bioeconomy* with an overall score of 75.38. [367]

Ag-Bio

As government regulations forbid local commercial production, the ag-bio sector in Israel is limited only to the import of biotech crops, either for consumption or as intermediary ingredients.[368] GM crops are grown for research purposes, carried out both by public and private entities.

Generally, Israel is highly reputed internationally for its genetic engineering research, which focuses mainly on improving plant resistance to pests, disease, and herbicide.[369] Field trials have been ongoing for 20 years, and concerned tomatoes, potatoes, eucalyptus, flowers, soybeans, cotton, corn, strawberries and bananas.[370] Private companies carried out most of the recent field trials. One of them, Evogene, has attracted high international investments for their cutting-edge technologies.[371] The ban to commercialization could be lifted over the next few years, as the Ministry of Agriculture is currently contemplating the issue, prompted by industry pressure and a favorable view from the Israeli Plant and Protection Service.[372] However, the fact that most of Israel's agricultural exports head to the EU, traditionally wary of GMO, weighs against the liberalization of GMO.[373] Finally, based on MoH regulations under consideration, food products involving biotechnology would need to be registered and adhere to labeling rules (all products containing DNA or proteins and/or 1% or more of the products are derived from genetically-modified ingredients).[374]

Industrial Biotechnology

In 2011, Israel has set itself the ambitious goal to reduce the share of oil in its transportation sector by 30% by 2020 and by 60% by 2025, and becoming a global leader in developing alternative fuels.[375] Since 2013, the government's Fuel Choices Initiative program coordinates the effort to achieve this goal. Since then, the number of companies active in the alternative fuels sector in Israel has jumped fivefold to about 300, while associated research groups have risen fourfold to about 190,[376] overcoming the targets set in 2011[377] The Program was allocated a budget of NIS 1.5 billion over 10 years. To encourage breakthroughs in the field, the Prime Minister also established the Prize for Innovation in Alternative Fuels for Transportation was set up.[378] A co-invest fund offers a 50% top-up on private investments for R&D on alternative fuels.[379] Since launching the strategy, four clusters have been created, including one on Biofuels and Energy Agriculture. Capitalizing on the country's competitive edge on agro-biotechnology R&D, Israeli companies are at the forefront in developing innovative biological treatments for second and third generation biofuels, such as algae, garbage and agricultural waste products.[380] International companies, such as Ford and Porsche, are establishing their alternative fuel research centers in Israel.[381] Public research is carried out by the Agricultural Research Organisation Volcani Center and focuses on developing seeds for non-agricultural plants *Jatropha curcas* and Castor.[382]

While research activities flourish, the country lags behind in production and use, and the set goals are expected to be out of reach.[383] Overall, renewable quota in the country energy mix accounts only for 2% at present.[384] A bill that received first approval in the Knesset in December 2015 proposes to ramp it up to 17% and to draft more concrete, stringent plans for its achievements.[385]

Performance in key enabling factors

Human capital

Israel's young and highly educated workforce act as a natural breeding ground for biotechnology development.[386] Israeli universities are relatively well regarded. Six of the eight Israeli universities rank in the 2015-16 *Times Higher Education* rankings, of which three in the top-300.[387]

In terms of academic and research publications, Israel has compared to other *Building the Bioeconomy* countries a high number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Israel had 797.46 publications per million population; behind only Switzerland.[388] Israeli academic publications ranked highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard*

which measure of the quality of academic publications with 14.56% of publications among the 10% most cited; behind only Switzerland, the US and UK.[389]

A big share of Israel's workforce consists of researchers. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Israel had 8,282 researchers per million people,[390] the highest among all countries included in *Building the Bioeconomy*.

Infrastructure for R&D

Israel has a highly developed public and private sector research infrastructure. As of 2014, 4.11% of GDP was allocated to R&D activities, second only to Korea of the countries included in *Building the Bioeconomy*.[391] This number goes far beyond the OECD 2.2% average, and much more than many other countries at the same level of income.[392] The business sector R&D investments corresponded to 1.49% of the country's GDP, at 36% of total R&D spending.[393] Biotech R&D accounted for 5.7% of overall industry R&D spending in 2013.[394]

Israel has quite advanced medical and biomedical research facilities. Indicative of the competitive clinical environment is the high level of clinical trials. Israel so far has carried out has 5,680 clinical trials.[395] Israel also has one of the highest per capita rates of clinical trial activity worldwide, with close to 700 trials hosted to date and a large portion of these for the more complex and cutting edge early phase trials.[396] Looking at biologics a high proportion of clinical research in Israel is on biologic products. Between 2010-2015 Israel had the highest rate of clinical trials on biologics per million population of the countries included in *Building the Bioeconomy* at 22.76.[397]

Looking at biotechnology triadic patenting for a small country, Israel has a relatively high proportion of world biotechnology patenting on both an absolute basis and if adjusted for population. Israel's share of the global total average for the period 1999-2012 is 1.15% significantly higher than bigger countries such as Brazil, India or Russia.[398]

Apart from a significant strengthening of funding for innovation more broadly, the Israel venture capital market is healthy, with a large number of venture capital companies targeting biotech and biomedical innovation under the wider umbrella of life sciences now active.[399] VC firms targeting biotech are also arising, including a new USD100 million Israel Biotech Fund launched in 2015 focused on biopharmaceuticals.[400] As part of a broader effort to establish technology incubators (as mentioned above), a special focus has also been placed on creating and supporting bioclusters, such as RAD BioMed, that provide R&D infrastructure and scientific and business support and capacity building to local start-ups.[401] Another example is FutuRx, a biomedical incubator jointly set up by Johnson & Johnson Innovation and Takeda, who pledged more than $28 million to top up CSO's public funding in order to finance early-stage biopharma companies.[402]

Israel is viewed as a mixed market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Israel is ranked in the middle of *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 78.3.[403]

Intellectual property protection

Another area in which Israel has made significant strides in the context of its biotechnology innovation strategy is IP protection. Israel has historically had a difficult IP environment, particularly in relation to biopharmaceuticals (noted in the USTR's Special 301 Report for several years), however following a 2010 Memorandum of Understanding with the US, Israel carried out significant improvements in key areas of biopharmaceutical IP protection. Specifically, in 2011 the RDP term for chemical drugs was increased to 6 years from the date of registration in Israel or 6.5 years from the date of registration in one of the recognized drug regulatory authorities (primarily the FDA and EMA), although this term is not currently applied to biologics and continues to hamper further biotech R&D activities.[404] 2012 and 2014 amendments to patent legislation introduced several additional improvements, such as patent term restoration, speedier review and publication of patent applications (the latter, after 18 months

from the date of application) and legal remedies in case of infringement cases during the early publication period.[405]

The regulatory environment

Broadly speaking the current standards for approval of new and generic drugs are in line with international best practices. The Israeli Institute for Standardization and Control of Pharmaceuticals, responsible for the appraisal of all drugs pending marketing approval in Israel, was recently audited by the European Directorate for the Quality of Medicines & Healthcare, and was found to uphold the high-end ISO international standardization norms.[406] In terms of the market authorization process for innovative products, the Israeli Ministry of Health relies on the prior approval by a select number of drug regulatory authorities, primarily the FDA and EMA. The stated maximum time for approval of innovative products is 270 days (although in practice, challenges remain surrounding registration delays).[407] In addition, in 2006 a fast-track registration process was introduced for innovative drugs, setting a 45-day registration deadline for new drugs that are included in the Essential Drug List but, at the time of inclusion, were not registered in the country.[408]

Responsibilities for GMO use and R&D are shared by the Ministry of Agriculture and Rural Development and the Ministry of Health, in line with the 2005 Seeds Regulations.[409] The Israeli Food Control Services, which is part of the Ministry of Health, authored the proposal to introduce compulsory labelling of genetically modified pre-packaged food, fruits and vegetables.[410] The Ministry of Agriculture oversees all experimentation of plant GMOs and handles import and export activities, handling and commercialization. One of its bodies, the Plant Protection and Inspection Service, is in charge of approving all GMO experimentation.[411]

Technology transfer

A major shift in technology transfer towards the biotech and biomedical field has taken place over the last decades. Technology transfer is well established in Israel, with over 10 tech transfer offices and companies present at the major universities and research institutions for over 50 years. Israel was the smallest of the 9 countries with at least one institute among the top 50 patenting universities worldwide according to WIPO. The country accounted for 39 of the total 3,952 PCT applications by the top 50 applicants, about a third of the number of applications by British universities included on the list.[412] Israel's technology transfer model is similar to the US' Bayh-Dole framework but based on largely independent and corporate-style offices heavily focused on generating royalties and creation of new companies, and has been widely successful. Indeed, two technology transfer offices in Israel, Yissum from Hebrew University and Yeda from the Weizmann Institute, are ranked among the top tech transfer offices worldwide.[413] Technology transfer offices in Israel are quite active, with by some estimates an average of 150 new licensing deals, 15 start-ups and NIS1.5 billion (USD400 million) in royalties per year.[414] Reflecting wider emphasis on and growth of the biotech sector in Israel, today much of this activity targets biotechnology; for instance, around 60% of Yeda's portfolio focuses on biotechnology.[415]

Market and commercial incentives

Israel offers reduced corporate income tax for those firms that obtain the status of being an "R&D firm"; the rate ranges between 5% and 12% depending on company location and size.[416] Large MNCs located in priority areas benefit from the lowest tax rate; R&D activities must take place in Israel. Beginning in 2015 a company that develops intangible products (such as software or a drug) in Israel but then manufactures them abroad will be fully exempt from VAT and from paying credit tax on sales abroad.[417] An ongoing review of the 1959 Law for Encouraging Capital Investments recommended introducing new (unspecified) 3-year tax benefits for IP registered in Israel by multinational companies, and a 5% deduction for dividend tax on royalties for 5-10 years.[418] Finally, recent amendments ease eligibility criteria of the "Angels' Law", according to which private investors ("angels") in seed-stage high-tech companies can write off their investment as an expense (provided 75% of it is used for R&D purposes).[419]

The pricing and reimbursement environment for biopharmaceuticals remains mixed, in some ways rewarding biopharmaceutical innovation and in other ways putting significant price pressure and eroding reimbursement for cutting edge treatments. For example within Israel's "basic basket" of health services that are reimbursed within the national health system is a fixed annual budget dedicated specifically to innovative products with a special committee determining regular additions to the basket.[420] Yet at the same time, for other drugs the Ministry of Health uses an external reference pricing system to set pharmaceutical prices and price cuts are frequently imposed; most recently in December 2015 price cuts of over 5% were issued.[421]

Legal certainty (including the rule of law)

Israel regulatory environment is generally competitive and well established.[422] In the World Economic Forum Competitiveness Report 2015-2016, Israeli institutions are ranked 40th out of 140 in terms of efficiency. The country scored well in terms of lack of corruption, independence of judicial system, protection of investors and efficiency of legal framework.[423] On the other hand, government bureaucracy stood out as the main problematic factor.[424] Israel is not included in the 2015 *Rule of Law Index*.

Japan

Japan is the 4th largest economy in the world with an estimated 2014 total national output of over USD4 trillion measured on a PPP basis.[425] GDP per capita at current USD in Japan was USD36,194 for 2014 at current USD.[426] Japan is the 6th most open and competitive economy according to the World Economic Forum 2015-16 Global Competitiveness ranking.[427]

National Innovation Strategy

For many years the Japanese government has promoted innovation and scientific research through dedicated policy initiatives aimed at boosting competitiveness and economic growth. Since the Basic Law on Science and Technology was introduced in 1995 the government has issued five "Science and Technology Basic Plans".[428] The most recent plan, adopted in 2016, targets development of human capital and commercialization of technologies with the goal of addressing socio-economic challenges such as an ageing society, regional disparities and resource limitations.[429]

The Abe administration has further prioritized innovation, identifying it as one of the central pillars of economic growth and releasing an annual Comprehensive Strategy on Science, Technology and Innovation since 2013.[430] Supported by the Cabinet's Council for Science, Technology and Innovation and the Ministry of Education, Culture, Sports, Science and Technology, the central government body for Japan's innovation policy, the Comprehensive Strategy seeks to coordinate and align various agencies' innovation policies and programs to generate new levels of innovation in the country, with a focus on "cross-cutting technologies" such as ICT, nanotechnology and environmental technology and improving the "fundamentals" of innovation.[431] Specific objectives of the strategy include increasing government spending on R&D, including a target of at least 1% of GDP, raising spending on basic science and universities, and promoting technology transfer, including through intellectual property platforms, and industry-academia collaboration.[432]

Within key innovation plans, biotechnology is identified as a strategic focus and the sector is poised for growth, though is still relatively small (with the exception of pharmaceuticals). Spending on biotech R&D is near the top globally, at over USD1.2 billion, but remains below smaller markets such as Korea and Switzerland.[433]

Biotech sector by sector policy overview

Biopharmaceuticals

The biopharmaceutical sector is the most developed within the Japanese biotech sphere, as the second largest pharmaceutical market globally.[434] Among respondents to a 2015 survey of local biotech firms about 40% came from the biomedical and biopharmaceutical sectors.[435]

Although the Japanese biopharmaceutical sector consists of over 1,000 companies most are small and medium-sized enterprises traditionally heavily focused on the domestic market.[436] Pharmaceutical exports represent a very small portion of total exports at just 0.6%.[437] Private sector spending on biopharmaceutical R&D is also relatively low at 11% of total firm-level R&D expenditure.

The Japanese government has prioritized biopharmaceuticals within its long-term innovation policy goals, with a number of strategic initiatives focused on the sector issued over the past few years. These initiatives aim to position Japan to compete in the global market for regenerative medicines, rare diseases and cancer therapies through strengthening drug discovery and development in these areas. The Sakigaki Strategy launched in 2014 provides support for pre-clinical and clinical research targeting cancer and orphan drug treatments through public-private coalitions and networks, improvements to infrastructure and fast-track review.[438] Adding to this, amendments to the Pharmaceutical Affairs Act considerably shortened the time needed for commercialisation of regenerative drugs by granting them conditional marketing approval on the basis of successful Phase II human trials.[439] Approval times are expected to shrink from 7 to 10 years to around 2-3 years.[440] Building on this, the Comprehensive Strategy to Strengthen the Pharmaceutical Industry issued by the Ministry of Health in 2015 targets over JPY200 billion in the 2016 fiscal budget to the local innovative biopharmaceutical sector.[441] The strategy is focused on three main areas. First, becoming a top global host of clinical trials through establishing of a new clinical innovation network and coordinating agency focused on basic and clinical research, the Agency for Medical Research and Development.[442] The new network is aimed at increasing collaboration among hospitals, companies and government agencies and improving data sharing through building patient registries. The strategy also seeks to streamline regulatory approval for breakthrough treatment, including the above mentioned fast-track "sakigake" review of prioritized therapeutic areas such as oncology and rare diseases, with the aim of bringing down average approval times to six months.[443]

Additionally the Strategy seeks to expand the pricing system to reward brand new drugs as well as biosimilars, vis-à-vis existing equivalent treatments (while also promoting generics through lower prices and support for consolidation among local generics manufacturers).[444]

Looking at rates of product launches between 1983-2000, the percentage of products available in Japan within five years of global launch was 32%.[445] This was squarely in the middle of the sampled economies.

With regards to the BCI Survey Japan ranked in the top half of the economies included in *Building the Bioeconomy* with an overall score of 77.48. [446]

Ag-Bio

On the one hand, Japan represents a significant market for the governance and consumption of GM products and agricultural biotechnology, but on the other it remains relatively undeveloped in R&D and domestic production and with significant public concern about biotech crops. Japan is one of the largest importers of GM crops globally; by some estimates, around 75% of its food and feed imports are produced using agricultural biotechnology.[447] The Japanese Government plays an important role worldwide in the regulatory review and approval of GM-derived products for consumption, and Japan is in the top 5 globally in terms of number of regulatory approvals of GM crops, at over 200 approvals as of end of 2015.[448] Nevertheless, today R&D of biotech crops in Japan itself is limited and mainly concentrated in the public sphere (such as work by the Forest and Forest Product Research Institute and the National Institute of Agricultural Sciences on pollen allergies[449]), and very little commercial production takes place.[450] This is partly due to heavy central and regional government restrictions on planting of GM crops as well as limited acceptance by the public of biotech crops.[451] Nevertheless, the government has targeted ag-bio as a sector of focus in its overarching national innovation strategies, such as the Comprehensive Strategy discussed above, where agriculture and foodstuffs are identified as key priorities for addressing current health, demographic and security challenges.

Industrial Biotechnology

Industrial biotechnology has also represented a strategic area of focus for more than a decade, particularly in the fields of biomass (wood and waste-based) and marine biofuels. Though Japan has significant potential in certain areas – for instance, with around 6 billion cubic meters of forestry resources, a figure near the top globally[452] – the biorenewables sector is still relatively small. For instance, only about 2.5% of new energy-related firms established in 2014 belong to the biomass and biofuel sector.[453] Among Japanese biotech firms specifically just about 15% are focused on industrial biotechnology, as indicated by recent industry surveys.[454] Still among renewable energy, biomass has one of the highest uptake rates, relative to other types of energy consumption such as solar and wind.[455]

For the past half-decade the government has explicitly promoted the growth of the biofuel sector, with particular focus on biomass. The 2010 National Plan for the Promotion of Biomass Utilization set a number of targets for the biomass sector, including expansion of the use of biomass to 26 million carbon tons per year, creation of plans for utilizing biomass among 600 municipalities and growing the total biomass industry to a value of JPY500 billion (over USD4 billion) by 2020, with the long-term goal of biomass representing 4% of electricity generation by 2030.[456] In the wake of the 2011 earthquake and Fukushima nuclear power plant accident, the government launched an additional Biomass Industrialization Strategy in 2012 to strengthen alternative energy sources and significantly widen electricity generation from biomass. Key policies in the strategy include technical assistance in development of conversion technologies, promotion of "biomass towns", a new feed-in tariff scheme and tax incentives (50% reduction in property tax for biofuel manufacturing facilities and one-third cut in property tax on renewable power plants.[457] More recent initiatives, including the general comprehensive strategy mentioned above as well as those focused on energy innovation (such as the Energy/Environment Innovation Strategy under discussion in 2016 and the 2015 Roadmap for Establishing the Supply Chain for Next-Generation Aviation Fuels) continue to prioritize biofuels and biomass as key sectors for development.[458]

Performance in key enabling factors

Human capital

Japanese universities are relatively well-regarded, particularly in the biomedical and life science fields as well as engineering. For example, in the 2015-16 *Times Higher Education* rankings of the world's top 100 universities, three universities are included in the top 100, with the University of Tokyo ranked 45th and Kyoto University 59th.[459] Additionally, the country's universities are recognized as excelling in offering engineering training with 11 institutions ranked in the top 100 engineering and technology universities internationally.[460]

In terms of academic and research publications, Japan has compared to other *Building the Bioeconomy* countries a high number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Japan had 421 publications per million population.[461] Japanese academic publications were not ranked in the top according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with 8.82% of publications among the 10% most cited; behind only Israel, Korea and top-performers Switzerland, the US and UK.[462]

A big share of Japan's workforce consists of researchers. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Japan had 5,201 researchers per million people,[463] among the highest among all countries included in *Building the Bioeconomy*.

Infrastructure for R&D

Japan is a top investor in research and development. When measured as a percentage of GDP 2014 figures show R&D spending at 3.58%.[464] Internationally, this is in the top three among all countries included in *Building the Bioeconomy* OECD members and well above the OECD

average of 2.37%.[465] R&D spending in Japan largely comes from the private sector, estimated at 77.3% in 2014.[466] Biotech R&D accounted for 1.2% of overall industry R&D spending.[467]

Though Japan has traditionally been home to some of the world's leading innovative biopharmaceutical manufacturers, there are current gaps in biopharmaceutical R&D, particularly in the area of clinical research.

Looking at clinical trial intensity and the number of clinical trials to date per million population Japan has only around 27 trials, the lowest in the OECD save Mexico.[468] The majority of trials carried out in Japan are local, non-innovative trials. Moreover, a relatively small proportion of current trials (registered since 2013) are in early phase research. Out of a total number of 305 trials with a registered start date in 2013, 53 were Phase I and 81 were Phase II trials.[469] Japan also has relatively low levels of trials on biologics per million population, 1.76 for the period 2010-2015.[470]

Looking at biotechnology triadic patenting Japan is a top patenting nation on an absolute basis and if adjusted for population. Japan's share of the global total average for the period 1999-2012 is 14.28% second only to the US.[471]

Looking at the biopharmaceutical sector private R&D spending amounted at USD27.6 billion in 2012, three times higher than the public R&D budget allocated to the sector during the same year.[472] From 2007 to 2012, Japan was the country with the highest increase of private-injected biomedical R&D investment in absolute terms, at almost USD7billion, whereas the largest percentage increase was registered in China, where investment went from USD1.5 to USD 6.3billion.[473] In 2015, Japan also ranked second among Asian countries in terms of number of jobs in the biotech industry, after China. While traditionally big corporations such as Takeda and Astellas dominate the biopharmaceutical industry, the relatively high amount of money raised through IPOs in 2015 (USD263 million by five companies) shows the presence of a dynamic industry beyond that. Out of a total of over 1,000 biotech companies, a survey by the Japanese Bioindustry Association counted 591 bio-ventures in 2014.[474]

Japan is viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Japan ranked fourth in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 91.3. [475]

Intellectual property protection

In general, Japan is seen as having a strong environment for intellectual property protection. The country has a sophisticated IP system that offers patent rights holders multiple levels of protection and avenues for recourse against IP infringements.

Regulatory Data Protection is offered indirectly through a "re-examination period" during which data submitted to the drug regulatory authority, the Pharmaceuticals and Medical Devices Agency, cannot be relied on for follow-on applicants. The re-examination period is 8 years for new medicines and 4 years for previously approved drugs that receive approval for new clinical indications.[476] Patent term restoration is also available. Starting from January 2016, deterrence measures against trade secret infringements have been stiffened, namely by reducing the burden of proof for civil claims and imposing greater criminal penalties.[477]

The regulatory environment

Japan has a strong clinical and regulatory environment. For biopharmaceuticals the PMDA is responsible for the authorization and safety supervision of pharmaceuticals. PMDA has recently made strides in reducing a historically long lag of 5-10 years between approval of biopharmaceuticals in other major markets and in Japan increasing its review capacity significantly.[478] In addition, as part of the sakigake initiative discussed above, drugs that are developed and launched in Japan benefit from a fast-track review for clinical trials and for drug registration, with an expected approval time of 6 months.[479] In 2015, the first year of operation, six products were designated for accelerated review. Finally, the introduction of pre-market approval for regenerative medicine was also well received with R&D investments in stem cells and gene technologies reportedly having increased following Japan's deregulation of the sector.[480]

As mentioned Japan imports a large amount of genetically engineered food products and grains and has approved a high number of ag-bio products.[481] With regards to the use of biotechnology in agriculture, Japan has strict laws relating to the growing and sale of ag-bio products. GM products used for food and feed must obtain government approvals.[482] Labelling rules for genetically engineered foods are governed under the Food Sanitation Law and the Japanese Agricultural Standard Law as well as a new 2015 Food Labelling Law. GM ingredients exceeding 5% of the total weight of the food in a selected group of 33 foods (which may typically include GM products) and is one of the top 3 ingredients in terms of weight must be labelled as GM. In addition, a number of provinces have introduced local rules on top of the central government rules, particularly for the planting of GM crops that in many cases place significant restrictions on farmers.[483]

Technology transfer

Japan introduced a Bayh-Dole framework in 1999 under the Industrial Revitalization Special Law. It covers a range of IP rights, including patents, utility models and seed and seedling registration rights, and similar to the US Bayh-Dole framework allows universities and public research institutions to own IP rights associated with publicly funded R&D. The Law for Promoting University-Industry Technology Transfer provides funding and commercial advantages for approved technology transfer offices. Illustrating the strong link between academia and industry, in May 2016 Chugai Pharmaceutical agreed to pay Osaka University USD91.5 million over 10 years to be able to access the independent basic research projects at the University's Immunology Frontier Research Center. However, start-ups still play a small role in terms of in the realm of tech transfer and innovation. In recent years the Government has taken steps to support development of a startup culture. Among these, an incubator program (Kakehashi Project) allows 30 businesses to go to California for launch, and an exchange program between Japanese schools and Stanford's bio design unit.[484]

Market and commercial incentives

Japan offers R&D tax incentives to both small and large companies. SMEs can qualify for a credit of 12% of total R&D spending and large companies for an 8-10% credit (which for both should be equal or lower than 25% of the company's corporate tax rate).[485] For SMEs the credit rises to 30% for R&D taking place in partnership with a university or PRO.

Looking at biopharmaceuticals, Japan has a highly regulated pricing environment with the Government setting prices and determining whether a drug will be reimbursed in the national health system based on the recommendation of the Central Social Insurance Medical Council.[486] Drug prices are revised every two years, leading to significant price cuts for innovative products. Since 2010, a "premium" price has been afforded to eligible patented biopharmaceuticals as a manner of compensating for price cuts, such that the price remains the same throughout the patent term.[487] The premium is afforded to about half of patented biopharmaceuticals available in the national health system.[488] An additional "re-pricing", including an up to 25% price reduction, may occur for biopharmaceuticals that have unexpected high sales volumes (100% or more above sales projections).[489] In 2016, MHLW is discussing an extension of the re-pricing system to additional products and involving greater price reductions.[490]

Legal certainty (including the rule of law)

The Japanese legal environment is generally stable and certain. The country is ranked as the 13th most stable legal environment in the 2015 *Rule of Law Index* and received particularly high marks for low levels of crime and corruption.[491]

Korea

Korea, the world's 15th and Asia's 4th largest economy, is a high-income economy with a GDP of USD1.3 trillion in 2014, and a per capita GDP at PPP of USD27,970.[492] Korea was ranked 26th on the *Global Competitiveness Index* 2015–2016, benefitting from a stable macroeconomic environment, international openness and the world's highest education enrollment rates.[493]

National Innovation Strategy

Korea is a growing power in the biotech space. The country has a number of government bodies that oversee and direct national research and innovation policies including the Presidential Advisory Council on Science & Technology and the National Science and Technology Council.[494] Significant resources, time and energy have been expended by the Korean public and private sectors in encouraging biotech innovation and building a strong, viable biotech capacity, namely in the biopharmaceutical sector.

Gradually, biotech has been identified as the next growth engine after IT. This was recently confirmed by President Park Geun-hye, who endorsed suggestions by the Presidential Advisory Council on Science & Technology to beef up R&D efforts in the biotech sector.[495] In particular, the President promised to support the launch of 100 globally competitive biotech start-ups. At present Korea hosts approximately 600 companies, and the objective is to increase this. According to the Korean Venture Capital Association, 13 out of 14 firms that went public in 2015 where biotechnology companies. However, the number of bio venture start-ups plunged from 71 in 2007 to 2 in 2013.[496] A dedicated Fund will allocate KRW80 billion (USD67.62 million) to support start-ups. The panel also proposed creation of an R&D center tailored to early-stage companies, financial incentives, and programs to help them expand overseas. Finally, the Ministry of Science, ICT and Future Planning will roll out a KRW30billion (USD109.89 million) plan focused on commercialisation capacities.[497] The overall target is to increase the country's share of the global biotech market from 1.2% recorded in 2015 to 5% by 2025.[498] The Government also committed to raise R&D investment in the bio sector by more than the increase in the overall R&D budget, streamline spending and focus on stem cell and gene therapy.[499]

Government funded biotechnology research in Korea is overseen by the Korea Research Institute of Bioscience and Biotechnology.[500] The Institute functions as an umbrella corporation for a series of research centres focused on different aspects of biotechnology. The Targeted Medicine Research Centre undertakes R&D related to pharmaceutical development. The Centre's main focus is on developing new medications for the treatment of metabolic and inflammatory diseases, chronic disease modulation, and creation of biological products from plants and the creation of a Plant Extract Bank.[501] The Plant Extract Bank currently houses samples from 26,000 thousand different plant varieties found all over the globe. The samples are available to Korean researchers to help facilitate the use of plant-based molecules in novel drug treatments.[502] The Institute has also successfully licensed out two natural drug candidates to Korean pharmaceutical companies for further development, a synthetic drug compound and a nurtaceutical for atherosclerosis.[503] The Institute is also directly involved in the commercialization and exports of new biotech products. In 2015 the Institute announced that Mico Biomed (a joint venture between the Institute and Mico, a private company) had secured contacts worth USD57 million in exports for diagnostic devices and strips developed by the company.[504] The Institute also announced a new partnership with the private sector to further bio-convergence R&D.[505] This partnership involves 45 SMEs who together with the Institute will work to develop new technologies and cross-pollination between biotech silos.

Biotech sector by sector policy overview

Biopharmaceuticals

The Korean biopharmaceutical industry is growing rapidly in its capabilities. Pharmaceutical research made up 2.34% of total R&D business expenditure at KRW1.08 billion in 2013.[506] The share of biopharmaceutical products as a total percentage of pharmaceuticals went up from 6.5% in 2007 to 9.3% in 2010.[507] In 2014, it was estimated that there were 975 biotechnology companies in Korea. Of these, 60% operate in biopharmaceuticals and food.[508]

Biotech R&D is receiving a huge boost from the 2010 "Pharma 2020 Vision". Under this program the Korean Government will invest approximately USD8.9 billion over 10 years to build up the countries drug development structure.[509] In addition to spending targets, the 2020 Vision provides investment for the training of 10,000 new

researchers; the Government further estimates that projects undertaken by these new researchers will create 58,000 jobs.[510] Particular attention has been given to biosimilars, with the government setting the objective of capturing 22% of the global biosimilars market share by 2020, as well as reaching USD10 billion in exports and employing 120,000 people.[511] With this objective in mind, USD366 million was made available in 2015 to support R&D of products that can be put on the market within three years.[512] The fund is meant to facilitate exports of biosimilars by supporting local clinical trials and out-licensing to multinational companies.[513]

There are also a number of concrete private sector initiatives in place. Samsung Biologics is the most prominent example of a company investing and expanding its presence in the biologics space. In late 2015 the company announced construction of the world's largest biopharmaceutical plant outside Seoul, to be followed by further investments.[514] Once the plant will be operational in 2017, the firm expects to become the largest biologics contract manufacturing organization worldwide.[515]

Looking at rates of product launches between 1983-2000, the percentage of products available in Korea within five years of global launch was 43%.[516] This was fourth of the sampled economies.

With regards to the BCI Survey Korea ranked in the top third of the economies included in *Building the Bioeconomy* with an overall score of 77.94. [517]

Ag-bio

High levels of consumer skepticism surrounding the use of GMO products in food have limited the commercialization of agricultural biotechnology products in Korea.[518] Following pressure from vocal NGOs, in 2015 the Government submitted plans to expand biotech labeling to products containing detectable biotech ingredients.[519]

Still, despite the public doubts, there is a robust amount of research that takes place in the field. Between 1990 and 2007 experts from the government and academia in Korea published 380 papers on biotech food.[520] Further, in 2014 the Rural Development Administration approved 347 field trials.[521] In May 2015 it also disclosed results of the first phase of a USD260 million project (the Next Generation Bio-Green 21 Project), during which it decoded genomes of nine items.[522] The Rural Development Administration has 180 events in 17 different varieties of crops under development.[523] This is in addition to almost sixty varieties of modified crops being developed by the private sector that are currently in the laboratory phase.

At the conclusion of 2014 no products had been approved for commercialization, the product closest to approval is a GM grass variety that has been in and out of the review process since 2008.[524]

Industrial biotechnology

Korea is investing more attention and resources in the industrial biotechnology sector. The Korea Research Institute of Bioscience and Biotechnology operates the Biorefinery Research Center focusing on the development of industrial enzymes, biofuel, bio-refining technologies and the creation of industrial microorganisms.[525] The Center has had several successes including the development of a biofuel from agricultural residue, microbial strains that can produce important chemicals used in bio-plastics and micro-algal strains that produce a byproduct that can be used in biofuel.[526] The Ulsan National Institute of Science and Technology recently announced it developed a method to produce biofuels from human waste.[527] As part of the Korean Scientific Cooperation Network with the European Research Area, the country has developed the PROMOFUEL program to advance the study of next generation biofuels, notably fuel alternatives from rubber seed oil and fish oil.[528] After ten years of research, GS Caltex started construction of a USD44 million commercial-scale bio-buthanol plant at the beginning of 2016.[529]

Performance in key enabling factors

Human capital

Korean universities are relatively well regarded, particularly in the biomedical and life science fields. For example, in the 2015-16 *Times Higher Education* rankings the Pohang University of

Science and Technology (Postech) and Seoul National University are respectively ranked 80th and 93th in the life sciences ranking.[530]

In terms of academic and research publications, Korea has compared to other *Building the Bioeconomy* countries a medium number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Korea had 344.7 publications per million population.[531] This was ahead of the BRIC economies and Singapore but far behind world leaders in the US, UK and Switzerland. Korean academic publications ranked at a medium level according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with 9.99% of publications among the 10% most cited; this was ahead of Japan and the BRIC economies but far behind Switzerland, the US and UK.[532]

A big share of Korea's workforce consists of researchers. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Korea had 6,456 researchers per million people,[533] the second highest among all countries included in *Building the Bioeconomy*.

Infrastructure for R&D

Korea is the largest investor in R&D as a % of GDP, at 4.29% of all the countries included in *Building the Bioeconomy*.[534] Korean R&D spending is largely made up of private sector and industry spending. The latest data from 2014 show industry expenditure on R&D at 75.3% of the national total.[535] On the Government side, the 2016 R&D budget for the bio sector amounted to WON2.77 trillion (USD2.34 billion), the second largest of all technology sectors. [536]

Korea has quite advanced medical and biomedical research facilities. Looking at clinical trial intensity and the number of clinical trials to date per million population Korea performs well with around 133 trials.[537] Korea also has a medium level of trials on biologics per million population, 6.49 for the period 2010-2015.[538] A high level of these – 42% – were early phase trials.

Looking at biotechnology triadic patenting Korea is a top patenting nation on an absolute basis and if adjusted for population. Korea's share of the global total average for the period 1999-2012 is 2.31% behind only the US, Japan and the UK.[539]

Korea is viewed as a mixed market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Korea was ranked in the top half in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 80.1. [540]

Intellectual property protection

Overall, Korea has a strong system of protecting IP and enforcing IPRs. Korea provides a standard 20-year term of protection for patents as well as a 5-year term of patent restoration for pharmaceuticals. In conjunction with the US-Korea Free Trade Agreement, in force since March 2015, Korea introduced a 5-year regulatory data protection period similar to that in the US and a patent linkage system based on first generic exclusivity.[541] In the same year, the Korean Supreme Court overruled a prior decision and declared patentability of new medical uses.[542] Korea introduced legislation relating to the development of orphan drugs in 2003. Incentives include marketing rights for six years and nationally funded research programs along with support from the Ministry of Family Affairs, Health and Welfare and the Korean Centers for Disease Control and Prevention to encourage the development of orphan drugs.[543]

Still, important challenges over the implementation of the patent linkage system agreed between the US and Korea have remained in 2015.[544] The patent listing requirements appear to call for innovators to share patent information beyond what is typically provided in similar patent lists (e.g., in the American Orange Book), and listing applications can be rejected by the Korean Ministry of Food and Drug Safety if they do not meet specific criteria (although approximately 85% of patent listing applications are reportedly accepted). In addition, it is possible for patent information submitted by rights holders to be modified somewhat in the final list published by the Ministry. It also remains unclear how

the Ministry will apply the criteria to determine whether or not it should grant a sales stay of the potentially infringing product.[545] Furthermore, sales stay last only a maximum of nine months, which might not be sufficient to solve a patent dispute.[546]

The regulatory environment

Korea has a relatively strong clinical and regulatory environment. For biopharmaceuticals the Ministry of Food and Drug Safety (formerly the Korean Food and Drug Administration) is responsible for the authorisation and safety supervision of pharmaceuticals. The agency is highly regarded internationally and has been praised by the FDA.[547] Korea introduced a biosimilar pathway in 2009.

Korea has ratified the Cartagena Protocol on Biosafety in 2007 and implemented this through the Living Modified Organism Act in 2008. Imports of biotech grains as well as genetically engineered animals are regulated under this Act. Korea's regulatory review is a lengthy, complex process involving input from no less than five different government agencies.

Technology transfer

Korea early on recognized the importance of closer working relations between universities and businesses and encouraging the commercialization of publicly funded research. A number of technology transfer laws have been introduced.[548] These include the 2000 Technology Transfer Promotion Act as well as more recent laws such as the Technology Transfer and Commercialization Promotion Act. These acts provide direct support, opportunities and incentives for universities and research institutions to engage in technology transfer and commercialization activities. This includes support for tech transfer infrastructure, financial support through investment and loans to help small and medium enterprises as well concessions with regards to state property and IP. There are also legal provisions for assisting international cooperation in mutual transfer and commercialization between national and foreign governments, enterprises, colleges and universities, research institutes, and organizations.[549]

Since the early 2000s and the initial interest in developing technology transfer Korea has seen a steady growth in university licensing income and patent rates.[550] 2015 statistics from WIPO show Korean universities as some of the most prolific patenting entities in the world. The Seoul National University was the only top-10 applicant institution from outside the US in 2014.[551] Overall Korean universities in the top-50 university PCT applicants were responsible for 11% of total applications; behind only American universities. Between 2008 and 2013 Korean universities more than doubled their global share of PCT patent applications from 5.1% to 10.5%.[552]

Furthermore, the building of the Korean biotechnology industry has benefited directly from government-backed tech transfer initiatives through the Law for the Creation and Promotion of the Government Research Institutes enacted in 1999. This program sought to promote technology transfer and the commercialisation of biotechnology through start-ups, venture capital partnerships and spin-offs. As of August 2007, 1,386 ventures had been spun off from these institutes and 482 from universities.[553] A similar program, the Tech Incubator Program for Startups was launched in 2013, in order to off-set the negative impact of the 2008 crisis on small innovative business. The program is driven by private capital and by the end of 2015 had subsidized 85% of the initial investments of 18 start-ups.[554]

There are also a range of schemes in place in order to improve knowledge flow and commercialization from public sector research. Examples include the Technology Holding Company system (which seeks to promote the foundation of venture capital businesses from universities and research institutes); the Leaders in Industry-University Programme and the Brain Korea Programme, which are aimed at promoting collaboration between industry and academia.[555] Examples of government tech transfer institutions include the Korea Institute for Advancement of Technology, whose activities include developing a national technology strategy, supporting technology transfer and commercialization, and fostering international technological cooperation.[556]

Market and commercial incentives

Korea offers R&D tax incentives for both large companies and SMEs. The incentives are based around incremental and volume-based deductions ranging from 40-50% for qualifying expenditure.[557]

Looking at biopharmaceutical pricing and reimbursement policies Korea has in place a relatively strict system applicable primarily to innovative products.[558] For example, South Korea has instituted mandatory price cuts through a therapeutic reference price system that places innovative and generic drugs in the same baskets, with prices set based on the average price in the basket.[559] The innovative or therapeutic value of a given product is not factored into the price. This system is complemented by other measures including rebates associated with price-volume agreements.[560] Moreover, inclusion for reimbursement is dually determined by a ruling of cost-effectiveness by the Health Insurance Review and Assessment Service and price negotiations with the National Health Insurance Corporation. Further price cutting measures prioritizing cost over value and quality are under consideration, including incentives for public hospitals to negotiate lower prices from biopharmaceutical companies, which would then become the basis for centralized price negotiations.[561]

Legal certainty (including the rule of law)

The Korean legal environment is generally considered stable and certain. Legal redress, enforcement of contracts and administrative justice is generally available and viewed as effective. Korea ranked 11th overall in the 2015 *Rule of Law Index*.[562]

Malaysia

Malaysia is the 35th largest economy in the world with an estimated 2014 total national output of USD388,1 billion measured at current USD.[563] Measured on a GDP per head basis Malaysia has a per capita income of USD11,307 for 2014.[564]

Malaysia is the 18th most open and competitive economy according to the World Economic Forum's 2015-16 *Global Competitiveness Index* ranking.[565]

National Innovation Strategy

The New Economic Model launched in 2010 guides national innovation policy in Malaysia. Its general goal is to lay a foundation for implementing policies that will boost the growth of the domestic economy through structural reforms creating a more decentralized economy, allowing companies the freedom to grow organically.[566] Strategic guidelines for innovative investment are provided by the National Science, Technology and Innovation Policy, disclosed in 2013 and implemented through the Science to Action initiative. The 11th five-year plan (2015-2020) pledged to create a Research Management Agency and to "*encourage local and international collaborations for technology transfer, including strategic alliances between MNCs and SMEs*".[567] The plans puts forward a target of 2% GDP for R&D in 2020, up from the current 1,1%. It also proposes to increase the ratio of business to government R&D expenditure, the number of researchers and the commercialisation rate of R&D outputs.[568]

In 2005 the Government released the National Biotechnology Policy. The policy identifies three main policy phases to be completed by 2020: Phase I – Capacity Building (2005-2010), Phase II – Science to Business (2011-2015), Phase III Global Presence (2016-2020). Building on the National Biotechnology Policy is the Bioeconomy Transformation Program. Launched in 2012 the purpose of this program is to focus on the full commercialization and launch of biotechnologies.[569] As of December 2015, the BTP boasted 48 bioeconomy projects (20 ag-bio, 21 bioindustrial and 7 biomedical), up from 25 at the end of 2014. These projects generated a total GNI of RM5.97 billion, secured 25,355 jobs and cumulative investments of RM18.21 billion.[570] The BTP Fund covered up to 10% of total cost project, granting RM11.85 by the end of 2015.[571]

There are a number of biotech specific government agencies grouped into a cluster of organizations and institutions.[572] They include BiotechCorp Malaysia, which focuses on the

general promotion of biotechnology.[573] In 2015 BiotechCorp started collaborations in technological development and education with its counterparts in Germany, Italy and Belgium; Genom Malaysia, a non-for-profit that focuses on generating new intellectual property that can be used for large scale development in the areas of genetics, structural and synthetic biology, computational systems biology and metabolic engineering[574]; IPHARM, a research institute that focuses on drug discovery[575]; Agro-Biotechnology Institute Malaysia, which works with universities and industry to develop new ag-bio technology[576]; Inno Biologics, a government controlled API manufacturer available via contract to domestic companies[577]; and Technology Park Malaysia Corporation, which provides young companies with affordable access to real estate and technology along with innovation and commercialization support.[578] Several of these programs have made significant achievements. For example, since its start, the Technology Park Malaysia Corporation has provided business incubator services to 3,000+ different technology companies.[579] Biotech Corp has acquired the rights to several promising technologies that it makes available to companies including DotScan antibody microarray technology that can be used for biomarker discovery[580] and a Marker Assisted Selection technology that can assists ag-bio companies by identifying desirable DNA markers for plant breeding.[581]

Biotech sector by sector policy overview

Biopharmaceuticals

The biopharmaceutical and biomedical sector is receiving more domestic interest. In 2013 close to RM1 billion was invested in the biomedical sector.[582] The vast majority of this (over RM700million) was domestic Malay funding. Of this, close to 50% was concentrated in the medical devices field. In 2013 Agila Biotech (a subsidiary of Strides Arcolab) announced an USD35million deal to build a major R&D and manufacturing facility in the Bio-XCell cluster hub on the border to Singapore.[583] The facility is to be co-funded by Bio-XCell. In 2016, Biocon is set to start operation of its integrated insulin plant, located in the same cluster and built with an investment of USD160 million.[584] In addition, domestic manufacturers such as CCM Duopharma are diversifying and building a biopharmaceutical capacity.[585] The company announced in 2014 it would be conducting clinical trials of a biosimilar erythopoietinin in Malaysia in partnership with Pangen at an estimated value of RM9million.[586]

Looking at rates of product launches between 1983-2000, the percentage of products available in Malaysia within five years of global launch was 20%.[587] This was third from the bottom of the sampled economies.

Ag-bio and industrial biotechnology

Malaysia traditionally has a strong focus on the industrial biotechnology and ag-bio sectors through the palm-oil industry. Looking at the most recent data, the latest Annual Report by the Biotech Corporation (the agency charged with overseeing the Bioeconomy Transformation Programme) lists 95 projects as being at a "commercially ready" stage.[588] Out of those 95 projects listed the vast majority (81) are either in the ag-bio (50) or industrial biotechnology (31) sectors. The remaining 14 are in the biopharmaceutical/biomedical field.[589] Given the importance of the palm-oil sector the Malaysian government has a number of cross-sector industrial and ag-bio policies in place.

For example, to help promote the domestic industrial and agricultural biotech industries the Malaysian government has implemented the B5 biodiesel programme and the Oil Palm Replanting Incentive Scheme, and raised export duties to 5% in April 2016.[590] In a bid to support local demand of its main feedstock, crude palm oil, Malaysia has continued moving towards increasing its biodiesel mandate. Since the B5 blend mandate was reportedly fully implemented at the end of 2014, a new B7 program has been rolled out in 2015. Against the backdrop of this higher mandate, annual production in 2015 was forecasted at 537 million liters, up from 359 million liters in 2014.[591]An additional program to mandate a minimum 10% of bio content in diesel is expected to be implemented in 2016.[592]

Still, there are number of challenges. For instance, there are currently no products actively being

tested (papaya has been approved but no active testing in place) or approved for field trials and Malaysia has no ag-bio crops under cultivation.[593] More broadly, the infrastructure for seed registration is currently not in place.[594]

Performance in key enabling factors

Human capital

In 2015-16 for the first time the *Times Higher Education* world rankings features a Malaysian university in its top 500, the Universiti Teknologi Malaysia.[595] This university gained positions also in the *Time Higher Education* rankings of top universities in BRICS and emerging market economics, moving up from 93rd in 2015 to 56th place in 2016.[596]

In terms of academic and research publications, Malaysia has compared to other *Building the Bioeconomy* countries a low number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Malaysia had 29.56 publications per million population.[597] This was ahead of only India and Colombia and far behind world leaders in the US, UK and Switzerland.

Malaysia's research capacity is growing rapidly. In terms of number of researchers, Malaysia had 1,794 researchers per million population in 2012, the latest date for which figures are available.[598] This is a sharp increase over the levels in 2000 when the equivalent figure was 274 researchers.

Infrastructure for R&D

2012 figures show R&D spending as a percentage of GDP at 1.13%.[599] Internationally, while this is ahead of Turkey, India and South Africa this is below the OECD average of 2.40% and far behind top performers such as the US, Korea and Israel.[600]

Malaysia is a growing center for clinical research. Looking at clinical trial intensity and the number of clinical trials to date per million population Malaysia performs ahead of many bigger economies such as Mexico, China and India at 26.85 trials.[601] Malaysia has a low level of trials on biologics per million population, 1.5 for the period 2010-2015.[602] A relatively low level of these – 22% – were early phase trials.

Looking at biotechnology triadic patenting Malaysia is not a top patenting nation on an absolute basis or adjusted for population. Malaysia's share of the global total average for the period 1999-2012 is 0.04% ahead of only Turkey and Colombia.[603]

Malaysia is viewed as a relatively attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Malaysia is ranked sixth in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 85. [604]

Intellectual property protection

With regards to the protection of IP, Malaysia has made significant progress over the last decade and will full implementation the TPP treaty marks a significant milestone in strengthening Malaysia's national IP environment. If fully enforced the treaty would address a number of challenges faced by biotechnology innovators in Malaysia.

For example, looking at biopharmaceuticals, Malaysia introduced a five-year term of RDP protection in 2011. While this is a positive achievement, the full term of protection is not offered to new products introduced in Malaysia. Instead, the term of protection begins whenever a product was introduced globally. This significantly weakens the actual exclusivity and incentive being offered to pharmaceutical innovators through RDP. Similarly, Malaysia does not currently offer any restoration of a patent term on account of regulatory delays.

The agreed text of the TPP released in November 2015 contains very clear requirements that contracting parties make available a term of patent restoration for unreasonable delays. Introducing a term of patent restoration for any delays caused through the regulatory review process would be a positive step in strengthening Malaysia IP environment as it relates to the life sciences.

Similarly, the agreed text of the TPP contains very clear requirements that contracting parties

make available a minimum period of 5 years protection for submitted clinical data (with 8 years for biologics) as part of a market registration application. The adoption of these requirements will significantly strengthen the IP environment as it relates to the life sciences in Malaysia.

The regulatory environment

For biopharmaceuticals, the Drug Control Authority is responsible for the authorisation and safety supervision of biopharmaceuticals and operates under the guidance of the National Pharmaceutical Control Bureau.[605] While the agency and Ministry of Health have a target of 210 days for market approval industry reports suggest that lengthy delays are not uncommon.[606] In a positive step Malaysia introduced biosimilar guidelines in 2008.

With regards to the use of biotechnology in agricultural, Malaysia has strict laws relating to the growing and sale of ag-bio products.[607] The 2007 Biosafety Law stipulates that the National Biosafety Board must review and approve any modified organisms before they are released into the market. As of June 2014 the board had deemed six types of corn and five types of soybean marketable.

Technology transfer

Malaysia does not have in place a specific technology transfer law akin to the American Bayh-Dole framework. Instead, technology transfer at universities and public research institutions are guided by internal guidelines (often developed together with the main funder of the program, the Malaysian Government) and two Government regulations: the 1999 Government Circular and the 2009 Intellectual Property Policy.[608] While the former by and large retains IP ownership with the Malaysian Government, the latter policy vests ownership with the recipient of the relevant funding. As a result, under this policy publicly funded innovators and creators are able to retain ownership of their creations. While the data sample is limited, patenting rates by Malaysian universities and PROs has increased between 2005 and 2010. For universities this grew from a total of 80 applications in 2005 to 507 in 2010. For PROs the increase over the same time span was from 36 to 195. Significantly, there was a jump in patenting at academic institutions following the introduction of the 2009 Intellectual Property Policy.[609] Of the PROs the Malaysian Palm Oil Board had the second highest level of patenting activity with 98 patents filed between 2005-2010.[610] Its success is partly explained by participation of the industry at earlier stage of research activities.[611] However, no Malaysian university is listed in the top-50 of university PCT applicants.

The Malaysian Government promotes technology transfer primarily through the Malaysian Technology Development Corporation. The agency accomplishes this by linking individual entrepreneurs and small businesses with large companies, research institutions and government agencies. Major universities in Malaysia have also set up technology transfer offices in recent years to capitalize on their research. The technology transfer office at the National University of Malaysia works with multiple government entities, major industry players and investment funds to commercialize university R&D.[612]

Market and commercial incentives

There are a number of general as well as sector specific tax and commercial incentives in place. For the biopharmaceutical and biomedical sector there is the BioNexus incentive program. BioNexus status is available to biotechnology companies and companies that derive a substantial amount of their final product from biotechnology. Qualifying entities receive a tax exemption on 100% of relevant income for a period of five-ten years (depending on the age of the entity) and a 20% tax exemption after the initial period has expired. Further, the company will be exempt from income duties and sales tax of raw materials and machinery along with a generous tax deduction on R&D expenditures. BioNexus status also incentivizes private sector investment by making the entire amount of investment in seed capital and early-stage BioNexus status tax deductible.[613]

There are other general R&D incentives available including the Investment Tax Allowance and R&D super deductions.[614] The Investment Tax Allowance can take several forms including a 50%

tax allowance on capital expenditures for ten years for companies performing in-house R&D and 100% tax allowance on capital expenditures for ten years for R&D service providers. On top of these tax allowances, the government offers a 200% super deduction on non-capital expenditures for companies conducting in-house R&D, donations to research institutes and on the registration of patents, trademarks and licenses overseas if it promotes an exported product.[615] In addition, the Minister of Finance has the ability to grant Pioneer Status to domestic companies capable of producing high-class products that will benefit the Malaysian economy. Companies receiving this designation pay no income tax on statutory income for five years and this benefit can be extended for an additional five years.[616]

With regards to incentives for the biopharmaceutical sector, the pricing and reimbursement environment is challenging.[617] Reimbursement decisions are often delayed with industry reports suggesting delays of up to five years after regulatory approval. Moreover, there is, for example, no automatic inclusion of products onto the national formulary even if they were developed in Malaysia including through local clinical trials involving local patients.[618] Only drugs included in the National Essential Medicine List are exempted from the 6% Good and Services Tax in force since April 2015. [619]

Legal certainty (including the rule of law)

Malaysia ranked 39th of the 2015 *Rule of Law Index*, scoring high marks for public safety, levels of corruption and efficiency of the court system.[620]

Mexico

Mexico is the twelfth largest economy in the world with an estimated 2014 GDP of USD1.3 trillion.[621] Mexico has a per capita GDP at current USD of just over USD10,00.[622]

Mexico is the 57th most open and competitive economy globally according to the World Economic Forum's 2015-16 *Global Competitiveness Index* ranking, four spots higher than in the 2014-2015 rankings, in part due to improvements in fostering innovation and business conditions.[623]

National Innovation Strategy

Mexico has four main government bodies that oversee and direct innovation policies.

The National Council for Science and Technology is the primary body responsible for supervising financing, coordination and implementation of country innovation policies.[624] The Council works together with the Ministry of Economy, Ministry of Education, and the National Development Bank. The Ministry of Economy works to promote entrepreneurship in the public and private sector through the National System of Business Incubators.[625] This System is divided into six main categories and offers a focus on biotech: traditional business incubator, medium-technology business incubator, high technology business incubator, biotechnologies and health, advanced food processing, and energy and environmental remediation.[626] In addition, the Ministry of Education has been working with the incubator program to implement successful incubation models at local universities.[627]

The National Development Bank is a public development bank that provides funding for businesses that have advanced beyond the incubator phase. The Bank's primary focus is to provide funding, information resources, and facilitate access to private capital for companies that would not be able to do so on their own.[628]

Mexico has two major national innovation policies in place: the National Development Plan and the Special Programme for Science, Technology and Innovation.[629] The goal of the former is to institute innovation as a basis for economic development and growth with a specific goal of raising R&D spending to 1% of GDP. The latter seeks simply to "transform" Mexico into a knowledge-based economy.

Looking at biotechnology, Mexico has a modestly growing domestic industry. OECD data shows Mexico having some activity with 406 active biotechnology firms as of 2010-11.[630] However, looking at R&D spending and investment Mexican

rates are relatively and absolutely quite low. Figures from 2011 show dedicated Mexican R&D spending on biotechnology in the business sector at USD93,9 million at PPP.[631] This made up a total of 3% of total business R&D investment.[632] Similarly, looking at value added Mexico's biotech sectors are quite small. OECD estimates of private sector biotechnology R&D as a percentage of total industry value added was quite low at 0.007%.[633] This is in contrast to high performers such as Denmark and the US where value added from the biotech sectors was much more significant at 0.77% and 0.25% respectively. There is currently no equivalent available data for public sector expenditure.

Biopharmaceuticals

Biopharmaceutical R&D and innovation is increasing in Mexico with FDI growing steadily in the biopharmaceutical sector. Between 2005-2012 Mexico received a total of USD2.8 billion of biopharmaceutical FDI.[634] In 2012 alone this amounted to USD981 million.[635] Most research-based multinational biopharmaceutical companies are represented in Mexico with a number (including Merck and Boehringer Ingelheim) operating both manufacturing and R&D plants in the country.[636] Mexican biotech R&D has led to the discovery of new drugs including the scorpion antivenom Anascorp.[637] The drug, developed by the Biotechnology Institute of the National Autonomous University of Mexico and manufactured by the Bioclon Institue (a Mexican biotech firm specialising in fabotherapics) is FDA approved and actively used in the treatment of scorpion stings. The same institute is researching the use of venom proteins to cure cancer and Parkinson's disease.[638]

Mexico has in place a number of policies targeting biopharmaceutical innovation and has reformed its regulatory environment quite considerably over the last few years. For example, COFEPRIS (the Mexican drug regulator) has introduced a number of reforms and committed to cutting market authorization times.[639] In December 2015, Mexico was the first country to approve Sanofi's Dengvaxia dengue vaccine, which is waiting for approval in 19 additional countries.[640]

Looking at rates of product launches between 1983-2000, the percentage of products available in Mexico within five years of global launch was 37%.[641] This was in the top half of the sampled economies.

With regards to the BCI Survey Mexico ranked in the middle of the economies included in *Building the Bioeconomy* with an overall score of 65.32. [642]

Ag-bio

In regards to promotion of agricultural biotechnology, Mexico was one of the first countries to adopt the use of biotech crops.[643] In 2005, the government passed the Biosafety Law that clarified regulatory issues relating to the research, production and marketing of biotech foods.[644] One of the positive attributes of the regulatory system is that it allows the Government of Mexico to impute data on biotech crops from other countries as support for their adoption as an approved food substance in Mexico.[645] In order to bring a food product containing GMO material to market a company must conduct a study to determine any potential risks associated with the product, if no risks are found the product may be approved by the Department of Health. If approved, the product must be marketed with a label that identifies it as containing GMO ingredients.[646]

The Inter-Ministerial Commission on Biosecurity and Genetically Modified Organisms and its subsidiary bodies oversees food related biotech activities. The biotechnology regulations enforced by the Commission are not considered burdensome. The Commission has authorized 103 GMO products and the importation of 52 additional GMO products for food and feed uses.[647] In addition to regulating the biotech food industry, the Commission has also provided funding to advance the sector. It has funded research to investigate the drought tolerance of GM maize, the fungal resistance of GM cotton and beans as well as the genetic diversity of corn in the country using use the outcome of this research to support the approval or disapproval of future GE corn strains.[648]

However, despite these initiatives and overall regulatory capacity overall usage and growth of biotech crops is by international measures still limited. In 2015 Mexico was the 16th largest producer of ag-bio crops in the world at 0.1million hectares under cultivation with a focus on cotton.[649] As described by the USDA Mexico has the research infrastructure, regulatory capacity and market size to benefit from wide-spread ag-bio production but has yet to establish broad public acceptance and use of ag-bio products.[650] No product but cotton is commercially available or grown and commercial use and field work on GM corn is currently suspended due to a legal injunction.[651] In August 2015, a Mexican judge overturned the ban, but the decision was revoked in reply to the appeal submitted by a coalition of activists.[652] Furthermore, in November 2015, another Mexican court suspended a permit to farm GM soybean on 250,000 hectares in the Yucatan peninsula, claiming this would endanger local honey production by indigenous communities.[653]

Industrial Biotechnology

Mexico has been increasing its interest in industrial biotechnology and specifically biofuels and the development of clean energy for some time. In 2008 the Biofuels Promotion and Development Law (*Ley de Promoción y Desarrollo de los Bioenergéticos*) was passed. This law seeks to create an alternative energy market and is based on three pillars: maintaining food security, environmental sustainability and the promotion of energy diversification.[654] While the law has been lauded for its goals and the creation of an alternative energy market, its impact on generating incentives and increased biofuels production has so far been relatively limited. For instance, looking at biofuels production statistics Mexico's share of total global biofuel production in 2014 was 0.1%.[655] And while this figure reflects close to a 300% year-on-year increase in production capacity, Mexico's biofuels production capacity is still quite limited. However, in 2015 the national giant Pemex launched a program for sale of gasoline mixed with ethanol expected to increase on domestic ethanol production.[656] Pemex will indeed offer a blend of gasoline with 5.85% ethanol. The ethanol will be sourced entirely from Mexican producers who, as part of the agreement, will invest an approximate USD130 million in improving their production and refining capacity.[657]

Performance in key enabling factors

Human capital

Only one Mexican university is included in the top-500 general ranking by the *Times Higher Education* for 2015-16.[658] In terms of the life sciences, Mexico had 10,665 life sciences graduates in 2012, which is an increase of over 500% since 2000.[659]

In terms of academic and research publications, Mexico has compared to other *Building the Bioeconomy* countries a low number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Mexico had 30.05 publications per million population.[660] This was ahead only Malaysia, India and Colombia. However, Mexican publications were ranked relatively highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with 7.14% of publications among the 10% most cited; this was ahead of all the BRIC and Turkey.[661]

A small share of Mexico's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Mexico had 383 researchers per million people,[662] ahead only of India and Colombia and less than a third of Turkey.

Infrastructure for R&D

Mexico has a low level of R&D spending when measured as a percentage of GDP. According to CONACYT, in 2015 R&D expenditure amounted at 0.57% of GDP, up from 0.54% in 2014.[663] Similarly, the latest 2014 data from the World Bank suggest R&D spending totalled 0.54% of GDP which is behind all other OECD countries, whose average expenditure was 2.37% in 2014, as well as emerging economies, such as China (2.05%) and Russia (1,19%).[664] Besides, while in countries like

South Korea and Israel more than 75% of financing comes from private sector, in Mexico Government and public sector contribution outweighs business spending: in 2014, 23.8% of total spending came from private entities, declining from 36.8% in 2011.

Mexico is not a strong performer in clinical research. Looking at clinical trial intensity and Mexico is behind South Africa, Malaysia and high performing markets including Korea, Switzerland and the US. The number of clinical trials to date performed in Mexico per million population was 19.72 trials.[665] Mexico has a low level of trials on biologics per million population, 1.11 for the period 2010-2015.[666] A relatively low level of these – 21% – were early phase trials ahead of only Turkey.

Looking at biotechnology triadic patenting Mexico is not a top patenting nation on an absolute basis or adjusted for population. Mexico's share of the global total average for the period 1999-2012 is 0.04% ahead of only Turkey and Colombia.[667]

Mexico is not viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Mexico is ranked second to last in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 61.8. [668]

Intellectual property protection

Mexico has over the past two decades introduced significant reforms to its national IP environment, including as it relates to biotechnology. Mexico is a contracting party to the TPP treaty and, just as in Malaysia, full implementation of the TPP treaty would mark a significant milestone in strengthening the national IP environment. If fully enforced the treaty would address a number of challenges faced by biotechnology innovators in Mexico.

For example, looking at biopharmaceuticals, COFEPRIS published guidelines in June 2012 that provide protection against use of undisclosed test data by any person for the purpose of marketing approval for a maximum of five years. However, the effective application of the guidelines remains an ongoing concern. On the one hand these guidelines do not have statutory force as they are merely departmental guidelines not official regulations or primary legislation. Second, it is unclear the extent to which RDP will be granted to both large and small molecules. On top of ongoing uncertainty in the legal framework, in 2015 Mexican authorities reportedly indicated that RDP would not be considered as applicable to biologics. This differs from standards adopted in virtually other countries in which the term of protection for NCEs applies equally (if not longer) to biologics. In the US, for example, the term of protection for biologics is 12 years. The agreed text of the TPP contains very clear requirements that contracting parties make available a minimum period of 5 years protection for submitted clinical data (with 8 years for biologics) as part of a market registration application.

There are challenges in other areas too.

Although a 2003 Presidential Decree introduced a basic system for early adjudication of generic-innovator disputes, it does not represent a transparent pathway as the patent holder receives no notification of infringing issues and is not formally involved in the adjudication process. It is also not clear that formulation patents are recognized consistently by COFEPRIS when approving follow-on products. In addition, evidence suggests that COFEPRIS continues to approve use or import of large quantities of APIs under patent protection for testing purposes. Where cases of infringement are brought, substantial delays at both the administrative and judicial levels hinder rights holders' ability to secure damages effectively (reaching a total of around 10 years on average). Nevertheless, in a positive step for rights holders in 2015 a Mexican court ruled that notification of patent holders and their ability to be heard during the market authorization process (and not only after) is a constitutional right and should have a legal basis within the Linkage Regulation.

The regulatory environment

Mexico has reformed its regulatory environment quite considerably over the last few years. For example, COFEPRIS has introduced a number of reforms and committed to cutting market authorization times. The agency has been commended for quickly approving medicines

that meet urgent local needs,[669] reducing the approval time for drugs already approved in the US, Canada, and EU from 360 days to 60 days. COFERIS approved medications are also approved with less scrutiny in many other South American countries.[670] In 2014 the agency also cut the pre-approval time for clinical trials from 3 months to 1 month reflecting a desire to attract more biopharmaceutical investment and trial activity.

With regards to the use of biotechnology in agricultural Mexico has had a framework in place for over a decade. In 2005, the government passed the Biosafety Law that clarified regulatory issues relating to the research, production and marketing of biotech foods.[671] The Inter-Ministerial Commission on Biosecurity and Genetically Modified Organisms and its subsidiary bodies oversees food related biotech activities. The biotechnology regulations enforced by the Commission are not considered burdensome.[672]

Technology transfer

Mexico does not currently have a comprehensive technology transfer law in place or policies equivalent to an American Bayh-Dole style framework. In late 2013 as part of a broader reform package (including raising public investment in science and technology research) the new Mexican Government put forth proposal to clarify how publicly funded research could be commercialized.[673] At the time of research no law had been passed or put into effect. The existing Mexican technology framework is ad hoc and is based largely on the policies in place at the institution receiving the public funding.[674] There are however some initiatives in place to promote technology transfer. In August 2011, the National Council of Science and Technology launched a program to provide academic institutions with funding to promote technology transfer.[675] Academic institutions can propose projects to the council that would foster technology transfer. If accepted, the Council will cover a majority of costs related to IP management capabilities, developing a business plan for a technology transfer office, and enhancing the capabilities of any existing technology transfer office.[676] However, the method by which the Council funds researchers hinders efforts to promote technology transfer.[677] The Council pays for two-thirds of academic researcher's salary and the amount of published information is a major component of determining workload. As a result, researchers are continually encouraged to publish but provided with very little time or incentive to file for patents or collaborate with outside industry to commercialize technologies being developed.[678]

Market and commercial incentives

Mexico eliminated R&D tax credits and incentives in its 2010 tax reform.[679] Instead, R&D and scientific research is supported though direct grants from the National Council for Science and Technology.[680] These grants are available for both public and private institutions including commercial entities. However, they are primarily focused on research projects that include a partnering public research organization of higher education entity. Since the start of the program, MXN40.4 billion (USD2.2 billion) have been invested to innovative projects, of which around 50% came as contribution from private companies.[681]

For biopharmaceuticals Mexico has strict price controls in place with maximum retail prices for patented medicines capped by *Secretaría de Economía* (mainly for private sector). Mexico uses an international reference pricing system calculated on the basis of the average ex-factory price of the previous quarter in the six largest markets for a given product globally. In the public sector, Coordinating Commission for Medicines Price Negotiation oversees the procurement process.[682] The Commission determines recommended pricing for all medications available to public institutions; however, after determining prices Mexico's public institutions are able to further review pricing levels and request that they be lowered.[683] Public reimbursement of medicines in Mexico is primarily focused on cost and there are long delays with inclusion. Drug formularies under the major public schemes – *Cuadro Básico y Catálogo de Medicamentos*, *Seguro Popular* and the IMSS drug list – all contain relatively low levels of new, innovative drugs. The majority of products included are generic.

Legal certainty (including the rule of law)

In the 2015 Global Rule of Law Index Mexico was ranked 79th out of 102 countries, and 14th out of 19 Latin America countries.[684] The Index praised Mexico for having effective checks on government power and having an open government with an independent judiciary. However, the rankings also acknowledged that Mexico has issues with political corruption and civilian security.[685]

Russia

Russia is one of the largest economies in the world, with a total 2014 GDP at current USD of USD1.8 trillion; GDP per capita for 2014 was USD12,735 at current USD.[686] The Russian economy has contracted sharply since 2013 losing over USD200 billion in economic output between 2013 to 2014.[687]

Russia improved eight places to 45th on the World Economic Forum Competitiveness Ranking, though mainly due to a major revision of purchasing power parity estimates by the IMF.[688]

National innovation Strategy

Since the financial crisis in 2008-9, the Russian Government has targeted innovation and the development of its science and technology capabilities as a main impetus behind diversifying and modernizing the economy. The government's innovation strategy is focused mainly on enhancing and transforming its basic research capabilities into commercial activities, both in traditionally strong fields such as aerospace and nuclear energy as well as new fields such as nanotechnology, medical technologies and alternative fuels.[689] The Strategy for Innovative Development of the Russian Federation 2020 (2020 Strategy), introduced in 2011, is the main document guiding innovation policy in Russia today.[690] The 2020 Strategy sets out several benchmarks and targets in relation to science and technology indicators including the development of human capital and private sector innovation, promoting of a favorable environment in the public sector and building of international cooperation.[691]

Within this framework, President Putin launched in 2014 the National Technology Initiative, aimed at achieving Russian technological leadership by 2035 and creating new markets in nine priority areas, such as digital health markets and neuro-communications.[692] The Initiative is coordinated by the Agency for Strategic Initiatives, supported by Rusventure and the Skolkovo Innovation Center.[693] Roadmaps including coordinated projects linking public and private efforts (the Government will co-finance projects up to 50% for 5-7 years) are being drafted, including one for Intellectual Property and one for life science.[694] Work on the 'HealthNet' roadmap were finalised in June 2016, but no details were disclosed, apart from the objective to have at least five companies in the top 70 biomedical global players by 2035.[695]

In terms of general R&D support mechanisms, the Russian Foundation for Basic Research provides direct grants to researchers and scientists in basic research.[696] The Foundation for Assistance to Small Innovative Enterprises provides grants and loans to innovative SMEs seeking to commercialize basic research, including in the seed and start-up phases.[697] The Russian Foundation for Technological Development also offers loans to public-private ventures aimed at bringing to market new technologies.[698]

However, the business environment for innovators has deteriorated in recent years. Overall, private businesses lament persisting administrative barriers and lack of funding. Small businesses are facing important problems linked to increased insurance premiums, more complex procedure for registering companies, increased number of supervisory checks and high interest rates on loans. Significant public reductions in budget allocations for science, technology and innovation are expected for 2016 including a 28.9% reduction for the governmental program 'Development of science and technologies for the period 2013 to 2020', and 31.4% for the pharmaceutical and medical industry.[699]

Biotechnology is one of the Russian Government's strategic innovation priorities under the 2020 Strategy. The State Coordination Program for the Development of Biotechnology (BIO 2020) and the Strategy of Development of the

Pharmaceutical and Medical Industries (Pharma 2020) are among several policy instruments aimed at building a bio-industry in Russia, starting with creating the necessary human and physical capital.[700] The bulk of the funding is aimed at the bioenergy, biopharmaceuticals, agriculture and food biotechnology and industrial biotechnology fields, relying on a mix of government funding and FDI.[701] The field of biotechnology is also a key focus in research programs of the Russian Academy for Sciences, the Russian Academy of Medical Sciences and the Russian Agriculture Academy. In addition, state-owned enterprise, Rusnano (focused on developing the nanotechnology industry in Russia) co-finances R&D projects and infrastructure building including in biotechnology.[702]

Nevertheless, despite the market potential in Russia and the government's desire to attract investment in R&D in recent years, these policies have not yet generated significant investment in biotech R&D in Russia. For example, although the biopharmaceutical space has seen a few large investments by international research-based companies (including the St. Petersburg pharmaceutical 'cluster' and the RUB500 million – RUB1.5 billion through the Government's Russian Venture Company) on the whole significant challenges remain in terms of incentives for foreign companies with R&D capabilities and know-how to invest in facilities and conduct biopharmaceutical R&D in Russia.[703] In particular, government policies providing preferential treatment to domestic manufacturers and locally-produced products (see under "Biopharmaceuticals") have made it difficult for companies to establish more than manufacturing and production facilities in Russia.

Biotech Sector by Sector Policy Overview

Biopharmaceuticals

As mentioned Russia is pushing ahead with plans to develop a world-class biopharmaceutical sector through the implementation of the BIO 2020 document with plans to devote RUB106 billion to the development of the sector by 2020.[704] The Russian Government plans to focus this funding towards the creation of new vaccines and antibiotics, along with creating the infrastructure to be able to domestically produce a majority of the country's needed medication.[705] In particular, Russia has set as a goal to construct a series of state-based bio clusters that will act as a 'one-stop-shop' for biopharmaceutical development providing companies with the necessary infrastructure to move from R&D to commercialization.[706]

A significant focus of Russia's biopharmaceutical policies has been on localizing biopharmaceutical research and innovation. Yet in order to achieve these goals, instead of focusing on strengthening local innovative or manufacturing capacity, the Russian government has increasingly adopted (or proposed) a range of measures that impose localization. In 2010, the Government passed Federal Law 61-FZ on the Circulation of Medicines stipulating that clinical trials for innovative and generic medicines (bioequivalence studies) must be conducted in Russia if the product is to be submitted for registration.[707] In 2011, the Ministry of Economic Development issued Order No.211 creating a price preference of 15% afforded to locally produced drugs for state and municipal procurement.[708] In November 2015, the Russian Government adopted Resolution No. 1289 "On Restrictions and Conditions of Access of Foreign Essential Medicines to State and Municipal Tenders", which introduced a direct import ban within the procurement system. Access to state purchases of imported medicines will not be allowed when (at the time supplies are requested) at least two generics produced within the EEU are available for a given INN. Foreign manufacturers will only be able to participate in a public tender in cases where fewer than two bids from EEU manufacturers have been submitted. Adding to this, Russia has also adopted a stricter definition of "local production" requiring that a pharmaceutical company locally produce the API or final deliverable form of a product in Russia to qualify.[709] Moreover, Decree 1125/2015[710] made the National Immunobiological Holding Company owned by state Corporation Rostech the sole provider of immunobiological products for state needs for the period 2015-2017.[711] A similar monopoly expected to benefit Rostech's subsidiary has been proposed for insulin.[712] Finally, as decided in October 2015, grants will be available to reimburse a portion of the costs incurred for the production of medicines and/or APIs, as well as for carrying out clinical trials.[713]

With regards to IP there are significant challenges in Russia (see under 'Intellectual Property Protection). Adding to these uncertainties, the threat of compulsory licenses continue to loom over innovators, as the Federal Anti-monopoly Service (FAS) presented in March 2016 a compulsory license scheme as a method of reducing prices of certain high-cost specialty medicines.[714] According to the amendments to the Competition Act and the Civil Code, "*threats to the individual and the rights of citizens to health protection and medical care*" will justify issuing of compulsory licenses.[715] Deputy Prime Minister Dvorkovich has recently postponed its entry into force to December 2016, claiming it would put off investors in the Russian pharmaceutical market.[716]

Looking at rates of product launches between 1983-2000, the percentage of products available in Russia within five years of global launch was 14%.[717] This was second to last of the sampled economies.

With regards to the BCI Survey Russia ranked in the bottom third of the economies included in *Building the Bioeconomy* with an overall score of 53.76. [718]

Ag-bio

The Bio 2020 Plan also outlines the goals that the Russian government has set for the agricultural biotechnology sector, namely the development of novel plant varieties to increase overall crop yields.[719] However, at present guidelines for the registration of GMO do not exist and as a result it is not possible for companies to legally commercialize GMO seed products. In October 2010, the Government passed Resolution N.839 that authorized the Ministry of Agriculture and other relevant government agencies to develop such guidelines.[720] Originally, the guidelines were scheduled to come into effect in June 2014; however, in April 2014 the government announced that the original target was too optimistic and that a set of guidelines would not be prepared until mid-2017.[721] Adding to the existing *de facto* ban, in September 2015 the Government announced its intention to fully and officially forbid commercial planting of biotech crops in Russia,[722] and a few month later, in February 2016, enacted a ban of soybeans and corn imports from the US because of the risk of GMO contamination.[723]

Funds allocation for 2015 confirms the low priority granted to agricultural biotechnology. Financing of the Ministry of Agriculture's subprogram "Technical modernization and innovative development" that covers all innovation projects including in agricultural biotechnology was cut by almost RUB1 billion (USD18 million) to RUB2.15 billion (USD39 million). The funds were reallocated to production support programs, responding to the more short-term objective of import substitution.[724]

Despite this, Russian scientists are forging ahead with laboratory based GE crop research, although in a limited capacity. The majority of this research takes place at the Institute of Nutrition and Food Safety Assessment at the Russian Academy of Sciences and the Center of Bioengineering at The Russian Academy of Sciences.[725] In August 2015, the Skolkovo Innovation Center launched a new department for agricultural biotechnology within the biomedical technology cluster, in order to reverse the decline of the sector and increase national food security.[726] By 2020, the cluster should have about 200 resident startups for projects in biotech agriculture and industry. As of April 2016, 15 ag-bio companies had joined the cluster.[727]

Industrial Biotechnology

BIO 2020 sets goals for Russia to develop a world class industrial biotechnology sector that will be able to provide industry with products ranging from industrial enzymes to wood waste based biofuel.[728] There are targets for renewables and biofuels including having a 10% biofuels share in motor oil; a 20% share of the solid biofuels European market; and a 5% share of the world market of motor biofuels.[729]

However, evidence suggests that biofuels are a very small part of Russia's energy mix and an insignificant part of its energy infrastructure. For example, 2014 data on biofuels production lists the countries of the former Soviet Union (Russia included) as producing 0.3% of total global biofuel production.[730] Similarly, estimates suggest that biofuels only account for 1.2% of Russia's total energy production.[731]

Performance in key enabling factors

Human capital

The Lomonosov Moscow State University is the only Russian university featured on the 2015-16 *Times Higher Education* rankings (ranked 161st) and is also ranked 95th for life sciences, making it to the top 100 for the first time.[732]

Looking at academic and research publications, Russia has compared to other *Building the Bioeconomy* countries a medium number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 200-2011 Russia had 102.78 publications per million population.[733] This was ahead of all other BRIC economies but behind the top performers US, Switzerland and Israel. However, Russian publications were not ranked highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with only 4.08% of publications among the 10% most cited; this was last of all *Building the Bioeconomy* countries.[734]

A significant share of Russia's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Russia had 3,073 researchers per million people,[735] ahead of the other BRIC economies and almost double that of Malaysia.

Infrastructure for R&D

2014 figures show R&D spending as a percentage of GDP at 1.19%.[736] This is well behind the OECD average of 2.37% and countries like China (2.04%).[737] Russian R&D spending is largely made up of government spending – the latest data from 2014 show government expenditure on R&D at 69.2% of the national total.[738] Around one-tenth (9.8%) of government-funded R&D is performed by universities.[739] According to 2013 OECD data, biotechnological R&D accounted for only a small percentage of business enterprise R&D (0.5%).[740] Biotech R&D represented a little over 9% of total public sector R&D spending.[741]

Russia is not a strong performer in clinical research. Looking at clinical trial intensity Russia is behind South Africa, Malaysia and high performing markets including Korea, Switzerland and the US. The number of clinical trials to date performed in Russia per million population was 22.26 trials.[742] Russia has a relatively low level of trials on biologics per million population, 1.49 for the period 2010-2015.[743] A relatively low level of these – 26% – were early phase trials ahead of only Malaysia, Mexico and Turkey.

Looking at biotechnology triadic patenting Russia is a medium level performing patenting nation on an absolute basis or adjusted for population. Russia's share of the global total average for the period 1999-2012 is 0.27% ahead of Brazil and South Africa.[744]

An important and illustrative effort to attract and stimulate investment in high-tech R&D is the Skolkovo Innovation Center outside of Moscow, which includes a 'biomedical cluster' and R&D center involving international and local scientists, companies and venture capital funds. The biomed cluster has reportedly supported 80 R&D research projects, creating 1,300 jobs, one out of ten of total jobs created by the Skolkovo Center.[745] At April 2016, the cluster included 290 startups, about half of which develop new therapeutics.[746] Overall, the Innovation Center attracted RUB11.1billion in private investment from 2010 to 2015, generated RUR43.6 billion in revenues and resulted in 56 patents granted by foreign countries.[747] Yet reports suggest that development of the Skolkovo cluster has slowed down since 2014 with employment and investment targets not materializing.[748] Amid budgetary problems and the introduction of international sanctions, important cuts to the Skolkovo budget were proposed in 2015.[749] While the future of the Skolkovo project remains uncertain, in March 2016 the Russian Government officially sanctioned the creation of a similar project, the technological valley of the Moscow State University. USD1.6 billion has been allocated to the project that will enjoy the same benefits and tax reliefs as in Skolkovo, and is expected to become the largest scientific and technological center in Russia. [750]

Russia is not viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Russia is ranked in the bottom third in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 63.8. [751]

Intellectual property protection

As a WTO member Russia offers a standard 20-year patent protection term. However, while the protection has been available for biotechnological and biopharmaceutical inventions (with the exception of biological processes), the actual protection afforded to biopharmaceutical inventions is at times uncertain.[752] For example, there is no guarantee that the drug regulator will not approve a biosimilar product for market despite an active patent on the reference biopharmaceutical, and remedies through the judicial system are slow and ineffective.[753]

Under its WTO commitments and the 2010 Federal Law No. 61-FZ "On Circulation of Medicinal Products", Russia has committed to implementing a RDP term of six years. This was a positive step and has significantly strengthened the existing framework and protection mechanisms for pharmaceutical innovation. In 2014 amendments to this law were proposed and subsequently passed. These amendments come into effect on July 1 2015. While wide-ranging the amendments introduced changes to the law and its application to RDP. Specifically, the amendments did the following:

- The RDP term of protection is limited to and will apply only to cases of "commercial" use.[754]
- Follow-on generic and biosimilar products will be allowed to commence registration with the market authorization authorities four and three years respectively after registration of the reference product.[755]

In addition to the amendments and continued development of applicable regulations 2015 also saw the hearing and verdict on the first court case relating to the application and availability of RDP. In March 2015 Moscow's arbitration court heard and rejected claims made by Novartis that its submitted clinical test data had been relied on to grant approval for a follow-on product.[756] Of note is that in its interpretation of the existing statute the court also appeared to concur with an interpretation put forth by the Ministry of Health that it was not its responsibility (as the market authorization regulator) to confirm and check the exclusivity status of a given product and whether a regulatory data or market exclusivity period was in effect. However, this decision was reversed later in the year by an Arbitration Court which held that the local manufacturer company did in fact infringe Novartis' exclusivity and its submitted clinical research data as part of it original market authorization application. Local legal analysis suggests that the judgment provides important clarification on the scope of protection provided to clinical data submitted, strengthening the rights of innovators.

As detailed above, the Russian Government was at the time of research actively in discussions regarding the introduction and use of compulsory licensing for biopharmaceuticals. This would primarily be used as a cost-containment tool. Such use would be outside the scope of international standards and enshrined in the TRIPS treaty.

The regulatory environment

Russia's regulatory system is evolving towards a system more in line with international standards. For instance, one positive step involves efforts to ensure all biopharmaceutical, biomedical and microbiology production facilities comply with GMP. From February 2016, inclusion of GMP certification in a finished drug or API registration dossier will be compulsory. The body charged to conduct inspections is the "State Institute of Drugs and Good Practices" and the procedure is expected to take about 4 to 8 months due to limited number of inspectors.[757]

Still, both in the biopharmaceutical and ag-bio sectors a number of challenges remain.

First, the market approval process in relation to biopharmaceuticals is quite onerous and lacks transparency. There are currently no specific regulations or a pathway for registering biosimilars in Russia. Moreover, since 2010 registration

of biopharmaceuticals is dependent on the submission of locally-conducted clinical trial data. Overall, these factors have resulted in significant registration delays and costs for foreign innovative companies. In a positive move aimed at making drugs more quickly available on the Russian market, the Federal Antimonopoly Service has proposed to abolish the local trial obligation. However, the Ministry of Industry spoke against the proposal, claiming it would favor foreign drug companies to the detriment of the national pharmaceutical industry.[758]

Second, as mentioned above, in September 2015 the Government announced its intention to fully and officially forbid commercial planting of GMO in Russia.[759] At present, the Ministry of Agriculture is responsible for the regulation and approval of agricultural GM products. As for research, field testing of GE crops requires approval from the Variety Testing Commission within the Ministry.[760]

Technology transfer

The central legislative framework for technology transfer in Russia is somewhat unique in that it focuses mainly on enterprise partnerships as opposed to patenting and licensing agreements as platforms for technology transfer. Federal Law 217-FZ on the Commercialization of University Research (2009) provides universities with the exclusive right to market their research through launching their own SMEs or obtaining stock in companies that rely on their research. Specifically, Law N. 217 requires that universities have at least a 25-33% share in spin-offs, depending on the type of company, in exchange for the right to use the university invention.[761] As of September 2015, over 2,000 spin-offs had been created.[762] However, many of them have been criticized for focusing on securing short term funding and not on creating real valuable business.[763] Technology Transfer Centers have been created within some Russian universities, but they focus mainly on scientific rather than commercial assessment of inventions.[764] Private efforts at technology transfer are also ongoing, including the Russian Technology Transfer Network, which involves 60 R&D organizations and innovation centers and is aimed at linking potential academic and industry partners including from the biotech and biomedical sectors.[765]

Still, looking at data on patenting activities by universities and PROs it confirms that patenting has not been a priority for Russian publicly funded research institutions; as of 2011 Russia represented only 4% of PCT applications by universities and 2% of public research organizations among middle-income and selected low-income countries.[766] 2014 data from WIPO shows that no Russian university was among the top-50 institutions for PCT applications.[767]

Market and commercial incentives

Russia offers a generous 150% R&D tax deduction on qualifying expenses. This is available generally as well as for targeted industries.[768] In addition, entities operating in Special Economic Zones (such as the Skolkovo Innovation Centre) may qualify for additional tax credits and benefits including VAT exemption, profit tax exemption, a reduced rate of social security contributions and property tax exemptions. Adopted on 29 December 2015, Federal Law 396 introduces further tax breaks for investors in the innovation sector.[769] Until 2023, investors will not be taxed for revenues arising from sales of certain types of shares, bonds and stakes in innovative Russian companies.

Looking at the biopharmaceutical market and incentive structures, Russia has introduced several policies that provide preferential treatment to local companies at the expense of foreign companies; (see above discussion under "Biopharmaceuticals"). These conditions effectively represent indirect requirements for foreign companies to invest in local production in order to gain access to the market.

Also the approach to price registration for innovative medicines differs for foreign and domestic manufacturers, with foreign manufacturers' prices based on an external reference pricing system derived from the lowest price among reference countries, while local manufacturers' register price is based on companies' reports on cost of production. Recently adopted amendments to the pricing methodology allow prices of foreign medicines to be annually adjusted to the inflation rate, formerly possible only for local producers. However prices of local drugs are given an additional preferential adjustment for increases in production costs.[770]

Legal certainty (including the rule of law)

The Russian legal environment can be challenging and several barriers exist. Problem areas include corruption and the protection of property rights. In the 2015 *Rule of Law Index* Russia was ranked 75th out of 102 countries.[771]

Singapore

Singapore's economy is on an absolute basis one of the smallest economies included in *Building the Bioeconomy* with a GDP of just over USD300 billion at current USD. However, on a per capita basis Singapore is one of the richest countries in the world with per capita income of USD56,285.[772]

Singapore is ranked as having the world's most business-friendly environment according to the 2015 World Bank *Doing Business* report[773] and ranks as the second most competitive economy in the world according to the World Economic Forums' *Global Competitiveness Index* 2015-2016.[774]

National Innovation Strategy

Through a number of macro- and mico-economic policies Singapore has successfully built an economy recognized as one of the most commerce friendly and innovative in the world. A number of long-term policies have been in effect to develop and expand Singapore's high tech R&D capacity and target specific high-technology niches including biotechnology. The latest of them is the Research, Innovation and Enterprise 2020 plan, a five-year plan for the period 2016-2020.[775] Worth up towards USD13 billion, it represents the strategic direction of the Singaporean Government's research and innovation agenda for the next 5 years. Of note is that "Health and Biomedical Sciences" is one of the four key areas of developments. A particular focus of the plan will be public-private partnerships and leveraging private R&D investment to a greater extent than previously.

At the Government level a number of departments and agencies are involved in the creation of innovation and biotechnology policies and attracting foreign investment. The Ministry of Trade and Industry is responsible for the coordination of science and technology policies and for the formulation of key economic policies. The Singapore Economic Development Board is the lead government agency that promotes FDI and knowledge-based industries. The board focuses on raising the level of private-sector R&D in Singapore by attracting multinational companies to base their corporate R&D activities there.[776] A*STAR focuses on the development of domestic R&D capabilities, which includes the overseeing of public research institutes. Under A*STAR, the Bio-Medical Research Council promotes R&D and develops human capital in the life sciences. The Science and Engineering Research Council promotes similar outcomes but targets science and engineering. A*STAR at present oversees 21 research institutes, centres and consortia.[777]

2015 saw Singapore continue to attract significant private sector investment. Total capital investment was SGD11.5 billion, with a heavy concentration in high-tech business such as electronics (SGD3.3 billion), chemicals (SGD3.6 billion) and biomedical manufacturing (SGD0.6 billion).[778]

Biotech sector by sector policy overview

Biopharmaceuticals

A crucial element of Singapore's support for its local biopharmaceutical sector is devoting a substantial amount of resources and investing in capacity-building in biomedical R&D activities. As mentioned the latest 5-year R&D plan announced in 2016 listed "Health and Biomedical Science" as one of four key priority domains and allocated to the sector the highest budget spend of SGD4 billion over the next five years (over one-fifth of the total budget).[779]

Singapore's overall infrastructure and services are extremely well developed. The Biomedical Sciences Industry Partnership Office serves as a contact point and acts to match companies' R&D needs to expertise that can be found in research hospitals, academic research institutions and public research institutions in Singapore.[780] Singapore has developed world-class R&D and manufacturing

capabilities and has seen tremendous growth in the presence and investment by multinational, research-based companies. By and large the efforts by the Singaporean Government to make the country an attractive place for biopharmaceutical development have been successful. Abbot Laboratories, GlaxoSmithKline, Lonza, Novartis, MSD, Pfizer and Sanofi-Aventis have all set up global manufacturing bases in the country.[781] As of 2015, Singapore hosted 8 biologics manufacturing facilities,[782] and more than 50 companies carrying out biomedical sciences R&D.[783] Today a number of products are manufactured for global markets in Singapore with Government estimates of this manufacturing at circa SGD24 billion in 2012.[784] Examples of biological products being manufactured in Singapore include Roche's Lucentis, Avastin and Herceptin.[785]

In addition, the Government has several other initiatives in place to promote biopharmaceutical development. These include the Clinician Scientist Award, the Translational & Clinical Research Flagship Program and The Competitive Research Program. The Clinician Scientist Award is an award for clinicians who have a demonstrated track record of producing high quality work. The grant is open to principal investigators who have an advanced degree and are actively employed at an academic institution. Grants range from SGD250,000 to SGD350,000.[786] The Translational and Clinical Research Flagship Program supports biomedical R&D clusters and facilitates collaboration between local universities and hospitals and international partners to accelerate drug discovery and development.[787] Some concrete results and examples include Bayer Healthcare's partnership with five research institutions in Singapore to set up a new Translational Oncology Network.[788] Novartis and two Swiss research institutes joined efforts with Singaporean research institutions to develop a new drug against malaria, spiroindolone NITD609.[789] The Competitive Research Program is overseen by the National Research Foundation and provides funding to multi-disciplinary teams on the basis of a merit review process where potential programs are judged in areas such as potential for disruptive innovation and research significance.[790] While the program is not limited to biopharmaceutical research it provides significant funding to the area.[791] Finally, the Singapore Clinical Research Institute provides specific support for late-stage, more complex clinical trials and the NUS Cancer Science Institute supports and conducts cancer-related clinical trials.[792]

Looking at rates of product launches between 1983-2000, the percentage of products available in Singapore within five years of global launch was low at 26%.[793] This was in the bottom half of the sampled economies.

With regards to the BCI Survey Singapore ranked second of the economies included in *Building the Bioeconomy* with an overall score of 85.33. [794]

Ag-bio

As a city state Singapore imports 90% of its food supply and has limited investment in the agricultural biotechnology sector.[795] As of 2015 Singapore had no active field trials for GE food products.[796] However, the Government does recognize the growing importance of the agricultural biotechnology sector and has established a series of six agro-technology parks to promote research on seed technology, agro technology in tropical agriculture and aquaculture.[797] Currently, the parks comprise over 1,400 hectares and conduct plant-based research with the aim of exporting the research outcomes to other countries in the region.[798]

Industrial biotechnology

Despite the city-state's small size there is a strong tradition in industrial biotechnology and a growing interest in biofuels. For example, chemicals and industrial biotechnology giant DuPont has operated in Singapore since 1975, and recently announced its intention to significantly increase its presence in the country. Indeed, the company plans to establish in 2016 its ASEAN business and R&D headquarters in the Biopolis Park, focusing on food and agriculture, industrial bio-sciences and advanced materials.[799] DuPont currently has two main manufacturing sites producing engineering plastics and polymers.[800]

The Government has made clean energy (and bioenergy) a national commitment and identified this sector as a future area of economic growth

since 2007.[801] Singapore has a number of R&D policies in place to encourage and incentivize development of clean technologies. Since 2011 public sector investment in sustainable energy and clean energy has totaled SGD800million.[802] The number of clean energy industries has grown from negligible to almost 100 in 2015.[803] However, the majority of these projects and policies relate to non-biotechnological initiatives including wind, solar and tidal energy. There is, relatively speaking, limited specific policy infrastructure in place focused on the industrial biotechnology sector in Singapore. Still, the overall strong infrastructure and emphasis on innovation has resulted in a number of biofuel-oriented projects. For instance, Singapore-based Alpha Biofuels has partnered with the Westin hotel group in the city to provide 7% blended biodiesel to power the hotels fleet of luxury cars.[804] This is part of the company program "Waste Oil For Fuels", whereby small-scale refinery of waste cooking oil are set up in collaboration with various businesses.[805] Singapore is also home to the largest hydrotreated vegetable oil plant in the world operated by Finnish based Neste and can produce 800,000 metric tons of HVO a year.[806]

Performance in Key Enabling Factors

Human capital

Today, Singapore has a strong base of scientific expertise and human capital.

In 2015, the Times Higher Education world university rankings placed the National University of Singapore (NUS) and the Nanyang Technological University (NTU) in the 12th and 13th positions respectively, up from 22nd and 39th the previous year. In addition, NUS is internationally praised for its life science program, ranking 27th globally.[807]

In terms of academic and research publications, Singapore has compared to other *Building the Bioeconomy* countries and to its performance on other indicators a rather low number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 2000-2011 Singapore had 47.97 publications per million population.[808] This was less than half of Turkey's output and less than a tenth produced in the US.

A high proportion of Singapore's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Singapore had 6,442 researchers per million people, behind only Israel and Korea. [809]

Infrastructure for R&D

Singapore is a big investor in research and development. Measured as a percentage of GDP 2013 R&D spending was 2%.[810] Internationally, this is just below the 2013 OECD average of 2.37%, and still behind the biggest R&D spenders such as Korea and Israel.[811] The latest data from 2013 shows industry expenditure on R&D at 52.7% of the national total.[812]

Singapore's innovation infrastructure and services are extremely well developed. The Government's One North infrastructure initiatives, which comprise of R&D facilities; campuses for new higher education institutions; living amenities for researchers and offices for VCs and IP specialists; are highly regarded.[813] The initiative consists of two major research hubs or clusters: Biopolis is the biomedical hub and Fusionopolis is aimed at ICT, engineering and the physical sciences. Several biomedical research institutes within A*STAR focus on drug discovery.[814] Biomedical research makes up a substantial part of the overall R&D expenditure in Singapore. In 2011 Biomedical Sciences R&D accounted for SGD1,509 million of which SGD573.8 million came from the private sector and SGD 935.2 million from the public sector.[815] Singapore's high level of biomedical R&D capability is also illustrated by the number of researchers and scientists employed in the biomedical sector. In 2011 biomedical researchers and scientists (private and public sectors including in A*STAR) made up 22% of the overall number of researchers and scientists.[816]

The clinical research environment is world leading. Per capita Singapore has some of the highest rates of clinical trials in the world and is behind only Switzerland and Israel of the economies included in *Building the Bioeconomy*. The number of clinical trials to date performed in Singapore per million population was 278.08 trials.[817] Singapore has a high level of trials on biologics per million

population, 10.79 for the period 2010-2015.[818] A relatively high level of these – 42% – were early phase trials.

Looking at biotechnology triadic patenting Singapore is a top patenting nation on an absolute basis or adjusted for population. Singapore's share of the global total average for the period 1999-2012 is 0.38% – the same share as Russia and Brazil combined.[819]

Singapore is viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Singapore is ranked third in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 92.3. [820]

Intellectual property protection

Singapore has a robust system of IPRs. Standard patent terms are issued for 20 years and Singapore also provides for a five-year patent term restoration.[821] Singapore also offers a five-year term of regulatory data protection. Additionally, Singapore introduced legislation relating to the development of orphan drugs in 1991, which includes marketing exclusivity and subsidies as incentives for OD development.[822] Trade secret protection is generally strong and relevant mechanisms are in place. Singapore placed highly in the OECD Trade Secrets Protection Index.[823] The country also reformed its protection of plant varieties in 2014.[824] The new amendments provide protection for all genera and species. The new law came into effect July 30 2014.

The regulatory environment

Singapore has built up a strong and supportive biopharmaceutical environment over the past two decades. In terms of the regulatory framework, the Health Products Regulation Group within the Health Sciences Authority is in charge of the authorization and safety supervision of pharmaceuticals. This agency is also responsible for clinical trials. The group is highly regarded and is involved in the regulation of Western medicinal products as well as Chinese proprietary medicines and cosmetic products.[825] However, generally speaking the regulatory authorities in Singapore require new products and technologies to be approved in other jurisdictions prior to approval in Singapore.[826] The system is relatively efficient, with approximately 80% of marketing applications approved through an abridged route relying on evaluations from leading drug regulatory agencies in other countries.[827] Under this route the approval time is on average just 60-180 days (depending on the number of external evaluations available).[828] An additional priority review path is also available for certain life-threatening conditions with limited treatment options, which further reduces approval time to 60 days.

GM foods are regulated by the Genetic Modification Advisory Committee. This committee regulates the import and commercialization of biotech products and services. Singapore's regulations are science-based and the registration process is generally viewed as efficient. Approval for food imports (GM and non-GM) is contingent on the product having been approved as safe in the exporting country.[829]

Technology transfer

Singapore has a strong tradition of technology transfer with governmental bodies as well as academic institutions being closely involved in transfer activities. For example, the Biomedical Sciences Industry Partnership Office liaises between universities, public research institutes and industry. It promotes partnerships and links commercialization partners with public sector research.[830] WIPO 2014 data confirm that universities accounted for a large share of patent applications in Singapore (18.6%), as well as government and research institutions (18.7%). [831] And despite its small size Singaporean universities were present in the top-50 PCT applicants globally for universities accounting for 3% of total PCT applications among these 50 institutions.

Singapore's main bioclusters host domestic and international firms, biomedical research institutions and are also integrating governmental R&D bodies. Technology transfer is also being promoted and is made accessible by the close proximity of these bioclusters to the Singapore Science Park and the National University of Singapore.[832] In 2011, Singapore set up the Intellectual Property Intermediary to help local

enterprises enhance innovation capacity through technology transfer. This initiative is backed by collaboration and support from the Government. Activities included brokering licensing agreements between companies and research institutions, or assisting life science companies finding partners for research and clinical trials.[833]

From the Technology Transfer Office administered by the National University of Singapore, over 700 patent applications, 84 licensing agreements and equity in lieu of royalties reaching USD4.85 million had been managed from the period of its inception in 1990 till the mid-2000s.[834]

The latest five-year R&D plan 2016-2020 foresees to strengthen these initiatives, including expanding the role of TTOs, allocating more funds to support collaborations between public and industry researchers and supporting secondments to businesses.[835]

Market and commercial incentives

Singapore offers an R&D tax credit of up to 400% on qualifying R&D expenditure, but subject to a cap of SGD400,000 or SGD600,000 (approximately USD292,000 or USD437,000, respectively).[836] The majority of this relief is available on R&D performed in Singapore.[837] Singapore also has an "angel investors tax deduction" program that provides a tax deduction for 50% of the investment amount, up to a cap of SGD500,000.

With regards to the biopharmaceutical market this is relatively free with government subsidies in place only for pharmaceuticals included on the Standard Drug List.

Legal certainty (including the rule of law)

The legal environment in Singapore is considered stable and certain. Legal redress, enforcement of contracts and administrative justice is generally available and viewed as effective. Singapore is ranked 9th on the 2015 *Rule of Law Index*.[838]

South Africa

South Africa is an upper-middle-income country with a GDP of just over USD350 billion at current USD,[839] and a GDP per capita of just under USD6,000.[840] Over the past decade economic growth rates have fallen significantly, from around 5.5% annual GDP growth in 2005 to just 1.5%-2% forecasted in 2015 (with growth expected to hover around this level for the next few years).[841]

Indeed, despite being one of the leading emerging markets in terms of GDP, South Africa ranks just 49th in the World Economic Forum's *Global Competitiveness Index* 2015-2016.[842]

National Innovation Strategy

In 2008 the South African government released the Ten-Year Innovation Plan. The plan was intended to be a high-level look at general areas the country could improve in by 2018 to become one of the world's leading knowledge-based economies. One of the key goals of this plan was for South Africa to host one of the fastest growing biopharmaceutical industries and to be identified as a world leader on climate change research.[843] As is discussed below, while remaining largely unfulfilled this aspiration is still an important part of South Africa's national innovation agenda.

Included in the 2008 document was the creation of the Technology Innovation Agency.[844] The Agency was created to bring all different avenues available for innovation under one roof with the primary objective of generating and utilizing technological innovation to grow the economy and improve the lives of all South Africans.[845] In terms of concrete activities the Agency has created four funds that provide assistance to innovative companies. The largest of these funds is the Industry Matching Fund that provides assistance to companies of all sizes. Businesses are encouraged to partner with universities or public science councils and must match 30-50% of the funding level with loans, royalty payments or shares. The Equity Fund is available to struggling start-up companies that do not have the ability to raise capital from public markets. In return for capital, the Agency acquires equity or convertible shares from the

company. Projects undertaken by universities or science councils deemed to be of exceptionally high quality can apply for funding through the Technology Development Fund. Projects receiving assistance through this fund typically are those identified by the Agency as ventures that can succeed without industry partnership. Lastly, very early stage companies have access to the Idea Development Fund that provides entrepreneurs with low-level funding to cover the costs associated with patents and business plan development.[846]

The Agency has seen some success through its funding initiatives. It has provided R90 million (USD7.84 million) to develop the Tshwane Animal Health Innovation Cluster to advance research in animal health biotechnology projects.[847] Other projects include the Metagenomics Platform that looks to develop novel products from genetic material found in the South African environment and a clinical trial for a vaginal gel based version of tenofovir that could help prevent the spread of HIV/AIDS.[848]

Looking at the biotechnology sector, in 2014 Ministry of Science and Technology released a flagship policy document for the biotechnology sectors titled *Bio-Economy Strategy*. This document builds on past Government initiatives including the 1996 White Paper on Science and Technology and the 2001 National Biotechnology Strategy. The Strategy seeks to further develop South Africa's bioeconomy making all biotechnology sectors into significant contributors to the country's national economic output by 2030.[849] In particular the Strategy focuses on expanding the ag-bio sector in light of its potential broader economic impact in South Africa.[850] It also includes a number of input and output indicators to measure its performance including patents granted, technology transfer transactions, GMO field trials, approval of new medicines and biomedical products, number of biotech firms, venture capital invested and a host of other important components of measuring biotech innovation.[851] One area where the report does not provide as clear a framework or reference point is the issue of IP rights and providing incentives for the creation of intellectual property assets. Instead, the report focuses on ways in which South Africa could better access existing and developed forms of IP. It states that: "*South Africa needs to implement a strategy to exploit expired, expiring or unenforceable patents to produce bioproducts locally, at a fraction of the cost of importation.*"[852] There is no equivalent discussion on the manner in which new intellectual property can be created, commercialized and become an industrial asset.

In terms of R&D support and investment the 2001 National Biotechnology Strategy allocated USD58 million in public sector support. It also established a system of Regional Innovation Centres set up to identify opportunities across all biotech sectors and regions of South Africa.[853] The Centers include Cape Biotech, Lifelab and BioPad and PlantBio (dedicated to ag-bio).[854] In addition the Government supports the EGoliBio initiative which serves as an incubator for biotechnology companies at various stages of development ranging from companies that have a commercial viable product to those that are still in early stage research.[855] EGoliBio has helped 25 different companies commercialize products. This includes Sliek, a company that provides enzymes to treat lactose intolerance, and AdhocWorks, which has developed a new product to prevent mosquito bites and the transmission of malaria.[856]

In terms of biotech outputs data suggests that South African biotechnology activity is still relatively limited. Contribution of the biotechnology sector to the national GDP is reported as limited and the number of biotechnology SME's since 2005 has grown slowly, ranging between 70-100 companies.[857] Latest available OECD data (2009) report 30 biotechnology companies in South Africa, the lowest level of all OECD countries excluding Slovakia.[858] Similarly, looking at value added South Africa's biotech sectors are still quite small. OECD estimates of private sector biotechnology R&D as a percentage of total industry value added was quite low at 0.02%.[859] There is currently no equivalent available data for public sector expenditure. Nevertheless, there are some international success stories. For example, South Africa's oldest biotech company Bioclones developed and successfully marketed Repotin an EPO used extensively in South Africa.[860]

Biopharmaceutical

The South African biopharmaceutical market is the biggest market in Africa worth an estimated USD3.5 billion in 2014/15, however only 6% from this is estimated to come from biologics.[861] A number of international biopharmaceutical manufacturers are present with both manufacturing and R&D capabilities in South Africa. For example, Sanofi has had a manufacturing site in South Africa since the 1970s.[862] The company has also invested in domestic research facilities targeting TB.[863]

A central part of the Strategy document was to strengthen local biopharmaceutical research, development and innovation capabilities with a view to increasing the local manufacture of active pharmaceutical ingredients, vaccines and biologics.[864] Specifically, the strategy envisions greater private investment in R&D and production particularly in the areas of biosimilars and bioprocessing technology platforms as well as creating public-private partnerships for the production of APIs needed for anti-retroviral drugs and for vaccines.[865] The document sets as a target that within a decade, 25% of current pharmaceuticals and 20% of vaccine imports should be replaced by local production.[866] In this sense the Strategy can be viewed as industrial policy geared towards localizing manufacturing and production through targets and erecting trade barriers. Indeed, the latest Industrial Policy Action Plan (IPAP 2016/17 – 2018/19) confirms the primary objective of import substitution together with export support as well as upgraded skills and technologies. To that effect, it proposes to create an Action Plan for the pharmaceutical sectors by 2017, including a study on key opportunities for biologic production, and a program on industry upgrading and operational excellence in pharmaceutical manufacturing.[867]

Looking at rates of product launches between 1983-2000, the percentage of products available in South Africa within five years of global launch was 29%.[868] This was squarely in the middle of the sampled economies.

With regards to the BCI Survey South Africa ranked in the middle of the economies included in *Building the Bioeconomy* with an overall score of 64.6.[869]

Ag-bio

South Africa is a major producer of ag-bio crops. In 2015 it was the ninth largest producer of biotech crops in the world with 2.3million hectares under cultivation.[870] However, this represents a sharp 23% decrease from the 3 million hectares cultivated in 2014, as a result of a devastating drought.[871] To avert a severe food crisis, the Government plans to ease GMO import rules, for instance by allowing imports to be stored and registering additional GMO varieties.[872] Drought tolerant maize with insect control (Bt) under the WEMA project will be launched in South Africa in 2017.[873] Crops under cultivation include corn, soybean and cotton.[874] Production of biotech potatoes was refused in September 2015 because it would allegedly be too difficult for farmers to keep genetically modified and conventional potatoes separate.[875]

South Africa has long been a user of biotechnologies and the majority of its major crops are planted with genetically engineered seeds.[876] For corn close to 87% of plantings are with GE seeds, over 90% of soybean plantings and all cotton plantings are grown from GE seeds.[877] All GE seeds used in South Africa are imported, primarily from the US. There is no South African commercial manufacturer of approved GE seeds.

Looking at R&D South Africa has focused primarily on grapevine research with universities and government partnering in the development of GE grapevine. Field trials by the Institute for Wine Biotechnology at Stellenbosch University were approved in 2009.[878]

Industrial Biotechnology

The South African Government has expressed an increasing interest in industrial biotechnology including biofuels. The 2014 National Strategy lists this sector together with ag-bio and biopharmaceuticals sectors as the focus of the Strategy. While it sees huge opportunity for South Africa in this sector the Strategy does concede that this sector has not been a priority in previous policies.[879]

In terms of biofuels South Africa is currently not a huge producer. Total production for the

entire African continent (including South Africa) of biofuels is less than 0.1% of the global 2014 total.[880] However, this amount is likely to increase as a result of the commitments to biofuels made by the South African Government in 2014. In January of that year a Draft Position Paper on the South African Biofuels Regulatory Framework was issued.[881] The Paper follows the 2007 Biofuels Strategy call for a 2% penetration of biofuels in the South African fuels supply.[882] It also proposes a 20-year general fuel levy to support biofuel manufacturing of between 4.5-6.5 cents per litre of fuel.[883] Although mandatory blending requirements of 5% for biodiesel and 2% for bioethanol have been in place from October 2015, no licensed biofuel producer has started building its plant, amid delays in promulgating the final Position Paper.[884] Legislative uncertainties and lack of adequate financial incentives are frustrating prospective producers.[885] Low oil prices have forced the Government to reconsider the subsidy system proposed in the draft paper, replacing a first-come first served model with a competitive bidding basis regarded as inadequate by the industry.[886]

Human capital

Globally, South African Universities have been gaining in prestige; *Times Higher Education* ranked University of Cape Town as the 120th best university in the listing and two other South African universities ranked in the top 400.[887] Further, University of Cape Town ranks fourth in the Times Higher Education rankings of top universities in the BRICS and emerging market economies and overall five South African universities are included in the top 100.[888]

In terms of academic and research publications, South Africa has compared to other *Building the Bioeconomy* countries and to its performance on other indicators a rather high number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 2000-2011 South Africa had 702.84 publications per million population.[889] This was ahead of the US and behind only the UK, Israel and Switzerland. South African publications were also ranked relatively highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with only 10.65% of publications among the 10% most cited; this was notably higher than other BRIC economies and ahead of Korea and Japan.[890]

A low proportion of South Africa's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that South Africa had 404 researchers per million people, behind all countries included in *Building the Bioeconomy* bar Mexico, India and Colombia.[891]

Infrastructure for R&D

In terms of R&D support and investment, the 2001 National Biotechnology Strategy introduced an annual public budget for R&D and also established a system of Regional Innovation Centers. However, in the last few years R&D spending has stayed at a relatively low level. South Africa invest relatively little in research and development; 2012 figures show R&D spending as a percentage of GDP at 0.73%, down from 0.84% in 2009 and below the OECD average of 2.34% for that year.[892] For the same year, only 38.2% of South African R&D spending was made up of private sector and industry spending, down from 42.5% in 2009.[893]

The Ministry of Science and Technology has pledged to double the amount of R&D spending by 2019, aiming at 1.5% of GDP, notably by attracting science and technology-orientated foreign investment.[894] At present, an estimated 15% of the annual investment in R&D performed in the country comes from international partners.[895]

According to the most recent available data from the Department of Science and Technology, biotechnology R&D spending remained relatively strong, rising by 11% to R1.2 billion in 2013, or around 5% of total expenditure.[896] The medical and health sciences continued to attract the largest share of domestic R&D spending, at 17% of the total (amounting to around R4.1 billion).[897]

South Africa's clinical research environment remains limited. The number of clinical trials conducted is still on an absolute and per capita

basis fairly small.[898] Per capita South Africa has a medium level of clinical trials compared to the other economies included in *Building the Bioeconomy*. The number of clinical trials to date performed in South Africa per million population was 38.96 trials.[899] This is ahead of all emerging markets but far behind Korea, Singapore and world leaders Israel and Switzerland. South Africa has compared to the other economies sampled a medium level of trials on biologics per million population, 2.26 for the period 2010-2015.[900] A relatively high level of these – 38% – were early phase trials.

Looking at biotechnology triadic patenting South Africa is not a top patenting nation on an absolute basis or adjusted for population. Its share of the global total average for the period 1999-2012 is 0.06% – half of Brazil and one-tenth of India's.[901]

South Africa is not viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* South Africa is ranked in the bottom third in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 64.3. [902]

Intellectual property protection

South Africa faces some significant challenges in the realm of protecting IP, particularly for biopharmaceuticals. A wide-ranging patent reform package is being discussed and consulted on by the South African Government and developed by the Department of Trade and Industry.[903] At the time of research, the reform bill is still under discussion. This package contains a number of measures that are not encouraging for rights holders, particularly in the life sciences. For example, it includes a more expansive use of compulsory licensing and the introduction of pharmaceutical patentability requirements in the style of Section 3(d) of the Indian Patent Act. The reform package also does not address the issue of patent term restoration or introduction of a regulatory data protection framework. In March 2015 the Department announced preparation of an eight-bill reform package, still undisclosed.[904] However, a recent speech of the Minister of Trade and Industry at the WIPO International Conference on Intellectual Property and Development confirms the trend anticipated in the draft IP policy. Indeed, the Minister was reported as saying that "*the evidence on the extent to which patent protection contributes to encouraging innovation is, at best, inconclusive*" and "*countries may require different approaches and policies dependent on their level of industrial development*".[905]

The regulatory environment

For biopharmaceuticals, the regulatory regime was significantly changed in December 2015, when amendments to the "Medicines and Related Substances" Act were passed into law. A new regulatory body, the South African Health Products Regulatory Agency is to replace the current DRA (the Medicines Control Council) in authorising and supervising the safety of pharmaceuticals.[906] The agency is expected to start working in April 2017.[907] Unlike the Medicines Control Council, the new agency will fall outside the Department of Health and be partly funded by applicants' fees in addition to government funding, thus enjoying greater independence. Also, approval of new products will not need consent by the Ministry of Health any longer, which will speed up the process and reduce political interference. At present it can take up to three years to register new products.[908]

South Africa is a major producer of ag-bio crops with a clear regulatory framework in place. The 1997 GMO Act and the 2011 Consumer Protection Bill regulate the production and consumption of GE food.

Technology transfer

South Africa introduced a modern technology transfer framework in 2008. The "Intellectual Property Rights from Publicly Financed Research and Development Act" established the parameters by which publicly funded research can be commercialized and, crucially, where ownership over the generated IP resides.[909] The stated purpose of the Act has been to stimulate research and the commercialization of publicly funded research. Broadly speaking the Act and its accompanying regulations establish the principle that the recipient will retain IP generated through publicly funded research.[910] Even though the Act

was not put into force until 2010, the positive effects of the legislation on rates of university technology transfer and patenting can be seen in the time leading up to the Act and following it. Data from WIPO covering PCT patenting applications by South African universities show a distinct increase from the period before promulgation of the Act and subsequent period. Between 2005-7 the five top patenting South African universities made 32 PCT applications.[911] In the following three-year period when the Act was promulgated, 2008-2010, this more than doubled to 78 PCT applications. By the latest data period available (2011-13) the application rate had grown even further to 98 total PCT applications by the same five universities.[912] Still, despite this increase no South African university was among the top-50 PCT applicants for universities in 2014.

There are dedicated government bodies to assist in technology transfer and commercialization. The Technology Innovation Agency (created in 2010) has as its mandate to facilitate and increase commercialization of research.[913] Similarly the National Intellectual Property Management Office (created through the 2008 Act) is charged with actively assisting in tech transfer at universities and PROs. The Council for Scientific and Industrial Research works to promote technology transfer through developing policies and guidelines and by directly facilitating transfer.[914] The Council maintains an online technology transfer portal where it runs the Instant Access Programme providing companies access to a searchable database of technologies available for licensing.[915]

South Africa also has a long-standing history with using local production requirements to encourage technology transfer. The National Industrial Participation Program has been in place since the late 2000s. The Program requires that foreign suppliers awarded government contracts commit to local investment in R&D and technology transfer.[916] Since 2013, the value of these "offset commitments" must be 30% of the value of the contract won.[917] As stated in the Industrial Policy Action 2015/16, the Government plans to develop more sector-specific programs, including one for biopharmaceuticals.[918]

Market and commercial incentives

South Africa offers relatively generous R&D tax benefits,[919] currently under review by a government-industry task group.[920] These include notably a 150% super deduction for R&D expenditures[921] and favorable accelerated depreciation for capital expenditures incurred to develop or construct assets used in R&D activities (40% for the first year and 20% in the three years after for infrastructure built after 2012).[922]

Since 2014 a number of additional incentives are available for foreign and domestic investments taking place within Special Economic Zones.[923] Projects located within these areas can benefit from preferential corporate income tax, as well as employment and building allowances.[924] These zones specifically target biopharmaceuticals; for instance in May 2015 the government announced it was investing R600 million for the creation of a Health Technology Park in Cape Town focused on biomedical innovation.[925]

However, with regards to biopharmaceutical commercial and market incentives these are relatively limited. Since 2005 biopharmaceutical prices have been capped at a rate in line with inflation,[926] which for imported medicines is typically considered to be under value in relation to the exchange rate.[927] On top of this, in 2015 a *de facto* external referencing price mechanism was introduced for innovative drugs.[928] Under the new regulation innovative manufacturers will have to provide the price of their drugs in Australia, New Zealand, Spain and Canada (or, if not present in these markets, in all the countries they are sold) and the Department of Health will reportedly request companies to forego the yearly price increases if the price applied in South Africa is higher than these reference prices.[929] In addition, beginning in 2003 and based on implementation of the 1997 Medicines Act, automatic generic substitution is permitted by pharmacists.[930] Since 2014 pharmacists also receive higher mark-ups for dispensing generics compared to innovative products.[931]

Legal certainty (including the rule of law)

The South African legal environment is considered stable, ranking 36th on the World Justice Project's 2015 *Rule of Law Index* and highest among the BRICS.

Switzerland

Switzerland is the 37th largest economy in the world with an estimated 2013 total national output of USD701 billion measured at current USD.[932] Switzerland is one of the richest countries in the world with a per capita income over USD85,000 for 2014 at current USD.[933] Switzerland is the world's most open and competitive economy according to the World Economic Forum's 2015-16 Global Competitiveness rankings and has dominated these rankings for years.[934]

National Innovation Policy

Switzerland has a well-established policy framework and long-standing success in promoting and incentivizing innovation. Its strengths reside in close ties between scientific and economic networks at local level, high-quality academic institutions and a well-established and flexible business environment.[935] Several government agencies and departments play roles in the national innovation system. Since 2013 the State Secretariat for Research and Innovation within the Federal Department of Economic Affairs coordinates all federal and regional level efforts relating to research and innovation, including financing of universities.[936] The State Secretariat for Economic Affairs makes sure the business environment is conducive to innovation and cooperates with the Commission for Technology and Innovation on technology transfer.[937] The Swiss National Science Foundation is the country's biggest supporter of basic research and supports National Research Programs proposed by stakeholders, the latest of which deals with antimicrobial resistance.[938] The Foundation provides direct grants to researchers and scientists in basic research. The Foundation provided CHF849 million in funding for basic research in 2014.[939] 38% of the money earmarked for project funding was dedicated to biological and medical research.[940] The Board of the Federal Institutes of Technology oversees and sets policy for federal institutes of technology. Finally, the Commission for Technology and Innovation acts as the national innovation promotion entity and is the main public funding source for applied R&D. The Commission assists with technology transfer and linking universities and Swiss start-ups to promote and commercialise new products and technologies. This extra-parliamentary commission will be replaced from 2018 by *Innosuisse*, a fully-fledged public agency that will take over all of the CTI tasks.[941] Since 2013 the CTI recognizes eight National Thematic Networks in specific areas of innovation aimed at fostering contacts between companies and public research entities, one of which in biotechnology.

Overall, the building of the Swiss biotechnology industry has benefited immensely from government-backed initiatives through the National Sciences Foundation and the government backed technology transfer efforts.[942] Biotechnology is finding more and more application by Swiss businesses looking for value-intensive business opportunities. For instance, Nestlé tackling illnesses such as Alzheimer's disease through the Nestlé Institute of Health Sciences and its cooperation with biotech firms.[943] The success of the biotechnology sector is reflected in the fact that, in 2014, the two top performers on the main Swiss stock market (Swiss Market Index) were two biotech companies (Actelion and Santhera).[944] The number of biotech companies has steadily increased since 2005, up to 207 developing firms in 2014.[945] In the same year, the industry spent over CHF1.5 billion in R&D activities, attracted CHF473 million in capital investments and generated CHF 4.9 billion revenue, compared to CHF 4.7 billion in 2013. [946]

Biotech sector by sector policy overview

Biopharmaceuticals

Switzerland has a globally competitive biopharmaceutical sector. The country is home to some of the largest biopharmaceutical manufacturers in the world. Biomedical research makes up a substantial part of overall R&D

expenditure. Its two dominant national champions, Roche and Novartis, were the top investors in biopharmaceutical R&D of all multinationals in 2015.[947] Two thirds of R&D spending in Switzerland is by industry and the largest part of this spending came from the Swiss-based biopharmaceutical companies (Actelion, Novartis, Roche, Gilead, Merck Serono and Vifor Pharma), which in 2012 accounted for 29.6% of all industry R&D at CHF3.8 billion.[948] By 2014, the amount had almost doubled to CHF6.4 billion.[949] This corresponded to 32.9% of their global R&D spending, whereas 12% went to the rest of Europe and 45% to the US.[950] Biopharmaceutical research represents a large share of the Swiss economy with pharmaceutical exports for 2014 estimated at an excess of CHF70billion, more than a third of the country's total export.[951] Switzerland's high level of biomedical R&D capability is also illustrated by around 42,000 people with direct employment in the industry, equal to 1% of all Swiss employees, and an estimated further 130,000 in related and downstream industries.[952] The success of the research activities of the sector is also reflected in the number of patents per capita. In pharmaceutical research more than 85 patents per million employees were registered from Switzerland between 2000 and 2010.[953] Finally, leveraging these R&D capabilities seems to be an important factor also in localization decisions. Novartis decided against setting up a plant in China in favour of Switzerland, with its CEO was reported as saying that "*labour costs are not a key factor for us.*"[954]

Looking at rates of product launches between 1983-2000, the percentage of products available in Switzerland within five years of global launch was 44%.[955] This was in the top for the sampled economies.

With regards to the BCI Survey Switzerland ranked in the top four of the economies included in *Building the Bioeconomy* with an overall score of 81.01. [956]

Ag-bio

The environment in Switzerland is generally not favorable towards agricultural biotechnology. In 2005 a public referendum was passed banning the use of genetically modified plants and animals in the country. The Swiss Parliament extended this moratorium for three years in 2010 and for another 4 years in 2013.[957] At the end of 2015 the Federal Council proposed to further extend it to 2021 (see discussion below).

Despite the public referendum and lack of public support for GM foods and ag-bio products, the Swiss Government does maintain avenues for agricultural biotechnology research. Researchers can apply to the Federal Office for the Environment to receive approval for the experimental release of a GMO product.[958] Since 1999, seven GM plants were approved for experimental release, the latest in 2015 (cisgenic apple trees with improved resistance to fire blight).[959] In addition to granting case-by-case approvals for field testing of GMO products, the Swiss Government has created a three hectare protected site at the Reckenholz Research Station.[960] In 2014, during its first operational field season, the University of Zurich launched a field trial with GM wheat lines.[961] In 2015, Agroscope conducted preliminary trials of GM late-blight resistance potatoes.[962]

Despite the lack of a domestic market Switzerland is home to one of the largest ag-bio companies in the world, Syngenta. While being a Swiss company Syngenta carries out most of its R&D outside of Switzerland with a strong presence in the US, Brazil, the UK, China and India.[963]

Industrial biotechnology

The industrial biotechnology sector in Switzerland is very small with less than 5% of biotech companies engaging in some sort of industrial related biotechnology.[964] However, Swiss industry recognizes the advantages of a strong industrial biotechnology sector and has been lobbying the government to become more involved in the promotion of the sector.[965] In 2014, the Science Industries Switzerland Business Association, Biotechnet, the Federal Institute of Technology and the Swiss Biotech Association launched BiocatCH+, a program to help foster research and technology transfer in the field of biocatalysts. In addition, since 2004 companies involved in various activities such as chemistry over pharmaceuticals or the flavours and fragrance sector (such as

Cerbios, DSM, Givaudan, Lonza, Merck, Novartis, Roche, and Syngenta) cooperate within the Swiss Industrial Biocatalysts Consortium to share knowledge and resources concerning biocatalysts, industrial enzymes and microbial strains with special properties. Switzerland is also home to the R&D facilities of some of the largest chemical and industrial biotechnology companies in the world. For example, DuPont has its European Technical Center in Meyrin outside Geneva. This Center is a global R&D facility cutting across most of DuPont's research and products from polymer and advanced materials to blow molding and extrusion.[966] In addition the company also houses its DuPont Geneva Innovation Center in Geneva Switzerland.[967]

Performance in key enabling sectors

Human capital

According to a survey of MNCs carried out by the Swiss Secretariat for Research and Innovation (SERI) in 2015, access to qualified human capital is the main reason for companies to establish R&D activities in Switzerland.[968] Swiss universities are generally highly regarded, particularly in the biomedical and life sciences. For example, in the *Times Higher Education* rankings the Swiss Federal Institute of Technology Zürich is ranked 11th in the life sciences, and five more universities are among the top-100.[969]

In terms of academic and research publications, Switzerland has compared to other *Building the Bioeconomy* countries the highest number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 2000-2011 Switzerland had 1,112.38 publications per million population.[970] This was almost 50% more than second place Israel. Swiss publications were also ranked the highest according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with almost a fifth (19.42%) of all publications among the 10% most cited.[971]

A high proportion of Switzerland's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Switzerland had 4,481 researchers per million people. This was ahead of the US but just over half of Israel's proportion. [972]

Infrastructure for R&D

Switzerland is a leading investor in R&D. The latest figures from 2012 show R&D spending as a percentage of GDP at 2.97%.[973] Internationally, this is higher than the 2012 OECD average of 2.34%, but still behind the biggest R&D spenders such as Korea and Israel.[974] Swiss R&D spending is largely made up of private sector and industry spending. The latest data from 2012 show industry expenditure on R&D at 60.8% of the national total,[975] which corresponded to CHF12.8 billion.[976] According to the Swiss biotech industry, the pharmaceutical and chemical industries accounted for 34% of this expenditure.[977] For the same year, Swiss companies invested CHF 15billion in R&D activities carried out outside Switzerland through their subsidiaries, and CHF2.3 billion through foreign contractors.[978] According to a 2015 industry survey of major multinationals overall companies consider the US the most attractive R&D destination, followed by Switzerland, Germany and China.[979]

Switzerland has highly advanced medical and biomedical research facilities and its clinical research environment is world leading. The number of clinical trials conducted is on an absolute and per capita basis high. The number of clinical trials to date performed in Switzerland per million population was 517.93 trials.[980] This is second only to Israel. Switzerland has a high level of trials on biologics per million population, 20.51 for the period 2010-2015; again second only to Israel.[981] A medium level of these – 39% – were early phase trials.

Looking at biotechnology triadic patenting Switzerland is a top patenting nation on an absolute basis or adjusted for population. Its share of the global total average for the period 1999-2012 is 1.99% – equal to all the BRIC economies put together.[982]

Switzerland is viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Switzerland

is ranked in the top third in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 85.7. [983]

Intellectual property protection

Switzerland has a very strong system and history of protecting and promoting IP. The country is a member of the EPO and a signatory party to the European Patent Convention. Standard patent terms are issued for 20 years. Switzerland also provides a Supplementary Protection Certificate (SPC) of five years.[984] RDP is also available at a ten-year term.

The regulatory environment

Switzerland has a strong clinical and regulatory environment. For biopharmaceuticals the DRA Swissmedic is responsible for the authorisation and safety supervision of pharmaceuticals. The agency is highly regarded internationally.[985]

With regards to the use of biotechnology in agriculture the Swiss public in 2005 voted for a five-year moratorium on the use of GM crops in Switzerland.[986] This was later extended by the Swiss Parliament in 2010 to the end of 2013 and was recently extended again till 2017. The extensions came despite a number of scientific reports being commissioned by the Swiss Government finding that GM crops present no clear danger to human or plant health. In December 2015 the Federal Council expressed its intention to extend the ban until 2021 under the Gene Technology Act, so as to allow "*a thorough and objective debate on the future use of GMOs…based on considerations which are not confined to the issue of biosafety, but also take into account the economic and agricultural aspects*".[987] Several Swiss cantons already banned GM crops permanently on their territories. As public opinion remains widely against GMO, some foresee a countrywide ban is likely to be endorsed in the future.[988] To protect non-GM from GM crops, the Federal Council also launched work on a draft law and a draft ordinance on the issue of coexistence.[989]

Technology transfer

Switzerland has a strong tradition of technology transfer with governmental bodies as well as academic institutions being closely involved in transfer activities. As mentioned, the Commission for Technology and Innovation has as one of its core goals to promote technology transfer between universities and industry including the Swiss Biotech association. It does so among others through innovation mentors providing support in drawing up project applications as well as interactive and physical platforms.[990] Academic institutions and professionals have their own technology transfer association through swiTT (Swiss Technology Transfer Association).[991] The association provides support services and has its mission to help facilitate technology transfer between public institutions and private companies.[992]

According to the European Patent Office, the Swiss Federal Institutes of Technology in Lausanne and in Zurich as well as the University of Zurich rank among the top 25 Swiss innovators, along with big companies such as Novartis, Roche, Nestle and ABB.[993] In the two Zurich institutions, a multidisciplinary translation science centre was recently introduced, aimed at bridging the gap between basic and pre-clinical research and development of treatment protocols and clinical therapies, as well as new smart technologies in the fields of regenerative medicine and robotic technologies.[994]

Switzerland's two federal institutes of technology (ETH Zurich and EPF Lausanne) entered the WIPO top-50 applicants for universities in 2014.[995] Together, they accounted for 0.02% of total PCT applications by top-50 institutions in 2014, just behind the UK and Singapore.[996]

Market and commercial incentives

Switzerland offers only a moderate amount of R&D tax incentives.[997] Overall its tax scheme is not very favourable in comparison to other OECD countries.[998] However, the ongoing overhaul of the existing tax regimes, known as Swiss Corporate Tax Reform III, puts forward two important proposals for innovators: firstly, a "patent

box" according to which IP-generated income would be exempted up to 90% on cantonal and communal taxes (local entities can determine a lower exemption rate); secondly, an R&D super deduction, the exact amount of which will need to be legislated by the cantons.[999] The overall aim of this very comprehensive tax reform is to increase the country's attractiveness as a location for multinationals.

There are tax incentives in place for the use of biofuels. Qualifying biofuels are partially or wholly exempt from "mineral oil tax" which can make up a significant portion of the per litre cost of fuel.[1000]

With regards to the biopharmaceutical market relatively strict pricing policies are in place for drugs and pharmaceuticals available through basic insurance. There are consequently a limited number of market incentives for these products, which total over 2,500 medicines. However, for both supplementary insurance and all medicines not listed on the public reimbursement list there is free pricing and a relative free market.

Legal certainty (including the rule of law)

The Swiss legal environment is generally considered stable and certain. Legal redress, enforcement of contracts and administrative justice is generally available and viewed as effective. Switzerland is not included in the 2015 *Rule of Law Index*.

Turkey

Turkey is an upper middle-income country, with a 2014 per capita GDP of USD10,15 and an overall total GDP of USD799 billion both at current USD.[1001]

The World Economic Forum *Global Competitiveness Report* 2015-2016 ranks Turkey at 51st place, a drop by 6 places compared to last year attributed to political and monetary uncertainties that have put off investments.[1002]

National Innovation Policy

The Scientific and Technological Research Council of Turkey is the primary government body tasked with overseeing innovation policies in Turkey.[1003] In December 2010, the body approved the National Science, Technology, and Innovation Strategy 2011-2016.[1004] This strategy aims to boost innovation and R&D in competitive innovation sectors and other sectors that are identified as areas of strong global demand.[1005] In 2011, the government created the Ministry of Science, Industry, and Technology to coordinate with the Council on implementing national innovation policies.[1006] To attract high-tech companies Turkey has created three types of special investment zones, 44 currently operational and 15 under construction.[1007] Technology Development Zones (also called Technoparks) were created for companies looking to increase their research and development capabilities in high technology fields. As of 2014, over 2,000 companies, research centres, and universities were operating in the Technoparks. Official estimates suggest companies in the Technoparks have contributed an estimated USD600 million in exports and filed 301 patents.[1008] Technoparks have had some success in housing biotechnology companies with 20% of all firms located in these special economic zones engaged in biotech.[1009] Organized Industrial Zones were created as areas with "ready-to-go" infrastructure that include access to roads, water, natural gas, electricity, communications, waste treatment, and other sector specific services.[1010] Lastly, Free Zones were created and identified as areas being within the political borders of the country but free from customs requirements. Free Zones are designed to attract export driven companies. 19 such Zones are active and the majority are located near major Turkish ports.[1011] However, Turkey also has in place a number of localization policies (primarily targeting the biopharmaceutical sector) which in many ways have counterbalanced some of these positive (see under "Biopharmaceuticals"). One of the principal measures affecting localization is Public Procurement Law N.4734, providing up to a 15% price advantage to local goods in government tenders. There are also local production targets and policies in place that favor local actors over foreign entities; see below discussion.

Looking at recent developments starting in March 2016, an R&D Reform Package (Law No. 6676) entered into force, aiming at increasing the share of R&D activities in the Turkish economy by lowering R&D costs for companies.[1012] Measures include tax and custom duties exemptions (see under "Market and Tax Incentives") as well as the establishment of specialized Trade Development Zones for priority and strategic sectors, including biotech.[1013] The Government also announced its intention to increase R&D spending from 1% to 3% of GDP, private R&D spending from 50 to 60% of total spending and the number of researchers to more than 300,000 – up from 115,000 in 2014.[1014] The targets should be achieved by 2023, marking the 100th anniversary of the Turkish Republic.

Biopharmaceutical

In November 2014, the Prime Minister presented the objectives of covering 60% of the national demand for pharmaceuticals and 20% for medical devices with local production, as well as increasing clinical research by 25%.[1015] In subsequent public discussion and meetings other important policymakers have again emphasized this policy position. For example, in 2015 the Ministry of Science reportedly re-emphasized that in the coming years the Government plans to take a much more "aggressive" approach to supporting the domestic production of pharmaceuticals, notably those making up the largest part of the public healthcare budget, including cancer drugs, antibiotics and blood products.[1016]

Along these lines, the 2015-2018 "Pharmaceutical Strategy and Action Plan" published in September 2015 aims to make Turkey a manufacturing base for mid and high level technological products.[1017] The Plan includes measures to support innovation, such as expedited registration applications for drugs developed as a result of R&D activities in Turkey, and improving the existing laboratory infrastructure for use in registration, license, market surveillance and supervision processes by the Ministry of Health. Policies are also in place to speed up the reimbursement procedures for domestic drugs and to delist imported products for which local equivalent exists from the reimbursement list.[1018] Furthermore, in January 2016, the Minister of Health announced new incentives to establish hepatitis A manufacturing facility in Turkey.[1019]

While the Turkish Government has been working to increase biopharmaceutical R&D, several laws are less successful in promoting this end-goal. As mentioned, increasingly restrictive localization policies have been and are limiting potential biopharmaceutical development. The draft IP Law recently disclosed introduces new elements of uncertainties for patent holders (see under "Intellectual Property Protection"). Furthermore, the Turkish Government through its P&R policies bluntly restricts spending on biopharmaceutical products.[1020] From 2009 to 2010 the Government's biopharmaceutical budget was cut by 10%, which was followed by a requirement that the biopharmaceutical industry reduces prices for 2010-2011 to cover spending overruns.[1021] Subsequent budgets have also seen significant cuts.[1022]

Looking at rates of product launches between 1983-2000, the percentage of products available in Turkey within five years of global launch was 25%.[1023] This was in the bottom third of the sampled economies.

With regards to the BCI Survey Turkey also ranked in the bottom third of the economies included in *Building the Bioeconomy* with an overall score of 56.85.[1024]

Ag-biotechnology

Agricultural biotechnology has become more limited in Turkey as a result of the 2010 Biosafety Law.[1025] While the law does allow researchers to study and develop ag-bio products commercialization is limited. The law also requires that the Biosafety Board approve all research prior to its initiation. Researchers in the country have voiced strong disapproval of the law and no GE seeds have been developed in the country since its passage.[1026] In 2015, an estimated 150 companies are being prosecuted for placing unapproved GE traits on the market, three of which under the charge of "biological terror".[1027] Prior to 2010 the majority of biotechnology companies in Turkey and most biotech research was in the area of ag-bio. A 2009 market research

study found that over 90% of biotech employees worked in the ag-bio sector.[1028]

Industrial Biotechnology

Industrial biotechnology has long been an important part of Turkish industrial processes and production. The Turkish yeast industry is of particular importance with a growing share of the world yeast market. Turkish Pakmaya has become a global presence selling its products in over 130 countries.[1029] The company has invested in micro-biological R&D since the 1980s with dedicated R&D activities centred on its Pbio Pak Biotechnology Centre.[1030]

In terms of Government support, companies focused on industrial biotechnology can receive research assistance from the Biotechnology and Bioengineering Application and Research Center. Established in 2009 by the Turkish Department of Planning, the Center provides researchers with access to technology and research facilities.[1031]

Government mandates for the use of bioethanol and biodiesel were announced in 2011 with ethanol set to be blended at a rate of 3% from 2014.[1032] At the time of research it was unclear if these measures had been implemented. Looking at biofuels production Turkey is not listed a major producer of biofuels per BP's annual statistical review.[1033]

Human capital

No Turkish university was included on the 2015-16 *Times Higher Education* top 100 and only one in the top 300.[1034]

In terms of academic and research publications, Turkey has compared to other *Building the Bioeconomy* countries a medium number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 2000-2011 Turkey had 93.44 publications per million population.[1035] This was ahead of Brazil and Singapore but far behind the UK, Israel and Switzerland. Turkish publications were not ranked highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with only 6.88% of publications among the 10% most cited; this was marginally ahead of the BRIC economies.[1036]

A medium proportion of Turkey's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that Turkey had 1,168 researchers per million people. [1037]

Infrastructure for R&D

Turkey has a low level of R&D spending when measured as a percentage of GDP. 2014 figures show R&D spending as a percentage of GDP at 1.01%.[1038] Just over half of Turkish R&D spending is made up of private sector and industry spending. The latest data from 2014 show industry expenditure on R&D at 50.9% of the national total.[1039]

In terms of biotech clusters and bioparks the major one is Istanbul Health Industry Cluster. This cluster brings together 12 universities, 13 NGOs and 75 companies. The cluster places an emphasis on new companies and provides business incubator programs. The cluster also assists in technology transfer for companies that have developed commercially viable products and works with the Turkish Government to establish industrial parks throughout the country focusing on biopharmaceuticals.[1040] Also the Izmir area saw the development of a strong biotech cluster, where Turkey's First Biomedicine and Genome Center opened in September 2015.[1041] The cluster hosts two major universities with almost 120,000 students focusing on health and life sciences, and two corresponding Technoparks (ideEGE-Life sciences Technopark, DEPARK- Health Technopark), in addition to hospitals and labs.

Turkey's clinical research environment remains limited. The number of clinical trials conducted is still on an absolute and per capita basis fairly small.[1042] Per capita Turkey has a medium level of clinical trials compared to the other economies included in *Building the Bioeconomy*. The number of clinical trials to date performed in Turkey per million population was 26.58 trials.[1043] This is ahead of the BRICs but far behind Korea, Singapore and

world leaders Israel and Switzerland. Turkey has compared to the other economies sampled a low level of trials on biologics per million population, 1.03 for the period 2010-2015.[1044] A low proportion of these – 14% – were early phase trials; the lowest of all economies included in *Building the Bioeconomy*.

Looking at biotechnology triadic patenting Turkey is not a top patenting nation on an absolute basis or adjusted for population. Its share of the global total average for the period 1999-2012 is 0.02% – ahead of only Colombia.[1045]

Turkey is viewed as a mixed market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* Turkey is ranked in the middle in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 67.1. [1046]

Intellectual property protection

Turkey faces a number of challenges with regards to the protection and enforcement of IPRs, particularly with regards to the life sciences. For example, while Turkey does provide for RDP in law, the actual protection afforded is quite limited. While the exclusivity period provided by the Regulation on Licensing Human Medical Products is six years, in practice the period can be as short as one or two years as the term is counted from the date of marketing authorization in any country of the European Union Customs Union.[1047] Moreover, Turkey does not provide RDP for combination products, which is incompatible with EU standards. Turkey does not offer any period of patent term restoration despite the fact that there are generally long delays in the market authorization process.

More broadly the protection of trade secrets is problematic. Legislation does not clearly define trade secrets; reference is therefore made to the unfair competition section of the Turkish Commercial Code (Law No. 6762) for guidance, and the Court of Appeal has made efforts to provide a definition. Nevertheless, the uncertainty as to defining and establishing trade secrets as well as delays caused by the judicial system and difficulty in obtaining preliminary injunctions generally render trade secret enforcement in Turkey ineffective.

Draft amendments to Decree-Law 551 on the Protection of Patent Rights remain under discussion and at the time of research had not been enacted. [1048] On the positive side, these amendments would introduce post-grant opposition and the ability to amend a patent after grant decision. [1049] This would aid in resolving the high rate of invalidations, and resulting uncertainty, due to the inability to revise patent applications even when opposition proceedings are taking place at the European Patent Office. They would also bring wider substantive examination and seek to reduce bad faith filing of patents. On the negative side, previous amendments that would have clearly provided for patentability of biotechnology inventions and second medical use claims for biopharmaceuticals were removed, meaning that the current situation in which lack of clarity on the issue results in a limited interpretation of patentability of these types of claims by some IP Courts is likely to persist. The amendments also continue to include a provision that would limit the ability of the patent applicant to protect against infringement before grant of the patent, only providing for a right of action for compensation. Moreover, the latest version of the draft law viewed at the time of research confirms, rather than removes the three-iteration limit on examination proceedings. Altogether the latest version would introduce greater uncertainty to the process of patenting and enforcement in Turkey, rather than reducing it. At the same time, in 2015 an online system for filing of patents and trademarks became available (along with reduced filing fees), which is intended to streamline the system and promote innovation (currently it takes two to five years from filing to granting).

The regulatory environment

For biopharmaceuticals, the Turkish Medicines and Medical Devices Agency is responsible for authorisation and safety supervision of pharmaceuticals. The Agency has for a number of years been working to harmonize its regulatory procedures with those of the EMA.[1050] Yet significant challenges remain, not least in the area of product approvals. Despite having committed

to having the approval process completed within 210 days of submission, Turkish industry surveys suggest that many companies experience waiting periods in excess of 1,000 days and that the average waiting period is 500 days.[1051] There are also significant delays caused by the requirement for on-site GMP certification by agents of the Turkish Government.[1052]

With regards to the use of biotechnology in agricultural production, the Biosafety Law passed in 2010 allows for the study and development of biotechnology in relation to agricultural under strict conditions but Article 5 of the law strictly forbids the production or importation of GM plants.[1053] Turkey does import large amounts of GM animal feed for poultry and livestock. The Biosafety Law requires that feed importers receive approval from the Biosafety Board to import any feed that is genetically modified. As of July 2014 the Board had approved the importation of three types of soybeans and 14 types of corn. However, the Biosafety Board also rejected the approval of six types of modified corn.[1054] These rejections have reportedly created a significant barrier for feed importers because the supply chain is not set up to differentiate each type of corn and the law identifies a feed batch as "contaminated", thus unusable, if 0.9% of the feed is from an unapproved substance.[1055] To date, there are no modified products approved for human consumption because the government has not designated a "contamination" threshold level.[1056]

Technology transfer

Technology transfer is still limited in Turkey. There is no comprehensive legal or regulatory framework in place clarifying ownership and rights with regards to publicly funded research. Traditionally, Turkish academics have operated under the 'Professor's privilege' doctrine which allows for freedom of commercialization by academics provided relevant costs (e.g. use of materials, laboratory space etc.) are reimbursed to the relevant institution.[1057] Turkish patent law draws a clear distinction between "free inventions" and "service inventions". In the context of academic research Article 41 of the Turkish Patent Law (Decree Law 551) states clearly that "*…inventions made by the teaching staff of universities during their scientific studies at universities or higher schools shall be free inventions.*"[1058] Only a limited number of Turkish universities have technology transfer offices and are actively engaging in licensing and tech transfer activities.[1059]

No Turkish university was included among the top-50 university institutions in terms of PCT applications.

Turkey has been working to improve technology transfer with local and regional partners. In conjunction with the European Union, the Turkish Government created the "Technology Transfer Accelerator Turkey". The primary objectives of the program are to set up a fund to assist in the commercialization of technologies developed at Turkish universities and research centres, and to promote local transfers especially in less developed regions.[1060] Funds for TTA Turkey are managed by the European Investment Fund and will total €30.5 million. The Fund has set a goal of selecting, at minimum, thirty projects to promote in Turkey by the end of 2017.[1061]

In 2013 TUBITAK announced a program called the 1513 Support Program for Technology Transfer Offices. The program aims to facilitate technology transfer between local universities and industry by providing qualified institutions with grants of up to 1 million Liras to set up technology transfer offices.[1062] During the first year, TUBITAK supported ten universities and ten more were added in 2014. Each university will have the opportunity to receive funding support for the next ten years if yearly performance measures are met.[1063]

Market and commercial incentives

Turkey has in place a number of generous R&D incentive programs and tax benefits. There is a general 100-150% deduction for qualifying expenditure depending on the size of the company; smaller companies qualify for the larger deduction.[1064] There is also an 80-90% reduced rate of tax withholding for personnel involved in R&D activity. In addition, government grants are not considered as income. There are also increased incentives within Turkish Technology Development Zones, including all profits derived

from qualifying R&D expenditure being exempt from income and corporation tax until 2023. Additional tax incentives are in place for staff working within qualifying entities in so-called Development Zones.

Production of pharmaceuticals and products developed by a government-funded R&D project can benefit from special treatment under the general 2012 Investment Incentive System afforded to strategic sectors for domestic manufacturing.[1065] This states that specifically in relation to the areas of biologics and biotechnology, investment of more than TRY20 million can benefit from tax allowances, customs duty exemption, Value Added Tax exemption and refund, support for the employer share of insurance premiums, land allocation and interest support.[1066] These include a 10-20% discount on corporate tax as well as 7-10 years of support/ subsidy for employers in terms of their share of contribution to the social security premium, depending on the region of investment.[1067]

Looking at commercial and market incentives for biopharmaceuticals the Turkish Government through its P&R policies bluntly restricts spending on innovative drugs.[1068] Within the public reference price system in place, prices are set for both innovative drugs and generics at 60% of the lowest price for the same product in a basket of five European countries.[1069] Moreover, until recently the reference price was calculated on the basis of a fixed and outdated euro-lira exchange rate (in terms of 2009 levels), despite the fact that the Turkish lira has devalued by more than 50% as compared to the Euro since 2009.[1070] A new system in place since July 2015,[1071] which mandates a conversation rate of 70% of the previous year's average exchange, is expected to raise the price for products slightly (by around 4%),[1072] though overall limits on spending on pharmaceuticals continue to be quite blunt.

Legal certainty (including the rule of law)

Legal redress, enforcement of contracts and administrative justice can be challenging in Turkey. In the 2015 *Rule of Law Index* Turkey ranked 80th out of 102 countries.[1073]

United Kingdom

The UK is one of the ten largest economies in the world with an estimated 2014 total national output of just under USD3 trillion measured on current USD.[1074] Measured on a GDP per head basis the UK had a per capita income of USD46,297 for 2014 at current USD.[1075]

The UK is the 10th most open and competitive economy according to the World Economic Forum's 2015-16 Global Competitiveness ranking.[1076]

The UK's referendum in June 2016 on EU membership and narrow popular decision to leave the European Union was conducted after the time of research for *Building the Bioeconomy*. The vote creates a high level of uncertainty for the biotechnology industries and innovators in the UK with regards to the type of trading environment, regulatory and administrative framework they will be operating in.

National Innovation Policy

For a number of years, UK government-led initiatives have sought to promote innovation and the development of new technologies. In its first term the Labour Government under Tony Blair emphasised how the British economy should be built and expanded through innovation. The Labour administration published a number of studies on how to improve British innovation and increased public funding in basic science and technology research; built clusters; launched R&D tax credits; increased higher education funding; and encouraged technology transfer.[1077] Subsequent governments have maintained this commitment to encouraging innovation, but moved policy towards a more market-driven approach.

The UK maintains a strong commitment to innovation coordinated by the country's Department for Business, Innovation and Skills. The Department has 2500+ staff and 10 offices situated around the country.[1078] In 2010 the Department published "Blueprint for Technology". This document outlined how the government would support and create the conditions of

technology companies to flourish and continue to expand. The headline policy initiatives were: a reduction of the main rate of corporation tax from 28% to 24% over a 5-year period; maintaining public funding levels for the sciences; reducing regulation; and reviewing the UK's IP framework (including patents).[1079] Through this blueprint the emphasis has been on encouraging the private sector to innovate and ultimately create jobs and growth.

In a view to boost competitiveness through innovation, the Intellectual Property Office launched in January 2016 the five-year strategy "Making life better by supporting UK creativity and innovation", reportedly intended to "*make the UK the best place in Europe to innovate.*"[1080] Notably, the text proposes to strengthen enforcement efforts against counterfeiters, launch an IP education program among businesses and students and commit to joining and shaping a EU-wide patent system.[1081]

IPR intensive industries generated approximately 26.7% (7.8 million) of UK employment and 37.4% (€640 billion) of GDP in 2010. As far as the life sciences are concerned, in 2014 the sector accounted for an estimated 4,398 companies that employed 183,000 people across the UK and generated a turnover of GBP56 billion.[1082]

Biopharmaceuticals

The UK is home to some of the most innovative biopharmaceutical manufacturers in the world and houses a globally competitive biotech sub-sector. Biopharmaceutical research represents a large share of the British economy with pharmaceutical exports accounting for almost 8% of all goods exported in 2015. [1083] Over the last decade the sector has constantly generated a large trade surplus of around GBP 5 billion per year, greater than any other industrial sector.[1084] The pharmaceutical industry employed 23,000 people in R&D in 2015.[1085] Figures from 2013 show that 22% of all business R&D expenditures were focused on the pharmaceutical sector; a percentage significantly higher than any other sector of the British economy.[1086] Many of its universities are ranked among the best in the world for the study of life sciences. This made the UK an attractive destination for investors. In 2015, the country had the largest amount of international new biopharmaceutical investments outside the US, and ranked fourth among all regions, after Boston/Cambridge area, Northern California and Southern California but before Switzerland, France, Germany and Israel.[1087]

Attractiveness to investors has been attributed to government efforts to support the biopharmaceutical sector and specifically to the creation of a "patent box" tax break (see under "Market and Tax Incentives).[1088] Shortly after the tax break was launched GSK announced that it would build a GBP350 million manufacturing facility in the country with the potential for further investment of GBP700 million.[1089] In announcing the decision the company specifically cited the UK's commitment to improving the overall environment for innovation.[1090]

As concerns the regulatory environment, in late 2015 the Government announced the Accelerated Access Review with the aim of encouraging medical innovation and helping the biotech sector gain greater uptake in the NHS (see under "Regulatory Environment").[1091]

Looking at rates of product launches between 1983-2000, the percentage of products available in the UK within five years of global launch was 51%.[1092] This was second only to the US.

With regards to the BCI Survey UK ranked third of the economies included in *Building the Bioeconomy* with an overall score of 81.59. [1093]

Ag-Bio

The UK has a unique relationship with agricultural biotechnology. While the country as a whole embraces GM food products the current list of genetically modified seeds approved for planting by the EU are not suitable to the UK's growing environment, so there is limited commercial biotech crop cultivation. In this sense, the ag-bio sector could benefit from greater regulatory autonomy if the country would leave the EU.[1094] In this regard, however, Scotland declared it would formally forbid GMO if the EU ban was no longer applicable.[1095]

Despite this EU legislation constraint the UK has launched a long-term project to look at the discovery and application of innovative technologies in the agricultural sector.[1096] This strategy, known as Agri-Tech, was officially launched in 2013 and aims to improve innovation in the agricultural industry through grants and centers of innovation.[1097] To support this project the British Government has created the Agri-Tech Catalyst Fund that allocates GBP70 million to innovative agricultural projects from early stage development through to commercialization.[1098] An additional GBP90 million has been earmarked to create Centers for Agricultural Innovation. The first center focusing on agricultural informatics to improve field productivity was launched in October 2015, and three additional centers were announced beginning of 2016 focusing on crop health and protection, livestock innovation and agricultural engineering precision.[1099]

Industrial Biotechnology

As of 2014, 112 pure industrial biotechnology companies were established in the UK, mostly SMEs. The sector generates a turnover of GBP860 million and employs 2,600 staff. Top performers are biofuels, followed by companies providing products into the food and drink market, and enzyme production.[1100]

Industrial biotechnology has for quite some time been viewed as an important component of the UK's future bioeconomy. In 2009 the then Labour Government published "Maximising UK Opportunities from Industrial Biotechnology in a Low Carbon Economy". The report emphasized the significant future opportunities opening up in the industrial biotechnology sector. Specifically, the report argued that the future value and size of the UK market could be large at GBP4-12 billion.[1101] The report identified the UK's strengths in research and technology capacity as well as an already significant chemicals industry presence.

The focus on promoting industrial biotechnology lives on in the current government. At the beginning of 2015 the Industrial Biotechnology Catalyst Program was launched.[1102] The program has been provided with GBP40 million in funding to distribute to companies working on industrial biotechnology projects that will generate biofuels, chemicals, proteins or natural products from biological resources. Companies qualify for funding based on size and type (academic or industry) with small companies having the opportunity to have up to 70% of their industrial research and 45% of their experimental development costs covered.[1103]

Looking at biofuels while the UK has traditionally been an active supporter its production remains relatively low-scale. In 2014 the UK accounted for 0.7% of global biofuels production,[1104] significantly less than smaller comparable countries such as the Netherlands and Belgium.[1105] Also, the roll-out of E10 gasoline has been halted amid concerns over increased cost to consumers; notably the owners of the 1.2 million non-compatible cars.[1106]

Performance in key enabling sectors

Human capital

The UK's universities are held in extremely high regard internationally with three institutions appearing in the top ten (and 58 in total) on the Times Higher Education rankings of the world's top 500 universities.[1107] Additionally, the country's universities are recognized as excelling in offering life science training with 18 institutions ranked in the top 100 life science universities internationally.[1108]

In terms of academic and research publications, the UK has compared to other *Building the Bioeconomy* countries a high number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 2000-2011 the UK had 708.66 publications per million population.[1109] This was ahead of the US and behind only Israel and Switzerland. British publications were also ranked relatively highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with 16.13% of publications among the 10% most cited.[1110]

A medium proportion of the UK's workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows

that UK had 4,055 researchers per million people less than half of overall leader Israel. [1111]

Infrastructure for R&D

The UK is compared to other high-income countries a middling investor in research and development; 2014 figures show R&D spending as a percentage of GDP at 1.7%.[1112] Internationally, this is below than the OECD average of 2.37% and far behind the biggest R&D spenders such as Korea and Israel.[1113] 46.5% of R&D spending in the UK comes from the private sector in 2014, against an OECD average of 60%.[1114]

The UK is a relatively attractive place to conduct clinical research. The number of clinical trials conducted is on an absolute and per capita basis fairly high.[1115] Per capita the UK has a high level of clinical trials compared to the other economies included in *Building the Bioeconomy*. The number of clinical trials to date performed in the UK per million population was 173.35 trials.[1116] This is ahead of Korea but behind Singapore and world leaders Israel and Switzerland. The UK has compared to the other economies sampled a high level of trials on biologics per million population, 9.18 for the period 2010-2015.[1117] A relatively high level of these – 45% – were early phase trials.

Looking at biotechnology triadic patenting the UK is a top patenting nation on an absolute basis or adjusted for population. Its share of the global total average for the period 1999-2012 is 5.35% – third highest of the sampled economies.[1118]

The UK is viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* the UK ranked second in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 94. [1119]

Intellectual property protection

In general, the UK is seen as having a strong environment for intellectual property protection. The country has a sophisticated IP system that offers patent rights holders multiple levels of protection and avenues for recourse against IP infringements.

Regulatory Data Protection is offered under the EU standard in an 8+2+1 formula whereby companies are provided with eight years of data exclusivity followed by two years of market exclusivity. Patent term restoration is also available.

It is not expected that the IP environment in the UK would change or weaken as a result of exiting the EU, but this would be one policy area biotech innovators would monitor closely.

The regulatory environment

The UK has a strong clinical and regulatory environment. For biopharmaceuticals the MHRA is responsible for the authorisation and safety supervision of pharmaceuticals. The Agency works hand-in-hand with the EMA to ensure the proper dissemination of drugs approved at the EU-wide level.

With regards to the UK leaving the EU and the EMA, there is a clear risk that this could lead to delays in approval and product launches.[1120] An estimated 130 products might also need to be re-registered.

Technology transfer

The UK maintains a sophisticated and active technology transfer environment. Universities such as Oxford, Cambridge and Imperial College are active participants in transferring and commercializing research and technology. In 2015 Oxford University through its commercial enterprise ISIS Innovation Ltd generated GBP24.6million, more than double the revenue of 2013.[1121] Of particular note to the biotechnology field is Imperial College's success. Imperial Innovations was founded in 1986 to encourage technology transfer between Imperial College London and the general business community.[1122] The group has grown considerably since that time and has facilitated the creation of a number of companies. Among the successes are RespiVert, a small-molecule drug discovery company, and Circassia, a biotech company that was listed on the London Stock Exchange in March 2014 after raising GBP200 million.[1123]

In terms of direct central government support for

technology transfer Innovate UK maintains a web portal that allows members of industry, academia, potential funders and entrepreneurs to collaborate on ideas.

Market and commercial incentives

The UK offers R&D tax incentives to both small and large companies. SMEs can qualify for a super-deduction on qualifying R&D activities of 230% and SMEs that post a yearly loss can additionally qualify for up to 33.3% cash back on R&D related spending.[1124] Until April 2016, large companies were able to choose between a super deduction of 130% on R&D activities or a tax credit through the Research and Development Expenditure Credit programme.[1125] From April 2016 only the taxable credit is available for companies operating under the large company tax scheme.

As mentioned above, a patent box regime offering a 10% rate of corporation tax to profits generated from patents is in place. This is a particularly attractive tax incentive notably to the biopharmaceutical sector given the significant investments required for R&D and product development.

Looking at the biopharmaceutical P&R environment, the UK has a highly regulated pricing environment with the NHS negotiating prices with the pharmaceutical industry through the PPRS. Companies that do not participate in the voluntary PPRS are subject to the statutory scheme that imposes a list price cut of 15% on products; 6% of branded medicines were covered by the scheme in 2014.[1126] In September 2015 the Ministry of Health launched a new consultation on changes to the scheme,[1127] which was criticized by the Association of British Pharmaceutical Industry for "*sending out negative signals globally about the UK's willingness to pay for new and innovative medicines*".[1128] Still, in contrast to other EU Member States the UK's system of price controls is indirect, with the PPRS only regulating the profits made on branded prescription drugs. While in comparison with the US market there are admittedly fewer market-based incentives for R&D, measured against the strict price controls in place in other European markets the UK has a relatively freer pricing market.

The Accelerated Access Review system mentioned above envisages to speed up access to the most promising new products through a managed access system accompanied by more flexible approaches to reimbursement. According to the interim report that launched this idea, flexibility could be achieved via "*simple discounts, but also as price-volume agreements, multi-year agreements conditional on the achievement of certain outcomes, patient cost caps or free/ discounted treatment initiation*".[1129] The final report on the proposal is to be published after the referendum on EU membership in June 2016. As part of this initiative reports suggest that there may also be an overhaul of the UK's HTA body's (NICE) decision-making process.[1130] This includes reforms to the existing Cancer Drugs Fund which, beginning in 2016, is to be managed by NICE. From July 2016, under the revised system, NICE will run the Fund and will thus become the sole arbiter deciding which new drugs are to be founded.[1131] Over the past years, NICE has consistently rejected some of the most funded medicines under its system, such as Roche's Avastin and Merck's Erbitux.[1132]

Legal certainty (including the rule of law)

The British legal environment is generally stable and certain. The country is ranked as the 12th most stable legal environment by the 2015 *Rule of Law Index* and receives particularly high marks for government accountability and low levels of corruption.[1133]

United States

The US is the world's largest and most dynamic economy. The latest World Bank national accounts figures from 2014 show total US GDP at USD17.42 trillion.[1134] The US is also one of the world's richest economies in terms of per capita income with an estimated 2014 GDP per capita of USD54,629 per the World Bank.[1135] The US economy is also one of the world's most open and innovative. The World Economic Forum's 2015-16 Global Competitiveness rankings ranked the US economy as the third most competitive economy in the world.[1136]

National Innovation Strategy

Promoting innovation has long been at the heart of US economic policymaking. Since the late 1970s and early 1980s the Federal Government has become more heavily involved in innovation policy, passing a number of laws and initiatives ranging from technology transfer to lowering taxes and introducing R&D credits.[1137]

The current administration has built and expanded on many of these policies. A number of strategy documents have been released including the 2009 "Strategy for American Innovation: Driving Towards Sustainable Growth and Quality Jobs", revised in 2011 and updated in October 2015. The latest document emphasizes the need to sustain high rate of R&D investments from the Government and build on open innovation and public participation to create a better environment for innovation. It also calls to direct R&D investments in priority areas with the greatest potential for the economy of the future, such as biomedical discoveries related to precision medicine and neuroscience".[1138]

With regards to biotechnology specific innovation policies the most recent initiative is the *National Bioeconomy Blueprint*. This document outlined a range of Federal policy initiatives aimed at furthering the building and development of the biotech sector in the US. The document was organized around five strategic objectives ranging from: supporting R&D investments; commercialization; improving regulations; updating training programs; and supporting public-private partnerships.[1139] The updated Strategy for American Innovation reiterates the commitment to spurring development of engineering biology and refers specifically to the benefits that increased investments could have in speeding up discoveries of new classes of therapeutics, such as cell-based therapies,[1140] as well as renewable bio-energy and bio-products.[1141]

In addition to policies at the Federal level there are also important state level initiatives that, while not formally part of a national innovation strategy, nevertheless contribute to the strengths of the enabling categories and to the overall national capability to perform biotech innovation. In some states, such as California and Massachusetts, these efforts have been the real key drivers in encouraging biotechnology innovation.

Biotech sector by sector policy overview

Biopharmaceutical

The US is the largest biopharmaceutical market in the world and American R&D activities are responsible for the vast majority of global clinical research. As of May 2016 more than 93,000 out of a global total of circa 215,975 clinical trials had been carried out or were taking place in the US.[1142] The US is home to the biggest proportion of private sector biopharmaceutical investment. Out of a total of USD51billion in R&D investment by the member companies of PhRMA in 2014, USD41billion was invested in the US.[1143] Looking at NMEs developed the vast majority of product development is conducted by US firms. A study of global drug development between 1970-2010 showed that the percentage of all new drugs originated from US-based companies rose from about 31% in the 1970s to 57% in the 2000s.[1144] Other sources estimate the current US drug pipeline as including roughly half of the around 27,000 new medicines developed worldwide.[1145]

Government funding and support for biomedical and biotech R&D comes through both direct support and tax credits. At the Federal level the NIH is one of the main sources of funding for biotech and biomedical research in the United States. The NIH funds over 300,000 researchers at 2,500 universities, medical schools and research institutes in the US and abroad.[1146] [1147] NIH was one of the main winners of the 2016 R&D budget. Remarkably, the 2016 spending bill increased its funding by 6.6%, or USD 2billion, up to USD32.3billion, the biggest raise in 12 years and double the amount requested by the President.[1148]

Historically, the NIH has allocated over 50% of its budget to basic fundamental research with translational and advanced research being pursued by biopharmaceutical and biomedical companies. Many commentators have noted that this has, by and large, been a successful combination in creating a steady stream of innovative and new medical products.[1149]

During the 2016 State of the Union Address, President Obama called on Vice President Biden to lead a new, national "Moonshot" initiative to accelerate research for new cancer detection and treatments. The proposed new fund will be focused on high-risk, high-return research identified by the research community.[1150] According to the proposal, USD1 billion should be allocated to the initiative, including USD195 million in new cancer activities at the NIH and USD755 million in mandatory for new cancer-related research activities at both NIH and the FDA.[1151]

The US has a large number of biotech and biomedical clusters. In particular, California and Massachusetts are home to a number of world-leading clusters. In California there are four major clusters that employee more than 20,000 people each in biotech and biomedical research: the Bay Area, Los Angeles County, Orange County and San Diego County. More broadly, together these four areas employ over two third of the 270,300 Californians who work in the biomedical industry.[1152] Overall, this is more than one in four of people employed in the biopharmaceutical industry in the US (854,000 in 2014).[1153] California also hosts the highest number of cutting-edge universities, where 1,228 life science doctorates were awarded in 2012.[1154] The total number of biomedical companies in the state is 2,636 with estimated revenues of USD101 billion.[1155]

The Massachusetts biotech cluster, located primarily in the Greater Boston area, is one of the oldest biomedical clusters in the US. It employs 60,459 workers, roughly half of which work in R&D.[1156] It hosts eight of the top 14 NIH-funded independent hospitals and is the second biggest receiver of NIH funding after California, first on a per capita basis.[1157] This cluster has grown to contain over 500 biotech companies.[1158] Like many American states, both California and Massachusetts offer tax credits to biotech and biomedical companies as an incentive to both start up and run their businesses.[1159]

Looking at rates of product launches between 1983-2000, the percentage of products available in the US within five years of global launch was 53%.[1160] This was the highest of all the sampled economies.

With regards to the BCI Survey the US ranked first of the economies included in *Building the Bioeconomy* with an overall score of 85.55. [1161]

Ag-bio

The US is the world's largest producer of ag-bio crops. In 2015 the US had 70.9 million hectares under cultivation.[1162] Crops under cultivation include corn, canola, sugar-beet, alfalfa soybean, cotton, papaya and squash. GM crops are widely used –more than 90% of corn, soybeans and cotton grown in the US is genetically modified[1163] – and public support for ag-bio is strong. In 2014 President Obama re-affirmed his support for the ag-bio sector in a letter praising the work of the late Nobel laureate Dr Norman Borlaug. The President stated that "*investment in enhanced biotechnology is an essential component of the solution to some of our planet's most pressing agricultural problems.*"[1164]

In the policy space discussion on GMO labeling intensified in 2015, after some states introduced mandatory GMO labeling. An anti-GMO labeling bill passed the House of Representatives in 2015 but was rejected by the Senate in March 2016.[1165] As discussion intensifies (a new bill requiring compulsory labeling was introduced to the Senate),[1166] some companies have already begun labeling, such as Campbell Soup Co. and General Mills.

The US is also home to some of the largest and most innovative ag-bio companies in the world including Monsanto and DuPont. At the end of 2015, Dow and DuPont announced their intention to merge and form DowDuPont, which will be split into three companies focusing on agriculture, materials and specialty products.[1167]

The ag-bio sector receives support from the National Institute of Food and Agriculture, USDA. The institute maintains three large grant programs to promote the sector including the 1890 Institution Teaching, Research and Extension Capacity Building Grants Program, the Agriculture and Food Research Initiative and Biotechnology Risk Assessment Research Grants Program. The 1890 Institution Program is available to US land grant institutions and concentrates on building

up agricultural science programs at universities to train the next generation of scientists.[1168] The Agriculture and Food Research Initiative looks to improve food security through the funding of projects that focus on issues such as crop sustainability. As of 2015, 15% of US wheat acreage was planted using cultivars resulting from AFRI investments.[1169] The 2016 budget of USD350 million is expected to double in 2017.[1170]

Industrial biotechnology

The industrial biotechnology sector is a large contributor to the US economy with revenues estimated at USD369 billion in 2013, of which USD 126 from direct sales.[1171] For the same year, the sector generated 4 million jobs. Overall, the use of biobased products is displacing about 300 million gallons of petroleum per year, equivalent to the average yearly consumption of 200,000 cars.[1172]

A majority of the revenue and research in industrial biotechnology is focused on bioenergy. Since the mid-2000s policies have been in place to promote the use of biofuels. In fact, the legislative framework has proven to be a significant driver in encouraging the production and use of biofuels, chiefly maize based ethanol. Main policy drivers include the Renewable Fuel Standards (part of the 2005 Energy Policy Act and Energy Independence and Security Act 2007).[1173] For 2015-16, the Environment Protection Agency announced blending mandates that – at 10.1% bioethanol – were lower than the 15% statutory requirement.[1174] Through the Biofuels Infrastructure Partnership, the USDA is financing constructions of pumps offering higher blends of ethanol (E15 and E85). In September 2015, USD100 million were allocated to the construction of around 5000 such pumps in 21 states.[1175]

In large measure as a result of these policies the US has increased its production of biofuels from just over 5,226 thousand tonnes oil equivalent in 2003 to over 30,000 thousand tonnes oil equivalent in 2014.[1176] It is now by far the biggest producer of biofuels in the world accounting for 42.5% of global production in 2014.[1177]

Since the 1970s to the present, the Department of Energy has invested more than USD4 billion, of which USD900 million in the 2009 American Recovery and Reinvestment Act, to finance R&D programs covering biofuels, biopower, feedstocks, municipal wastes and other biobased products.[1178] Various departments and agencies within the Federal Government also actively support a number of industrial biotechnology research initiatives. The Bioenergy Technology Office within the Office of Energy Efficiency & Renewable Energy organizes its research efforts around three key technical areas (feedstock supply and logistics, conversion, demonstration) and three key crosscutting elements (sustainability, analysis, communication).[1179] In May 2016, USD 10million were allocated to six projects aimed at reducing investors' risk in developing biofuels from non-food biomass feedstock.[1180]

Additional programs to support industrial biotechnology are available through the Advanced Research Projects Agency-Energy in the Department of Energy. This initiative was created in 2007 to conduct energy research that is at too early of a stage to be considered viable for private-sector development.[1181] A primary element of the Agency's mission is to transfer its discoveries to the private sector for commercialization and the Agency maintains a Tech-to-Market program that determines the best way for each project to be developed in the private sector.[1182] The Department of Energy and the USDA jointly manage the Biomass Research and Development Initiative which in 2015 made available around USD8.7 million for grants of up to USD2 million in the areas of feedstock development, biofuels development and development analysis.[1183] Another joint program, the Plant Feedstock Genomics for Bioenergy program, supports research that aims to improve biomass feedstock for bioenergy purposes.[1184] In 2015 the program provided about USD5 million in funding for five projects.[1185]

Performance in key enabling factors

Human capital

American universities consistently top world rankings in almost all subject fields and the US remains the top destination globally for international students.[1186] In the life sciences the US dominates the Times Higher Education 2015-16

rankings as American universities make up 11 out of the top 20 universities.[1187]

In terms of academic and research publications, the US has a high number of scientific and technical journal articles published per capita. Data from the World Bank shows that on average for the period 2000-2011 the US had 634.78 publications per million population.[1188] This was behind only South Africa, the UK, Israel and Switzerland. American publications were also ranked relatively highly according to the OECD's 2015 *Science, Technology and Industry Scoreboard* which measure of the quality of academic publications with 16.43% of publications among the 10% most cited; this was second only to Switzerland.[1189]

A medium proportion of the American workforce consists of researchers in R&D. Looking at the number of researchers in the population the latest available (2012) data from the World Bank shows that the US had 4,018 researchers per million people, less than half of leading Israel and two-thirds of second place Korea. [1190]

Infrastructure for R&D

The US is a strong investor in R&D. 2013 figures show R&D spending as a percentage of GDP at 2.74%.[1191] As a whole, the US is the world's largest spender on R&D, and spends twice as much in absolute terms as the second-highest spender, China. Internationally, this is higher than the OECD average of 2.40%, but still behind the biggest R&D spenders such as Korea, Israel and Japan.[1192] US R&D spending is largely made up of private sector and industry spending. The latest data from 2013 show industry expenditure on R&D at 60.9% of the national total.[1193]

The US is a highly attractive place to conduct clinical research. The number of clinical trials conducted is on an absolute and per capita basis high.[1194] The number of clinical trials to date performed in the UK per million population was 278.94 trials.[1195] This is behind only Israel and Switzerland. The US has compared to the other economies sampled a high level of trials on biologics per million population, 10.35 for the period 2010-2015.[1196] A very high level of these – 66% – were early phase trials.

Looking at biotechnology triadic patenting the US is the top patenting nation of the economies included in *Building the Bioeconomy*. Its share of the global total average for the period 1999-2012 is 41.19% – the highest of the sampled economies.[1197]

The US is viewed as an attractive market for venture capital or private equity. Of the economies included in *Building the Bioeconomy* the US is ranked first in *The Venture Capital & Private Equity Country Attractiveness Index* with a score of 100. [1198]

Intellectual property protection

The US has one of the most sophisticated and elaborate forms of IP protection in the world. It offers standard patenting exclusivity of 20 years with data exclusivity provisions of up to 5 years for new chemical entities and 3 years for new indications of existing drugs.[1199] The US has a separate and distinct term of protection for biologics. The Biologics Price Competition and Innovation Act of 2009 (BPCIA) provides 12 years of data protection to biologics (i.e. 12 years until a biosimilar can be approved), with no filing of biosimilar applications for the first four years and an extra six months (added to both the four years and the 12 years) for submission of studies on paediatric use. The 2011 patent reforms and the change from a first-to-invent to a first-to-file system of patenting was greeted by many innovators as a positive enhancement of existing patent protection.[1200] Patent term restoration is also offered of up to a period of 5 years.

Still, challenges remain even in the US. In particular in the biotech sector question-marks have been raised over the patentability of basic biotech inventions due to the Supreme Court decisions in the 2013 *Molecular Pathology v Myriad Genetics* and 2012 *Prometheus Laboratories, Inc v Mayo Collaborative Services* cases. The former ruling has raised uncertainties over the patentability of DNA molecules that mimic naturally-occurring sequences as well as other patented products and technologies isolated from natural sources.[1201] The latter ruling has made the field of personalized medicines and the patentability of biotechnologies and products that make use of the application of natural laws highly uncertain.[1202]

Some analysis suggests that a high number of patent applications have been rejected following the 2012 and 2013 court rulings.[1203] There was also a drop in biotech patenting in 2015; the latest figures from Thomson Reuters suggest there was a 3% drop in activity compared to 2014.[1204]

In April 2014 the USPTO issued new guidelines on the patentability of biotechnology inventions aimed at providing further clarification and interpretation of these decisions.[1205] These guidelines extended the holdings from these decisions by introducing restrictions on patenting of naturally occurring substances (including genomic DNA, proteins and stem cells), even if isolated and purified, if there is not sufficient distinction shown between a claim and the substance as found in nature. In a break from its typical approach of providing guidance on certain gray areas and leaving it to the courts determine specific limits on wider issues, the new guidelines placed broad restrictions on key areas of biotechnology. The guidelines generated significant uncertainty as to the scope of patentable subject matter for biotechnology inventions and risk widening the gap between current US practice and that in other jurisdictions, such as the EU, Australia and Japan where, for instance, purified genomic DNA and proteins are patentable. Revised guidelines were issued in December 2014 and subsequently updated in July 2015 and May 2016. The May 2016 update is intended to improve the quality of examiner correspondence with applicants, and includes a memo instructing patent examiners on how to formulate a subject matter eligibility rejection and evaluate an applicant's response. More importantly, the 2016 revision puts forward examples of claims from life sciences,[1206] including for claims, methods of diagnosis or treatment, genetic screening, and chemical reactions, that may be deemed to be patent eligible. They also provide further guidance relating to the "markedly different" and "significantly more" tests that can provide enough substance for eligibility. Broadly speaking these examples are expected to help find more life science claims patent eligible.[1207]

Nevertheless, despite this guidance the situation remains highly uncertain for innovators. Compared to the pre-2012 situation fundamental questions remain unanswered on what types of biotechnology inventions are patentable and the extent to which the US now stands outside international biotech patenting standards.

In other news a new Federal trade secret bill was signed into law in May 2016. The Defend Trade Secret Act is expected to reinforce trade secret protection, including by allowing federal courts to hear cases involving trade secret theft which had previously been dealt with at a state level. In case of misappropriation, the trade secret owner will be able to file a civil action seeking remedies, such as damages and injunctions. The theft of trade secrets costs the economy over USD300 billion a year, reports the Commission on the Theft of American Intellectual Property.[1208]

The regulatory environment

The American clinical and regulatory environment is highly regarded and internationally well recognised.

With regards to the regulation of products and technologies developed using modern biotechnology, the Coordinated Framework for Regulation of Biotechnology is generally viewed as being one of the key building blocks and drivers of biotech innovation. Since its announcement in 1986 the policy and subsequent sector-specific regulations are seen as having been instrumental in promoting the development of the American biotechnology industry and bringing a wide array of biotechnology products and technologies to consumers.

With regards to biopharmaceuticals the FDA sets and enforces rigorous standards. The FDA plays a leading role in efforts to harmonise regulatory standards through the International Conference on Harmonisation. Moreover, the regulatory standards of the FDA are frequently emulated and recognised as a gold standard amongst clinicians, health economists and the academic community.[1209] In response to criticism of long approval times new expedited pathways have been introduced and in 2015 the FDA approved a record 45 NME and BLA products; the highest rate over the last decade.[1210] Significantly, a growing portion of these approval were for biologic medicines and therapies.

With regards to the regulation of biotechnology crops, the USDA has in recent years taken steps to cut the approval time by half for petitions for nonregulated status for genetically engineered organisms including biocrops.[1211] Approval times have increased from six months to 3-5 years since the mid-1990s. Key changes include streamlining internal USDA review processes, setting timeframes for the completion of specific review steps, and expedited internal review and decision-making procedures.[1212]

Technology transfer

One of the key drivers of American biotech innovation and commercialisation has been the success of technology transfer in the US. The Patent and Trademark Law Amendments Act of 1984 and 1986 (commonly referred to as the Bayh-Dole Act) and the Stevenson-Wydler Technology Innovation Act, which was later amended by the Federal Technology Transfer Act of 1986 and the Technology Transfer Commercialization Act in 2003 have all been instrumental in incentivizing technology transfer. These laws gave institutions that received federal support (such as American universities, small businesses and non-profits) control and the rights to any resulting intellectual property of their inventions or research.

Studies have found a significant correlation between increased patenting activities at US universities following the Act. For example, a 2004 study found that university share of total patenting in the US increased from 0.69% of total patents at the time of legislation to just under 5% in 1996. Moreover, in a range of 117 industries (including drugs) the increase was from a decrease of 87% in 1969 to an increase of 1,648% in 1996.[1213]

Similarly, the economic impact has been substantial. For example, using eighteen years of data from the annual AUTM survey a 2015 study estimating the economic contribution of licensing activity by academic institutions found that in the US the contribution of academic licensing to gross industry output ranged from USD282-1,180 billion (measured in 2009 USD).[1214] Contributions to GDP were equally significant estimated at between USD130-518 billion (measured in 2009 USD).[1215] In addition, this study found that this licensing activity was also a major contributor to the American jobs market, responsible for between 1.1million-3.8million person years of employment. The latest figures from the AUTM survey show how licensing revenue and technology transfer is continuing to grow in the US and presents an important income stream for higher education institutions. Results from the latest available survey (published in 2015) show that executed licenses grew by 4.5% year on year, almost 1,000 new commercial products were created (representing an increase of over 34% from the previous year) and over 6,000 new patents were issued.[1216]

The life sciences play a critical role for universities and account for the vast majority of licensing income at American universities. Figures calculated by *Nature* magazine for a sample of the major research institutions in the US showed how, out of the USD860 million of licensing income received in 2014, USD734million came from the life sciences.[1217] Also, two third of total licenses executed and startups created related to life sciences.[1218]

Other more recent initiatives to promote tech transfer include the National Science Foundation's Innovation Corps (I-Corps) program, specifically mentioned in the revised the Strategy for American Innovation. The program, which includes a dedicated biomedical pilot program, provides entrepreneurship training for federally-funded scientists and engineers.[1219]

Market and commercial incentives

The US provides a number of, by comparison to other *Building the Bioeconomy* economies, limited R&D tax credits, both at the federal and state level. The federal Research and Experimentation Tax Credit allows companies to claim a tax credit of between 14-20% of qualifying amounts.[1220] After 30 years of uncertainties, during which this rather convoluted and complicated credit lapsed six times and was extended seventeen times, it was made permanent in December 2015 and expanded to cover R&D investments by small businesses.[1221] The number of small businesses eligible is expected to experience a ten-fold growth.[1222] In addition, two draft bills were introduced in 2015 to make CROs eligible for tax

credit.[1223] At present, 65% of payments to CROs qualify for tax credits, but CROs cannot claim the R&D benefit, unlike other countries like Canada and the UK.[1224]

In addition, 39 US states offer R&D tax credits at varying rates.[1225] For example, California offers a research credit of 15% of qualifying supplemental research activity conducted within the state, Maryland a credit of up to 13% of qualifying expenditure, Massachusetts 10% on R&D expenses and 15% for donations to universities for basic research.[1226] Many states also offer additional incentives and tax credits such as seed capital tax credits, state venture capital investments and state sales tax exemptions for R&D equipment.

By international standards, the US has a relatively free market in the purchase and sale of biopharmaceutical products. There are no national price regulations or national reimbursement agencies. Instead, private health insurers and public payers (such as Medicare, the VHA and Medicaid) negotiate prices with manufacturers and only indirectly set reimbursement limits and influence prescribing and patient usage through the use of formularies. Drug formularies (which often include therapeutic interchange or so-called switching mechanisms) and differential cost-sharing (such as tiered co-payments) are two of the more commonly used techniques to influence prescribing practices. Arguably, one of the strongest drivers of biopharmaceutical innovation in the US has been the existence of this relatively free market in the pricing of pharmaceuticals.[1227]

Legal certainty (including the rule of law)

The US legal environment is generally considered stable and certain. Legal redress, enforcement of contracts and administrative justice is generally available and viewed as effective. However, the US faces challenges as is reflected in its ranking on a number of international indices measuring the rule of law. In the 2015 *Rule of Law Index* the US ranked 19th.[1228]

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